Aspects of Subcortical Ischaemic Vascular Disease

Early clinical manifestations and associations with Type 2 diabetes mellitus

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door

Barbera van Harten

geboren te Anna Paulowna

promotor: prof.dr. Ph. Scheltens
copromotor: dr. H.C. Weinstein

Climb the mountains and get their good tidings
Nature's peace will flow into you as sunshine flows into trees
The winds will blow their own freshness into you and the storms their energy,
while cares will drop away from you like the leaves of Autumn

John Muir (1838-1914)

Ter nagedachtenis aan mijn vader
Voor mijn moeder
Rein
Elin en Dagmar

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Chapter 1

General Introduction

General Introduction

Subcortical ischaemic vascular disease

Vascular dementia is considered the second most common type of dementia, accounting for ten to fifty percent of all dementia cases. The major subtypes of vascular dementia are cortical vascular dementia, strategic infarct dementia and subcortical vascular dementia, each of which has unique aetiological mechanisms and manifestations. The concept of vascular dementia covers a wide spectrum of cognitive dysfunction, ranging from subtle and clinically often undetected deficits to overt dementia[1]. Clinically important cognitive impairments that are associated with vascular disease frequently do not fulfil the traditional criteria for dementia, as these criteria tend to be based on the context of Alzheimer's disease and require the presence of prominent memory impairment[2,3]. Early diagnosis is impossible, as patients must fulfil the clinical criteria for dementia. The concept of vascular cognitive impairment was therefore introduced to refer to all forms of cognitive impairment, ranging from mild to severe cognitive deficits due to cerebrovascular disease[4,5]. Because of the different clinical symptoms of vascular cognitive impairment and the heterogeneity of the aetiological mechanisms, the specific concept of subcortical ischaemic vascular disease (SIVD) has been suggested as the most prevalent subtype of vascular cognitive impairment. This syndrome has been defined by clinical symptoms and specific features on magnetic resonance imaging (MRI) and has been described in multiple studies[1,6-9].

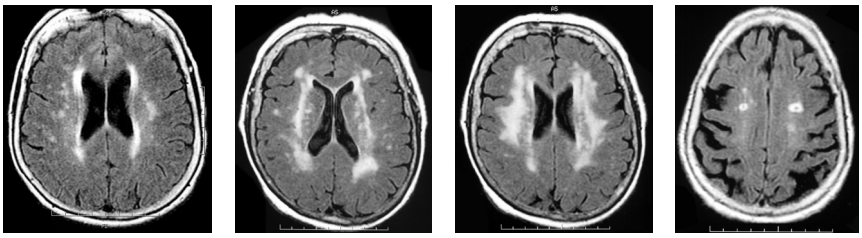
SIVD is caused by small-vessel disease, which results in cerebral white-matter lesions (WML) and lacunar infarcts in subcortical white and grey matter, as demonstrated by MRI of the brain[1,8,10]. Because individuals who suffer from SIVD frequently do not fulfil the traditional criteria for vascular dementia (according to the criteria from the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences [NINDS-AIREN][11]) diagnostic consensus criteria have been introduced for the cognitive syndrome of SIVD[12]. The neuropsychological profile is characterized by early impairment of attention and executive function, with a slowing of motor performance and information processing. Although episodic memory is believed to remain relatively unaffected, depression, emotional lability and apathy are particularly frequent in these patients, as compared to those who suffer from AD[12]. In addition, these modified criteria do not require any clear temporal relation between the onset of cognitive impairment and vascular disease, as the onset of vascular cognitive impairment due to SIVD is frequently more insidious. Because empirical data describing the clinical and cognitive manifestations of SIVD are still sparse, there is a pressing need to validate and further refine these criteria[9,10].

The assessment of cognitive impairment caused by SIVD poses a challenge for both clinicians and investigators. Patients with SIVD often do not present with marked focal neurological deficits or abrupt deterioration in cognitive functions. The subtle clinical symptoms are often neglected by physicians, and both patients and physicians tend to consider these symptoms as normal signs of ageing. Because of the distinct cognitive profiles of patients with SIVD, these deficits are not detected by screening tests, such as the Mini Mental State Examination (MMSE)[13], the Seven Minute Screening test[14] and the Memory Impairment Screen (MIS)[15], as these tests were designed to identify the cognitive symptoms of Alzheimer's disease (AD). Because of the frequency with which SIVD is identified as a cause of vascular cognitive impairment, there is need for a brief and simple cognitive screening test in order to allow early diagnosis and to facilitate the recognition of cognitive problems in everyday practice with patients who are at risk for SIVD.

Risk factors for SIVD

Subcortical ischaemic vascular disease (SIVD) is caused by small-vessel disease with cerebral white-matter lesions (WML) and lacunar infarcts in subcortical white and grey matter as the primary type of brain lesions on MRI (Figure 1, *see page 3*). WML on MRI scans of the brain are clearly associated with age[16,17]; this finding is consistent throughout all studies that have investigated large numbers of individuals across a sufficiently wide age range. The association of WML with cerebrovascular risk factors, however, is less straightforward[16,17]. Although associations with arterial hypertension have been frequently described, other cerebrovascular risk factors, including diabetes mellitus (DM), cardiac disease or smoking have been less frequently identified as possible contributors to the development of WML[16,18]. Many studies have had major methodological limitations, including small sample size, inability to adjust for confounding factors and unclear operationalization of risk factors and structural brain changes.

Type 2 DM and cognitive decline in the elderly are major public health problems. More than ten percent of all elderly people suffer from Type 2 DM, and cross-sectional studies have suggested that cognitive impairment and DM are interrelated with each other[19]. The neuropsychological studies that establish this relation lack neuro-imaging data, however, and neuro-imaging studies largely lack any assessment of cognition. To provide important clues to the pathogenesis, it is important to combine these assessment modalities, in order to establish how DM may affect the structural integrity of the brain. This may ultimately lead to the development of therapeutic strategies that can prevent accelerated cognitive decline in DM patients.



1a. 1b. 1c. 1d.

Figure 1. Axial fluid attenuated inversion recovery (FLAIR) of periventricular and deep white-matter lesions (a, b,c) and lacunar infarcts (d)

Aims of the thesis

The general objective of this thesis was to investigate clinical aspects of patients with subcortical ischaemic vascular disease (SIVD) and associations with Type 2 diabetes mellitus (DM). To this end, we validated a newly developed cognitive screening test for use with these patients, and we investigated the value of a clinical neurophysiological test. In addition, we investigated the association between Type 2 DM and cognitive impairment due to SIVD.

It is known that the generally accepted cognitive screening tests are not able to detect cognitive decline in patients with SIVD. We therefore attempted to validate the Human Immunodeficiency Virus (HIV) dementia scale (HDS)[20] in elderly SIVD patients. The HDS is a reliable and quantitative scale for identifying HIV dementia, which has a profile with subcortical features comparable to that of SIVD. We hypothesized that this test would be able to detect cognitive impairment in patients with SIVD and that this test would be superior to the MMSE and other widely used bedside tests. The results are described in Chapter 2. In Chapter 3 we investigated whether a clinical neurophysiological test (similar to the the Auditory Oddball Paradigm), which has prolonged latencies of different deflections (e.g. N200 and P300) in dementia, could differentiate between patients with vasculair cognitive impairment (VCI) caused by SIVD in an early phase of the disease and age-matched control subjects. If so, both tests could contribute to the diagnosis of cognitive impairment in patients who are at risk for SIVD.

Second, hypertension is the most important and consistent risk factor for white-matter disease and lacunar infarcts[16]. DM is a known risk factor for vascular disease and increases the risk of cerebral large-vessel disease, leading to stroke[21,22]. Data on the association between small-vessel disease and DM are not consistent, however, and correlations of subcortical structural brain lesions with cognitive decline in Type 2 DM have never been investigated. In Chapter

4, we performed a systematic review of the literature addressing the association between DM and changes on brain imaging, including SIVD. In Chapter 5, we investigated the association between Type 2 DM and changes on brain imaging within a well-defined group of independently living elderly patients with Type 2 DM. We hypothesized that concomitant hypertension could be defined as a relevant disease variable in DM patients and that DM is not an independent risk factor. In Chapter 6, we performed a cross-sectional case-control study in a well-defined group of elderly patients living independently at home with Type 2 DM, in order to describe the neuropsychological profile in detail. We also investigated the relationships between cognitive performance in DM patients and such MRI measures as WML, lacunar infarcts, medial temporal lobe atrophy (MTA) and cerebral atrophy, which are often associated with cognitive decline and dementia in general.

The main conclusions are summarized and discussed in the last chapter.

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Chapter 2

Validation of the HIV Dementia Scale in an Elderly Cohort of Patients with Subcortical Cognitive Impairment Caused by Subcortical Ischaemic Vascular Disease or a Normal Pressure Hydrocephalus

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Abstract

Introduction:

Most cognitive screening instruments are tailored to detect symptoms of cortical dysfunction in the elderly. Therefore, subcortical cognitive dysfunction may be missed using these tests. The aim of this study was to validate the Human Immunodeficiency Virus (HIV) Dementia Scale (HDS), a screening test developed to detect subcortical cognitive dysfunction in young HIV-infected patients, in a group of elderly patients with subcortical cognitive impairment (SCI) caused by subcortical ischaemic vascular disease (SIVD) or a normal pressure hydrocephalus (NPH).

Materials and methods:

53 patients with SCI caused by SIVD or a NPH and 54 age-matched control subjects without cognitive impairment were included. All subjects underwent the HDS and the Mini-Mental State Examination (MMSE). A neuropsychological examination was used as the best reference test for the diagnosis of SCI.

Results:

The mean HDS score (maximum 16) was 5.1 ± 3.5 in the SCI patients and 13.0 ± 2.4 in the controls ($p<0.0001$). The mean MMSE score (maximum 30) was 26.5 ± 3.1 in the SCI group and 28.6 ± 1.4 in the controls ($p<0.0001$). Among subjects, who had an MMSE score of more than 26 points, SCI patients (n=35) also scored significantly lower ($p=0.002$) on the HDS than controls (n=50), mean scores being 6.2 ± 3.4 and 13.0 ± 2.4, respectively ($p<0.0001$).

A receiver-operating characteristics curve was used to detect the optimal sensitivity and specificity of the HDS. A cut-off score of 9 yielded 91% sensitivity (95% CI: 79-97) and 96% specificity (95% CI: 87-99). With this cut-off score, the positive predictive value was 96% (95% CI: 86-99) and the negative predictive value was 91% (95% CI: 81-97).

Conclusions:

These results suggest that the HDS is able to detect SCI in an elderly population with SIVD or NPH and a normal MMSE, and warrant its further development as a screening tool for SCI.

Introduction

As the aged population grows, cognitive decline is a public challenge of increasing importance. Nevertheless, it has been demonstrated that cognitive impairment remains unrecognized by primary care clinicians and physicians until the disease is well advanced[1]. Adequate care and future therapeutic interventions require that the impairment is recognized and its cause determined at a very early stage. This emphasizes the need for brief and simple screening tests, which could facilitate recognition of cognitive problems in everyday practice. Most screening tests, however, like the Mini-Mental State Examination (MMSE)[2], the Seven-Minute Screening Test[3] and the Memory Impairment Screen (MIS)[4] have been tailored to the recognition of cognitive symptoms with cortical features as in Alzheimer's disease (AD). These tests have a low diagnostic accuracy for the detection of subcortical cognitive impairment (SCI) which is present in many brain diseases, such as vascular dementia, normal pressure hydrocephalus (NPH), Huntington's disease, progressive supranuclear palsy and Parkinson's disease[5,6,7].

Cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia and also has a contribution in cognitive decline in AD. The whole concept of vascular dementia has been traditionally based on stroke and the multi-infarct model and definitions for cognitive deterioration were based on criteria for AD according to the DSM-IV[8]. However, there is now agreement that cognitive impairment associated with cerebrovascular disease frequently does not fulfil these criteria and the term 'vascular cognitive impairment' is proposed to cover individuals who have cognitive impairment related to stroke, multiple cortical infarcts, multiple subcortical infarcts, strategic infarcts or small-vessel disease[9]. There is a need for classifying these different subtypes of vascular cognitive impairment and refine the diagnostic criteria. Recently, clinical criteria for vascular cognitive impairment caused by subcortical ischaemic vascular disease (SIVD), a homogeneous subtype of vascular cognitive impairment, have been developed[10]. The clinical identification consists of the following features: (1) slowing of psychomotor functions; (2) memory deficits with relatively intact recognition; (3) disturbances of executive function, and (4) emotional and psychological changes[1,10,11]. Patients with NPH have an identical cognitive profile and are clinically difficult to differentiate from patients with SIVD[11]. Because of the frequency of SIVD as a common cause of vascular cognitive impairment, there is a need for a simple screening test, which has to be validated in this patient group.

Recently, a brief mental test, the 'Human Immunodeficiency Virus (HIV) Dementia Scale' (HDS), has been developed and has been shown to detect SCI with high accuracy in a young population with HIV infection[12]. The aim of this study was to validate the HDS in a group of elderly patients with SCI as a result of SIVD or NPH.

Materials and methods

The study population consisted of patients with SIVD or NPH and control subjects of 60 years or older. Patient selection was based on the clinical syndrome of SCI characterized by slowing of psychomotor functions, memory deficits with a relative intact recognition, executive dysfunction and mood abnormalities[10,11]. The clinical syndrome of SCI was assessed by an experienced neurologist and clinical identification was based on the proposed criteria[10]. Patients were included when the clinical diagnosis of SCI was confirmed by neuropsychological assessment. SIVD was diagnosed according to NINDS-AIREN criteria[13]. However, according to these criteria, at least 25% involvement of the white matter is necessary to support a clinical diagnosis of vascular dementia. We allowed a lesser degree of white matter changes as support of our clinical diagnosis of SIVD as it has been suggested recently that even less extensive leukoaraiosis may cause vascular cognitive impairment[14]. In this study, patients with subcortical vascular cognitive impairment were defined as having a clinical and neuropsychological assessment of SCI, and having periventricular and deep white matter lesions or leukoaraiosis on MRI or CT, respectively. Nearly all patients with subcortical vascular cognitive impairment had a history of vascular risk factors, like hypertension, diabetes mellitus, atrial fibrillation, hypercholesterolaemia and peripheral artery disease, or a history of focal neurological deficits. Patients with an NPH were diagnosed by an experienced neurologist in this field as having the triad of gait disorder, urge incontinence and the clinical syndrome of SCI with dilated ventricles on MRI[15].

The control subjects were recruited from healthy spouses of the patients, or out-patients without apparent cognitive problems and with normal results on neuropsychological testing. Patients with a depression according to the DSM-IV criteria were excluded[8].

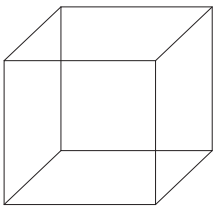
The neuropsychological test battery used as the gold standard consisted of five tests, all aimed at subcortical cognitive dysfunction: (1) an eight-word auditory verbal learning task, a subtest of the Amsterdam Dementia Scale (ADS)[16]; (2)

the fluency subtest of the Groninger Intelligence Test (a Dutch version of the Primary Mental Abilities Test)[17], requiring the subject to name as many animals and professions for 1 minute each; (3) the trail-making test parts A and B[18], which assess visuo-motor tracking and divided attention; (4) the Stroop colour word test parts I, II and III[19], measuring speed and focused attention, and (5) the Wechsler Adult Intelligence Scale digit symbol test[20], assessing complex scanning and visual tracking. Scores in the first decile were defined as impaired. A case was classified as SCI if less than 6 of the 8 test parameters were normal and at least 2 were impaired.

Educational attainment was rated on an ordinal scale ranging from 1 (incomplete primary) to 7 (university).

Based on the clinical and neuropsychological diagnosis, 53 patients were included in our study and 54 control subjects. The underlying diagnoses in the patient group were 36 patients with SIVD and 17 patients with a normal pressure hydrocephalus.

All subjects were administered the MMSE and the HDS. The HDS consists of 4 subtests (***figure 1***): (1) Recall. The patient is asked to repeat and remember 4 words. The presentation of the words is repeated until the patient can repeat all 4. Recall is tested after 5 minutes. Spontaneously recalled words are awarded 1 point, words remembered in response to a cue are given a half point. The maximum is 4 points. (2) Anti-saccadic error task modified from Currie et al.[21]. Patients are asked initially to focus on the examiner's nose and then look to and fro the examiner's moving index finger and nose. This is done with alternating hands, with the examiner's hands held at the patient's shoulder width and eye height. When the patient is comfortable looking at the finger that moves, he/she is asked to look at the index finger not moving. This task is practiced until the patient is familiar with the task. The patient is then asked to perform 20 serial anti-saccades. An error is recorded when the patient looks towards the finger that moved. The total number of errors out of 20 trials is coded on a scale with a maximum of 4 points. (3) Psychomotor speed. The time taken to write the entire alphabet in upper case letters with a ballpoint is recorded. Before performing the task, the patient is asked to recite the alphabet. Patients unable to do so correctly are asked to count from 1 to 26. If this succeeds, the time needed to write the numbers 1-26 is recorded. The time taken to complete this task is converted into a numerical value with a maximum of 6. (4) Construction speed. The time needed to draw a recognizable copy of a picture of a cube is recorded. Prior to the task, the examiner explains that the figure has to be copied as precisely and quickly as possible with a ballpoint pen. The time taken is converted into a numerical score with a maximum of 2.

Max score	Score	
		MEMORY-REGISTRATION Give four words to recall (dog, hat, green, peach)[1] 1 second to say each. Then ask the patient all 4 after you have said them.
4	**( )**	**ATTENTION** Anti-saccadic eye movements: 20 commands. ___ errors of 20 trials ≤ 3 errors = 4, 4 errors = 3, 5 errors = 2, 6 errors = 1, > 6 errors = 0.
6	**( )**	**PSYCHOMOTOR SPEED** Ask the patient to write the alphabet in upper case letters horizontally across the page and record the time: ___ seconds. ≤ 21 seconds = 6; 21.1- 24 seconds = 5; 24.1- 27 seconds = 4; 27.1- 30 seconds = 3; 30.1- 33 seconds = 2; 33.1- 36 seconds = 1; >36 seconds = 0.
4	**( )**	**MEMORY - RECALL** Ask the 4 words from registration above. Give 1 point for each correct answer. For words not recalled prompt with a semantic clue, as follows: animal (dog); piece of clothing (hat); color (green); fruit (peach). Give ½ point for each correct answer after prompting.
2	**( )**	**CONSTRUCTION** Copy the cube below; record time: ___ seconds. <25 seconds = 2; 25- 35 seconds = 1; >35 seconds = 0, cube wrong=0. 
TOTAL SCORE: ___/ 16		

[1]In the Dutch version we used the words kat (cat), hoed (hat), geel (yellow), perzik (peach).

Figure 1. *The HIV dementia scale*

The numerical score of the different items was based on the mean performance scores of the first 20 HIV-seronegative patients tested in the original study[11]. It was not clear from their study how an incorrectly drawn cube was scored, but in our study we decided to give zero points when the patient was drawing the cube incorrectly.

In a subgroup of the study population, the HDS assessment was repeated during the second and third visit by the same investigator or by an independent

investigator to assess the test-retest reliability and the inter-observer reliability, respectively. In all cases, the results of the first HDS assessment were used for the main analysis.

Statistical analysis

The data were analyzed using SPSS 11.0 for Windows. The t test was applied to test significance of differences of the demographic factors between the two groups and the Mann-Whitney U test was applied to test significance of differences of the results of the HDS between the two groups. Significance was accepted at the level of $p<0.05$ (two-sided). A receiver-operating characteristics (ROC) curve was generated graphically by plotting paired sensitivities and specificities at different cut-off values. The optimal cut-off value was determined. The predictive values corresponding with the optimal cut-off value were calculated. Inter-observer and test-retest variabilities were calculated with kappa statistics.

Results

Demographic characteristics are given in ***table 1***. There were no significant differences between SCI patients and controls in the distribution of age, gender and education. The results of the HDS are shown in ***table 2 (see page 22)***.

Table 1. *Demographic characteristics of the SCI and the control group (mean values with standard deviations).*

Group	SCI	Controls	SCI vs. Control
Number enrolled (N)	53	54	
Age (yrs)	74.9 ± 5.9	73.9 ± 6.0	NS
Sex (% male)	53	56	NS
Education	3.6 ± 1.6	4.2 ± 1.7	NS
MMSE	26.5 ± 3.1	28.6 ± 1.4	p<0.0001
NS = Not significant			

Test-retest reliability was assessed in 42 consecutive SCI patients or controls and yielded a kappa score of 0.80, indicating good agreement. The median duration between visits was 17 days.

Inter-observer reliability was assessed in 26 consecutive patients or controls and yielded a kappa score of 0.62, indicating moderate agreement. The median duration between the inter-observer visits was 14 days.

Table 2. *Instrument values of each group (mean values with standard deviations).*

Group	SCI	Controls	SCI vs. Control
HDS	5.1 ± 3.5	13.0 ± 2.4	p<0.0001
Subanalysis:			
MMSE score ≥ 27, n	35	50	
MMSE score	28.1 ± 1.1	28.9 ± 1.0	p=0.002
HDS	6.2 ± 3.4	13.0 ± 2.4	p<0.0001

Item results are shown in ***table 3***. The mean raw score was on all counts significantly lower in SCI patients than in controls. The patients with SCI failed to copy the cube correctly more often than the controls.

Table 3. *Mean raw and numerical scores with standard deviations on HDS items in the SCI group and in the control group.*

Group	SCI (raw score)	Controls (raw score)	SCI (numerical score)	Controls (numerical score)
Item 1 (anti-saccadic eye movements)	5.6 ± 4.2 errors	2.5 ± 2.1 errors	1.9 ± 1.8	3.5 ± 1.1
Item 2 (alphabet)	53.8 ± 31.2 s	22.2 ± 5.2 s	0.9 ± 1.7	4.9 ± 1.3
Item 3 (memory task)	1.8 ± 1.2 words	3.3 ± 0.8 words	1.7 ± 1.2	3.3 ± 0.8
Item 4 (cube copy time, rightly drawn)	56.2 ± 71.0 s	22.8 ± 16.5 s	0.5 ± 0.8	1.3 ± 0.9
Cube wrong, (%)	71	26	-	-

Because almost all control subjects had an MMSE score of 27 or higher, a subanalysis was performed comparing SCI patients and controls who scored in this range (***table 2***). There were no significant differences between these subgroups with regard to mean age, sex and education. The mean difference in MMSE score was significant but small (0.8 points) and clinically not relevant, whereas the difference in HDS score was large (6.8 points).

To determine the optimal cut-off score for identifying SCI versus controls with the HDS, an ROC curve was constructed (***figure 2***). The ROC curve yielded an optimal cut-off value for an HDS score of 9. Based on this cut-off value, the sensitivity was 91% (95% CI 79-97), the specificity 96% (95% CI 87-99), the positive predictive value 96% (95% CI 86-99) and the negative predictive value 91% (95% CI 81-97).

Discussion

Our results show that the HDS discriminates well between patients with SCI and normal controls in an older population. Further, we showed that the HDS is of additional value in subjects whose MMSE score falls within the normal range.

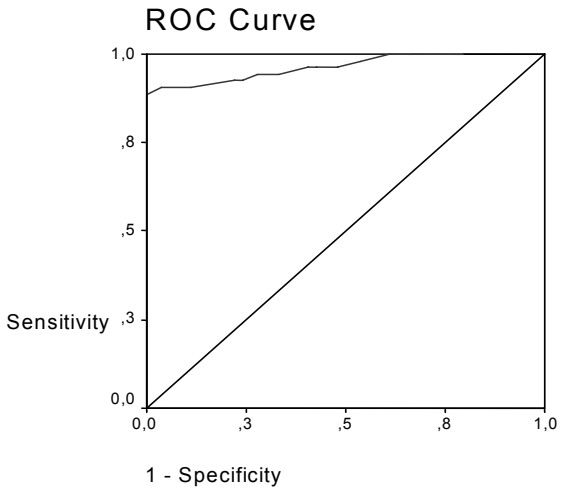


Figure 2. *ROC curve for HDS to determine the optimal cut-off score for diagnosing SCI.*

The HDS consists of 4 items and is easy to administer. The time needed for performing the items lies between the 4 and 6 minutes, depending on the severity of the clinical symptoms. All items of the HDS represent characteristics of SCI: psychomotor speed, concentration and memory skills. Executive functions are evaluated to a certain degree by the anti-saccadic eye movement task and the cube copy task.

Several screening tests for the detection of SCI have been described, but none is generally accepted for adaptation in general practice. The Mattis Dementia Rating Scale[22] is mentioned frequently and seems to be sensitive to frontal and subcortical dysfunction. However, considering the structure of the Mattis Dementia Rating Scale and the time needed to perform it, it does not seem to be useful in clinical practice. The Frontal Assessment Battery has recently been designed by Dubois et al.[23]. It is a short cognitive and behavioural battery to

assess frontal lobe functions. This test has been investigated only in patients with frontal lobe dysfunction, like in Parkinson's disease, multiple system atrophy, corticobasal degeneration, frontotemporal dementia and progressive supranuclear palsy. Patients with SIVD, probably one of the most important causes for SCI, however, were not included. The clock drawing task strongly associated with executive functions has been tested in control subjects versus patients with probable AD, but not in patients with SCI[24].

Patients with AD were not investigated in this study. Generally, these patients present with a different clinical picture and a lower score on the MMSE. However, patients with mild cognitive impairment (MCI) and a normal MMSE score may fail the HDS. It would be interesting to evaluate the HDS in patients with MCI with and without vascular risk factors, in order to differentiate between MCI and subcortical vascular cognitive impairment in patients with an MMSE score of 27 or more.

Furthermore, studies have to be performed to validate the HDS in other diseases causing SCI, like Parkinson's disease, multiple sclerosis or Huntington's disease.

We deliberately chose a group of patients with SIVD as the most important cause of SCI in this study. Very often, these patients do not present with focal neurological deficits but primarily manifest with gradually deteriorating cognitive functions. The extent of ischaemic disease on neuroimaging that is both sufficient and necessary to cause cognitive impairment is yet unclear. Because SIVD is an important cause of cognitive decline in the elderly population, the HDS may be very useful as a screening test in a population with vascular risk factors[23,25].

These results suggest that the HDS is able to detect SCI in an elderly population with SIVD or NPH and a normal MMSE score.

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Chapter 3

The Auditory Oddball Paradigm in Patients with Vascular Cognitive Impairment: A Prolonged Latency of the N2 Complex

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Abstract

Objective:

The event-related potential (ERP) evoked by the auditory oddball paradigm has been investigated mainly in patients with Alzheimer's disease and in patients with different causes of subcortical dementia. Subcortical ischaemic vascular disease (SIVD) seems to be an important cause of vascular cognitive impairment (VCI) frequently not fulfilling the criteria for dementia. Recognition of VCI is needed in order to provide adequate care and therapy. The aim of this study was to investigate the diagnostic value of the different elements of this response (N1, N2 complex and P3 latencies) in a group of elderly patients with VCI caused by SIVD.

Methods:

The study population consisted of patients with a clinical and neuropsychological diagnosis of VCI caused by SIVD (N = 38) and healthy control subjects (N = 53) aged 60 years or older. The mean Mini Mental State Examination score of both groups was 27.6 and the mean HIV Dementia Scale score was 6.1 in the patient group and 12.3 in the control group.
In all subjects, the ERP was recorded under standardized conditions, and the latencies and amplitudes of N1, N2 and P3 were analyzed by two clinical neurophysiologists in consensus. Both were blinded to the diagnosis.

Results:

The N2 latency was significantly longer in patients with VCI than in age-matched controls, whereas the latencies of the P3 and N1 were not significantly different. The peak-to-peak amplitude of the N2 complex to the P3 wave was significantly lower in the patient group. White matter abnormalities on MRI were not significantly correlated with the N2 latency.

Conclusion:

Our findings suggest that the latency of the N2 complex is prolonged and the peak-to-peak amplitude of the N2 complex to P3 wave is lowered in patients with VCI caused by SIVD.

Introduction

The auditory oddball paradigm is a neurophysiological method for eliciting an event-related potential (ERP). This multiwave response contains different deflections and the highest amplitude is usually measured at about 300 milliseconds (P3)[1]. The late responses elicited by the auditory oddball paradigm are considered to be related to cognitive processing[2]. The latency of the N2 complex and the P3 is prolonged in patients with Alzheimer's disease, Parkinson's disease, Huntington's disease, Binswanger's disease and depression[3,4,5,6,7]. Moreover, subcortical dementia can be distinguished electrophysiologically from cortical dementia by changes in the latency of the early waves of the ERP and especially in the latency of the N1, which is delayed in subcortical dementia[8,9]. Thus, the latency of the different deflections of the ERP may be useful in diagnosing dementia. However, in most patients the disease is already advanced at diagnosis [3,4,5,6,7], whereas early diagnosis is needed in order to provide adequate care and therapy.

Subcortical ischaemic vascular disease (SIVD) is an important cause of vascular dementia[10]. However, recently the term vascular cognitive impairment (VCI) has been proposed because clinically important cognitive impairments associated with SIVD do frequently not fulfil the criteria for dementia[10]. Criteria for dementia are traditionally based on the concept of Alzheimer's disease and require the presence of prominent memory impairment which is not necessarily a key symptom in VCI. VCI is characterized by slowing of psychomotor functions and executive dysfunction[10,11,12]. The frequently used mini mental state examination (MMSE)[13] as a screening tool is therefore not sensitive for the detection of VCI, whereas the recently validated HIV dementia scale discriminates well between patients with VCI and normal control subjects[14].

Only five studies have investigated the auditory oddball paradigm in patients with vascular white matter disease, i.e. leukoaraiosis or lacunar infarcts [6,15,16,17,18]. However, in these studies the definitions of cognitive decline were based on criteria for Alzheimer's dementia according to DSM-IV[19], the tests of cognitive function were not described in detail, and the studies were limited to the analysis of the P3 wave only.

In this study, we aimed to determine whether the different deflections of the ERP (N1, N2 complex and P3) evoked by the auditory oddball paradigm could differentiate patients with VCI caused by SIVD in an early phase of the disease from age-matched controls.

Methods

The study population consisted of outpatients living independently with VCI due to SIVD and healthy control subjects. All patients and control subjects were older than 60 years. The clinical diagnosis of VCI due to SIVD was made by an experienced neurologist and was based on the research criteria according to Erkinjuntti[12]. The cognitive syndrome was characterized by slowing of psychomotor functions, executive dysfunction, memory deficits with a relatively intact recognition and mood abnormalities[12]. The clinical diagnosis was supported by neuropsychological tests performed by a qualified neuropsychologist.

The neuropsychological test battery consisted of five tests aimed at subcortical cognitive dysfunction: (i) an 8-word auditory verbal learning task, a subtest of the Amsterdam Dementia Scale (ADS)[20]; (ii) the fluency subtest of the Groningen Intelligence test (a Dutch version of the Primary Mental Abilities test)[21], in which the subject is required to name as many animals or professions as possible in 1 minute each; (iii) the Trail-making test parts A and B[22], which assess visuo-motor tracking and divided attention; (iv) the Stroop color word test parts I, II and III[23], which measure speed and focused attention; and (v) the WAIS digit symbol test[24], which assesses complex scanning and mental speed, or the Grooved Pegboard Test[25] which measures motor speed. A patient was classified as having subcortical cognitive impairment if fewer than six of the eight test parameters were normal and at least two were impaired, i.e. a score in the lowest decile.

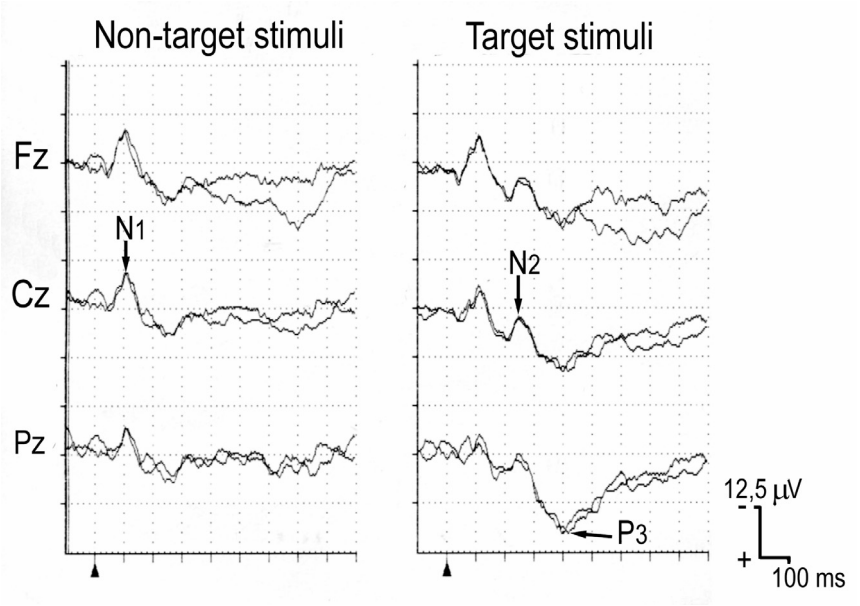
In this study, patients with VCI were defined as having a clinical and neuropsychological profile of subcortical cognitive impairment and white matter hyperintensities, lacunar infarctions or leukoaraiosis, i.e. SIVD on magnetic resonance imaging (MRI) or computed tomography (CT). SIVD was diagnosed according to the NINDS-AIREN criteria[26]. However, according to these criteria, at least 25% involvement of the white matter is necessary to support a clinical diagnosis of vascular dementia. We allowed a lesser degree of white matter changes as support of our clinical diagnosis of VCI because it has been recently demonstrated that even less extensive leukoaraiosis may cause VCI[10,27]. All patients with VCI had a history of vascular risk factors, such as hypertension, diabetes mellitus, atrial fibrillation, hypercholesterolemia or peripheral artery disease. The white matter hyperintensities and lacunar infarctions on MRI were scored according to the semi-quantitative rating scale described by Scheltens et al.[28]. This scale rates periventricular and white matter signal hyperintensities as well as basal ganglia and infratentorial signal hyperintensities separately[29]. The control group consisted of healthy spouses or outpa-

tients without cognitive problems and with normal results on neuropsychological testing. Patients as well as control subjects with a depression according to the DSM-IV criteria were excluded[19].

On the basis of the clinical, neuropsychological and radiological findings 38 patients and 53 control subjects were included in our study. All patients and control subjects were evaluated with the Mini Mental State Examination (MMSE)[13] and the HIV dementia scale (HDS)[14]. The HDS was chosen as a screening tool, because as mentioned previously the HDS is more sensitive and clinically more relevant for the detection of VCI than the MMSE[13]. Twenty-four patients underwent an MRI and 14 patients a CT of the brain.

Recording conditions

Figure 1.



The ERP of an individual patient. The results of the replicable waves of the standard stimuli are seen on the left side, the results of the target stimuli on the right. The electrode positions were located on Fz (mid frontal), Cz (mid central) and Pz (mid parietal). The arrows signify the locations where the N1, N2 and P3 latencies were measured. The first 100 ms reflects the prestimulus interval; the arrowhead indicates the start of the stimulus.

Electroencephalographic (EEG) activity was recorded at the frontal (Fz), central (Cz) and parietal (Pz) electrode sites of the 10-20 system using Ag/AgCl

electrodes affixed with electrode paste, referred to linked earlobes with a forehead ground and impedance of 5 kΩ or less. The digitization rate was 512 Hz with a resolution of 8 bits. The analysis period was 1000 ms including a 100-ms prestimulus baseline. The recording bandpass was 0.1-50 Hz. The artifact rejection level was based on a signal amplitude of 200 μV. Waveforms were averaged by a Nihon Kohden Neuropack Minifour MEB-5304K Electromyograph, which also controlled the stimulus presentation and artifact rejection. All experimental conditions were recorded with eyes closed and subjects resting comfortably on a couch. Each subject was presented with a sequence of 100 binaural tones (80 dB SPL, 100 ms duration, including 10 ms rise and fall times). In 80% of the trials, the tone had a pitch of 1000 Hz (frequent tone) and in 20% of the trials it was at 2000 Hz (target or oddball stimulus). The sequence of tones was pseudorandom with the constraint that no two rare tones occurred consecutively. The stimulus rate was 0.5 Hz with a random occurrence of 20%. Subjects were instructed to listen to the tones and raise the index finger of one of their hands whenever the target tone was detected to ensure optimal attention. A total of 20 artifact-free reponses to standard or target stimuli were averaged at each location. The procedure was recorded twice for reproducibility. A typical wave form of a patient is shown in ***figure 1 (see page 31)***. The average ERPs were analyzed by two clinical neurophysiologists blinded to the diagnosis of the patient. The latency of the N1 was measured from the standard tone wave and identified as the largest negative peak within the 70- to 150-ms range derived from the Cz electrode. The latency of the N2 complex was measured from the target wave as the largest negative peak within 150-320 ms derived from the Cz electrode. The P3 was the largest positive peak around the 300 ms within a range of 250-600 ms and was measured from the Pz derivation of the target wave. If a bifurcated P300 was present, the top P3b was chosen for analysis[2]. The amplitudes of the P2-to-N2 peak and of the N2-to-P3 peak were measured from the Cz derivation of the target wave.

Statistical analysis

The data were analyzed using SPSS 11.0 for Windows (SPSS, Chicago, Ill., USA, 2001). Data are reported as means with standard deviation. The two-tailed Student t test was applied to test for differences in age between group means. The Pearson χ^2 test was applied to test for differences in sex. The Mann-Whitney U test was used to test for differences in the MMSE and HDS scores and to compute differences in amplitudes. Differences in latencies were tested with the general linear model with patient group as fixed factor and age and sex as covariates. Correlations between the different latencies of the ERP and signal hyperintensities on MRI or scores on the neuropsychological tests were computed with Spearman's correlation coefficient. Significance was accepted at the level of $p<0.05$ (two-sided).

Results

Table 1. *Mean values with standard deviations of the demographic characteristics in patient group (VCI) and controls*

	VCI (n=38)	Controls (n=53)	p-value
Sexe, m/f	15/23	33/20	0.03[1]
Age, years	75.2 ± 6.9	73.6 ± 6.0	NS[2]
MMSE	27.6 ± 1.6	27.8 ± 2.4	NS[3]
HDS	6.1 ± 3.7	12.3 ± 3.1	<0.001[3]

MMSE: Mini Mental State Examination

HDS : HIV Dementia Scale, a screening test for subcortical cognitive impairment

[1] Pearson χ^2 test

[2] Student t test

[3] Mann-Whitney U test

Baseline characteristics are given in ***table 1***. The patients and control subjects differed significantly in mean HDS score and in sex distribution, but not in age or mean scores of the MMSE. The latency of N2 complex was significantly longer in the patient group than in the control group (p=0.001, 95% CI of difference of means 9.7- 34.7; ***table 2***). N2 was not detected in 2 (5.3%) patients and in 4 (7.5%) control subjects. The mean latencies of the N1 and the P3 waves did not differ significantly between the patient group and the control group (p= 0.66 and p= 0.12, respectively). The N1 wave was not detected in 1 patient (2.6%) and in 2 control subjects (3.8%), and the P3 wave was not detected in 6 patients (15.8%) and in 6 control subjects (11.3%). The demographic variables and the neuropsychological scores of patients without an N1, N2 or P3 wave were not significantly different from those of the patients with detectable waves.

Table 2. *Results of the different waves of the auditory oddball paradigm in the patient group (VCI) and control group*

	VCI (n=38)	Controls (n=53)	p-value	95% CI of difference of means
N100 (ms)	101.5 ± 14.3	100.8 ± 10.3	0.66	-4.3 to 6.7
N200 (ms)	254.6 ± 25.1	232.5 ± 28.6	0.001	9.7 to 34.7
P300 (ms)	413.8 ± 57.3	394.4 ± 49.2	0.12	-5.5 to 44.5

Data are mean values of the latencies in milliseconds with standard deviations. The general linear model was applied to test for differences in latencies between both groups. For p values and confidence intervals (CI), means were adjusted for age and sex.

The peak-to-peak amplitude of the N2 wave to the P3 wave was statistically significantly lower in the patient group (***table 3, see page 34***).

The severity of white matter hyperintensities were assessed according to the Scheltens' rating scale only in patients who underwent MRI (n=24)[28]. The mean Scheltens' score was 10.5 ± 6.7 (range 2-24). The N2 latency was not significantly correlated with the Scheltens' total score (ρ = -0.255; p = 0.3) or with Scheltens' sub-scores for deep white matter hyperintensities and periventricular hyperintensities. Also the presence of lacunar infarcts on MRI was not correlated with the N2 latency. However, the N2 latency was significantly correlated with the total neuropsychological score (ρ = -0.310; p = 0.004), while the P3 was not.

Table 3. *Results of the peak-to-peak amplitudes of the auditory oddball paradigm in the patient group (VCI) and control group.*

	VCI (n=38)	Controls (n=53)	p-value (Mann Whitney U test)
P2N2 (μV)	11.42 ± 6.6	11.09 ± 5.9	0.92
N2P3 (μV)	11.47 ± 7.0	15.44 ± 9.4	0.02

Data are mean values of the amplitudes in microvolts (μV) with standard deviations.

Discussion

We found the latency of the N2 complex to be significantly different in a well-defined group of patients with VCI and age-matched controls, while this was not the case for the latency of the N1 and P3 wave. Also the peak-to-peak amplitude of the N2 complex to the P3 wave was statistically significantly diminished in the patient group. Usually the latencies of both the N2 complex and the P3 waves are prolonged in demented patients, regardless of the underlying pathology[8]. However, in contrast to other study populations, our patients had cognitive impairment but not clinical dementia demonstrated by MMSE scores within the normal range and HDS scores outside the normal range[14]. This finding is consistent with the results of Cicconetti et al.[29], who found that the N2 latency, but not the P3 latency, was significantly prolonged in a group of elderly hypertensive patients with an MMSE score of 27 or higher. Although MRI or CT of the brain was not performed in that study, it is conceivable that the patients had some form of mild cognitive impairment, due to vascular white matter abnormalities caused by hypertension, which is a major risk factor for SIVD[30]. However, a significant positive correlation could not be demonstrated in the present study between the severity of white matter abnormalities, the presence of lacunar infarctions and the N2 latency in a subgroup of our study population who underwent MRI. This may be explained by the small sample size, but tentatively it could suggest that the difference in N2 complex between

groups is not caused by the changes identified on MRI but by unknown factors. The lack of correlation is not completely surprising since the clinical impact of the severity of WML on cognition is also under discussion[31,32]. However, we did find a significant correlation between the N2 latency and the total neuropsychological score, while this was not the case with P3. This supports the clinical value of our finding.

A prolonged N2 latency with a normal P3 latency supports the idea that the N2 and P3 components are generated separately and not in orderly sequence[33]. Indirect evidence of a different possible subcortical generator of the N2 could be inferred by a delayed P3 component while the N2 was not altered after cortical inhibition by low-frequency transcranial magnetic stimulation[34].

A diminished peak-to-peak amplitude from the N2 complex to P3 was found in the patient group with VCI of the present study. While measuring peak-to-peak amplitude it is not clear if this is due to either a diminished N2 amplitude or a diminished P3 amplitude. Another option is that both amplitudes are diminished. However, latency is a much more reliable indicator than amplitude, since latency is difficult to alter with attention[35]. Moreover, it is known that amplitudes have a large variance even within several measurements in the same patient, as these amplitudes depend on a high number of parameters, such as electrode position or impedance[8,36]. Even data from a normative ERP aging study show larger coefficients of variation for amplitudes than for peak latency[37].

We did not include patients with Alzheimer's disease in our study. Although Goodin and Aminoff[9] reported that the N1 latency is prolonged in subcortical dementia compared with cortical dementia, we did not find a prolonged N1 wave in our patients compared with the controls. However, the study of Goodin and Aminoff[9] included patients with Huntington's disease or Parkinson's disease but not patients with VCI[9]. Moreover, their patients had advanced disease whereas the patients in our study were clinically characterized by subcortical cognitive impairment and not dementia. Therefore, it would be interesting to compare the ERP evoked by the auditory oddball paradigm in patients with early Alzheimer's disease with that in patients with VCI.

In conclusion, the latency of the N2 complex is longer and the peak-to-peak amplitude of the N2-to-P3 wave is lower in a well-defined group of patients with VCI compared to healthy controls. Further research is needed to clarify the pathophysiological mechanism underlying the prolonged latency of the N2 complex in patients with VCI and to compare the ERP responses of patients with early Alzheimer's disease and patients with VCI.

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Chapter 4

Brain imaging in patients with Diabetes Mellitus. A systematic review

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Abstract

Background:
Diabetes mellitus is associated with impaired cognitive functioning and dementia. Brain imaging studies can provide clues on the pathogenesis, but the nature and severity of imaging abnormalities that are associated with diabetes are debated. We performed a systematic review of studies addressing this association.

Methods:
Eligible studies were evaluated against predefined inclusion criteria: i.e. clear imaging outcome measures, a clear definition of diabetes and a sample size of at least 20 patients. From 55 included articles data on study design, diabetes type, treatment and associated co-morbidity, imaging modality (MRI, MRS, CT, SPECT or PET) and imaging findings were extracted.

Results:
Methodology regarding population selection, diabetes assessment, neuro-imaging rating methods and data analyses were heterogeneous. Diabetes was associated with cerebral atrophy in 8 out of 10 studies reporting this outcome. Eight out of 19 studies reported an association between diabetes and lacunar infarcts. There was little evidence for an association with white matter lesions. PET and SPECT studies reported regional abnormalities of cerebral blood flow and cerebral glucose metabolism. None of the studies assessed the relation between imaging findings and cognition. Data on the relation between imaging findings and disease variables (e.g. age, hypertension, medication use, glycaemic control) were scarce.

Conclusions:
Diabetes is associated with cerebral atrophy and lacunar infarcts. The association with white matter lesions is equivocal. High quality prospective studies are needed, with objective, sensitive and quantitative neuroimaging rating methods and assessment of cognition, vascular disease and other co-morbidity.

Introduction

Diabetes Mellitus (DM) is associated with impaired cognitive functioning and an increased risk of dementia[1,2]. Patients with type 1 DM (DM1) may show mild to moderate slowing of mental speed and diminished mental flexibility, whereas learning and memory are relatively spared[3]. In patients with type 2 DM (DM2) cognitive impairment may be relatively more pronounced, particularly affecting verbal memory or complex information processing[4,5]. The pathogenesis is still uncertain, but chronic hyperglycaemia, vascular disease, repeated hypoglycaemic episodes, and possibly direct effects of insulin on the brain have been implicated[6]. Brain imaging studies can help to clarify the pathogenesis. An increasing number of studies report both focal vascular and more global (e.g. atrophy) cerebral changes, but the results are not always consistent.

Our aim was to systematically review brain imaging studies in patients with DM. Data on the relation of imaging with cognition and with relevant disease variables were also recorded.

Methods

Study Selection

MEDLINE and EMBASE (1966 to February 2006) were searched with the following medical subject heading (MeSH) terms and textwords: computed tomography (CT) and magnetic resonance imaging (MRI) studies: *white matter, leukoaraiosis, lacunar infarction, subcortical, periventricular, brain, cerebral, hippocampus, atrophy, MRI, magnetic resonance imaging, CT, tomography*; magnetic resonance spectroscopy (MRS) studies: *magnetic resonance spectroscopy, MRS, brain, cerebral*; positron emission tomography (PET), single photon emission CT (SPECT) and Xenon-enhanced CT studies: *cerebral blood flow, glucose metabolism, brain, cerebral, PET, SPECT, Xenon, positron emission tomography, single-photon emission tomography, tomography; all combined with "diabetes".*

The abstracts were screened and potentially relevant articles retrieved. These articles were included if they met the following four criteria. 1) original article, written in English, on brain imaging in adult patients with DM in comparison with controls, 2) diagnostic criteria for DM specified, 3) sample size of at least 20 DM patients, or a total sample size > 200 if the number of DM patients was not specified, 4) for CT or MRI studies: specification of the rating method for WML, or atrophy. Eligible articles were evaluated against the inclusion criteria

by two independent authors (BvH, FEdL or GJB). In case of disagreement a consensus meeting was held. If multiple articles reported on the same imaging outcome measure from the same study population, the article with the most detailed data on brain imaging and/or the largest study population was included.

The search strategy for MRI and CT studies yielded 271 articles. Three additional articles were identified through bibliographies of included articles[7-9]. After screening of title and abstracts, 117 were retrieved full-text, of which 46 were included. The search for MRS studies yielded 75 articles, of which 3 were included. The search strategy for PET, SPECT and Xenon-CT yielded 84 articles, of which 6 were included.

From included studies the source population (e.g. population or clinic based), experimental design (e.g. cross-sectional, longitudinal), sample size, and age of the participants were recorded. The procedure for diagnosing DM was recorded (e.g. based on history, based on oral glucose tolerance test) as well as the DM type of the population involved (DM1, DM2, mixed or unknown). If the DM type was not specified and the mean age of the patients was 60 years or higher, the population was classified as "predominantly DM2". The imaging modality and the methods to rate WML, atrophy, lacunar infarcts, cerebral blood flow (CBF) or cerebral glucose metabolism were recorded. Effect sizes (Cohen's d), odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI) for these outcome measures were recorded or calculated based on the available data. Data on the relation between relevant co-morbidity (e.g. hypertension) and DM related variables (e.g. glycaemic control, microvascular complications, DM duration, medication use) and the imaging outcome measures were also recorded.

The source of the study populations in CT or MRI studies varied considerably, from true population-based sampling to populations with vascular or cognitive pathology. To improve clarity we therefore classified the 46 included articles into three main categories: 1) "general cohorts" (n=11): this category included articles on population-based studies or case-control studies, in which the cases were recruited from the general population or a DM clinic; 2) "vascular cohorts" (n=23): this category included articles on studies that primarily recruited patients with stroke or other cardiovascular risk factors, and assessed the effects of DM within these selected populations ; 3) "outpatient cohorts" (n=12): this category included articles on cohorts of neurological or psychiatric outpatients, for example with cognitive complaints or other neurological or psychiatric conditions, and assessed the effects of DM within these selected populations.

Meta-analyses were performed on dichotomous outcome measures if a given outcome measure was available from at least two independent studies on the same cohort type with the same imaging modality (CT or MRI) and if the required data could be extracted from the articles. Analyses were performed with Review Manager Version 4.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003) on unadjusted data. For individual studies no systematic differences were observed between these unadjusted ORs and adjusted ORs as presented in ***tables 1 and 2 (see page 44/45 and 46/47).***

Results

CT and MRI studies

*Diabetes mellitus and WML (**table 1**)*

The majority of the studies used ordinal rating scales with 3 to 4 levels, ranging from absent to severe, confluent WML. Other studies made a dichotomization into presence or absence of WML. Five studies used an ordinal scale that included 9 or more grades of WML severity[7,10,11] or an interval scale[12,13]. Only 3 studies used actual volumetric measurements[9,14,15]. From the 7 studies categorized as "general cohorts", one observed a significant association between DM and WML although the actual median total deep WML volume in the DM group was small (<0.1 ml) [16]. From the 11 studies categorized as "vascular cohorts" 3 reported an increased severity of WML in patients with DM [17-19]. From the 9 studies categorized as "outpatient cohorts" only one study reported a statistically significant association between DM and WML[20], although in 4 studies WML scores tended to be higher in the DM group[21-24]. Nine of the 27 WML studies could be included in the meta-analysis (***table 4, see page 50***). In the "vascular cohorts" there was no association between DM and WML (OR 1.1 (95% CI 0.9-1.4)). In contrast, in the "outpatient cohorts" there appeared to be a modest association between WML and DM (point estimates for ORs varied from 1.8 to 2.4; ***table 4***).

*Diabetes Mellitus and lacunar infarctions (**table 2**)*

Twenty articles on lacunar infarcts were included, dealing with 19 study populations. For one population both cross-sectional[8] and longitudinal[25] analyses were reported. Both articles were included, but only the cross-sectional data are presented in ***Table 2*** and included in the meta-analysis.

The majority of studies used MRI. The definition of lacunar infarcts (i.e. focal hyperintensities on T2-weighted images with corresponding hypointense lesions on T1 or FLAIR imaging) was consistent across the studies.

***Table 1**. Relation diabetes mellitus and white matter lesions*

No	Study population*	Subjects total/DM	Mean age (yrs)	DM type	Imaging
General cohorts:					
Dejgaard 1991[16]	Case/control	60/20	40	1	MRI
Yousem 1991[37]	Case/control	35/25	31	1	MRI
Longstreth 1996[7]	Population-based	3301/369	>65	2¶	MRI
Den Heijer 2003[12]	Population-based	506/41	>60	2¶	MRI
Schmidt 2004[13]	Population-based	1252/114	69	2¶	MRI
Jerekathil 2004[9]	Population-based	1814/91	54	ND	MRI
Jorm 2005[15]	Population-based	475/?	>60	2¶	MRI
Vascular cohorts:					
Hijdra 1990[19]	Stroke	376/59	>65	2¶	CT
Schmidt 1992[17]	Stroke/vascular risk factors and control	234/38	55	ND	MRI
Manolio 1994[10]	Stroke and control	303/76	>65	2¶	MRI
Fukuda 1995[63]	Hypertension	238/52	>40	ND	MRI
Jorgensen 1995[64]	Stroke or TIA	1084/203	>70	2¶	CT
Awada 1996[39]	Stroke	398/131	>60	2¶	CT
Henon 1996[65]	Stroke	610/83	64	2¶	CT
Padovani 1997[34]	Stroke and control	100/20	>60	2¶	MRI
Coskun 2003[38]	Stroke	288/57	>65	2¶	CT
Streifler 2003[18]	Stroke	596/110	>60	2¶	CT
Kario 2005[47]	Hypertension	20/20	69	2	MRI
Outpatient cohorts:					
Raiha 1993[41]	Geriatric department	204/55	74	2¶	CT
Araki 1994[21]	MRI for any indication	2725/159	60	2¶	MRI
Fukuda 1996[66]	Neurologically normal	253/50	66	2¶	MRI
Kobayashi 1997[22]	Neurologically normal	933/66	58	ND	MRI
Hogervorst 2002[24]	Alzheimer's disease and controls	414/29	74	2¶	CT
Masana 2003[23]	Mild headache and vertigo	1674/87	51	ND	MRI
Biessels 2005[11]	Memory clinic	347/29	73	2¶	MRI
Lazarus 2005[20]	Memory clinic	177/20	>65	2¶	MRI
Taylor 2005[14]	Depressive disorder and controls	399/34	70	2¶	MRI

Studies are listed in chronological order

* Study populations: general cohorts: population-based or case-control studies; vascular cohorts: cohort with stroke or other cardiovascular risk factors; outpatient cohorts: neurological outpatients.

DM type: 2¶: population classified as predominantly DM2, see methods. ND = not determined

† Rating scales: Dich: dichotomous scale; Ord: ordinal scale; Int: interval scale; **: dichotomization was performed for analysis.

‡ Outcome and results in DM patients compared with controls. WML = white matter lesions, DWML = deep white matter lesions, PVH = periventricular hyperintensities, GML = grey matter lesions, BG = basal ganglia. Odds ratio's (OR) are presented with 95% CI within brackets. ה where possible, we calculated OR or effect sizes (d) if they were not provided in the original paper. r = Pearson correlation coefficient. Mean differences (mean diff, with 95% CI within brackets), d, β and t values > 0 reflect more severe WML in the DM group relative to controls. Studies marked with # were included in the meta-analysis presented in table 4.

p-value: NS = not significant, ? = not specified

§Adjustments/matching: Edu: education; BP: blood pressure (including hypertension, mean arterial pressure, systolic blood pressure, use of antihypertensive drugs, left ventricular hypertrophy, ankle-to-arm index); HL: hyperlipidemia; AF: atrial fibrillation; PVD: peripheral vascular disease (including peripheral artery disease, coronary artery disease, cardiac disease, congestive heart failure, ECG changes); ICD: ischaemic cerebrovascular disease (including TIA, stroke, leukoaraiosis, white matter lesions, ultrasound examination of carotids or intracranial arteries)

Table 1. *Continued*

Rating scale†	Outcome and results‡	p-value	Adjustments/matching§
Dich	OR 15.4 (3.8 - 63.2)ת	<0.05	Age
Dich	No WML in either group	NS	Age, sex
Ord (0-9)	NS		Age, sex
Ord (0-9) PVH	PVH: difference +0.4 (-0.2 to 1.1), d = 0.4ת	NS	Age, sex
Int WML	WML: difference +0.01 ml (-1.0 to 1.0), d = 0.2ת	NS	
Int	PVH: median diff 0	0.1	Sex, age, edu, BP, smoking, BMI, HL, PVD
	WML: median diff +0.2	0.2	
Volumetry	WML: β = 0.02	0.8	Age, sex
Volumetry	WML: r = 0.03	NS	No
Ord (0-4)**	OR 2.0 (1.1 - 3.5)ת#	0.02	No
Ord (0-3)	β = 0.2 (SE 0.1)	<0.001	Age, BP, sex, ICD, PVD
Ord (0-8)	DM mean diff 0.4	0.1	No
Ord (0-5)	DM mean diff 0.1, d = 0.2ת	0.3	No
Dich	OR 0.8 (0.5 - 2.3)ת#	0.3	No
Dich	OR 0.9 (0.6 - 1.5)ת#		No
Ord (0-3)	estimated coefficient 1.2, (SE 0.8)	0.1	Age, sex, BP, alcohol, HL, ICD, cerebral atrophy
Ord (0-3)	β=0.02, SEB 0.1	0.9	age, sex, BP, PVD, ICD, ventricular index
Ord (0-4)**	OR 0.6 (0.06 - 0.3)ת#	NS	No
Ord**	OR 1.6 (1.0 - 2.6)ת#	0.04	No
Ord**	OR 2.2 (0.5 - 9.0)	NS	age, sex, BP
Dich	OR 0.9 (0.5 - 1.7)ת	NS	No
Dich	OR 1.4 (0.7 - 2.8)ת#	NS	No
Ord (0-4)	d = 0.1ת	0.6	Age, sex, BP, smoking, HL, ICD
Ord (PVH: 0-4)**	PVH: OR 2.0 (0.8 - 4.8)ת#	0.2	No
Dich (WML)	DWML: OR 0.8 (0.3 - 2.8)ת#	0.6	
Ord (0-3)**	OR 1.4 (0.5 - 4.3)	0.5	Age, sex, diagnosis, smoking, DM, BP, Apo E4
Ord (0-3)	OR 1.6 (0.8 - 3.0)#	0.2	Age, sex, BP, HL, family history, smoking, alcohol, ICD
Ord (0-6)	PVH: mean diff 0 (-0.5 to 0.5)	NS	Age, sex
Ord (0-24)	DWML: mean diff -0.5 (-2.0 to 1.5)	NS	
Ord (0-4)**	PVH: OR 1.6 (0.6 - 5.2)#	NS	Age, BP, AF, ICD
	DWML: OR 2.9 (1.0 - 7.8)	?	
Volumetry	WML: t =-1.3	0.2	Age, sex, BP
	GML in BG: t =-1.08	0.3	

Four studies were categorized as "general cohorts"[8,13,25,26]. Two of these studies reported an association between DM and symptomatic infarcts, but no association with silent lacunar infarcts[8,26]. The only longitudinal study observed an association between DM and silent incidental lacunar infarcts (OR 2.9 (95% CI 1.0-8.5)) without a significant association between DM and silent infarcts at baseline (OR 1.9 (95% CI 0.4-4.8))[25].

Of the 12 studies categorized as "vascular cohorts" one showed a significant association between DM and silent lacunar infarcts[27] and 4 between DM and symptomatic lacunar infarcts[28-31]. Of the 4 studies categorized as "outpatient cohorts" one showed a significant association between DM and silent lacunar infarcts[22].

Table 2. *Relation diabetes mellitus and lacunar infarcts*

No	Study population*	Subjects total/DM	Mean age (yrs)	DM type	Imaging
General cohorts:					
Longstreth 1998[26]	Population-based	3660/519	>65	2¶	MRI
Vermeer 2002[8]	Population-based	1077/75	>60	2¶	MRI
Schmidt 2004[13]	Population-based	1252/114	69	2¶	MRI
Vascular cohorts:					
Jorgensen 1994[40]	Stroke	494/79	>70	2¶	CT
Konemori 1995[67]	Stroke and control	324/36	>50	ND	MRI
Hsu 1997[28]	Stroke and control	132/20	>60	2¶	CT
Adachi 2002[42]	Stroke	171/50	69	2¶	MRI
Revilla 2002[29]	Lacunar infarcts and control	164/28	65	2¶	CT/MRI
Arauz 2003[27]	Lacunar infarcts	175/72	64	2¶	MRI
Selvetella 2003[43]	Hypertension	195/40	>60	2¶	MRI
Giele 2004[68]	Atherosclerotic vascular disease or risk factors	308/59	58	ND	MRI
Karapanayiotides 2004[30]	Stroke	4064/611	67	2¶	MRI
Sarkar 2004[31]	Stroke	450/171	51	ND	CT
Kario 2005[47]	Hypertension	20/20	69	2	MRI
Kawamoto 2005[44]	Stroke	453/40	76	2¶	CT
Outpatient cohorts:					
Araki 1994[21]	MRI for any indication	2725/159	60	2¶	MRI
Kobayashi 1997[22]	Neurologically normal	933/66	58	ND	MRI
Uehara 1999[69]	Neurologically normal	219/37	63	2¶	MRI
Biessels 2005[11]	Memory clinic	347/29	73	2¶	MRI

Studies are listed in chronological order

* Study populations: general cohorts: population-based or case-control studies; vascular cohorts: cohort with stroke or other cardiovascular risk factors; outpatient cohorts: neurological outpatients.

DM type: 2¶: population classified as predominantly DM2, see methods. ND = not determined

‡ Outcome and results: LI = lacunar infarcts, BG = basal ganglia. Odds ratio's (OR) are presented with 95% CI within brackets. ת where possible we calculated ORs if they were not provided in the original paper.

p-value: NS = not significant

§Adjustments/matching: Edu: education; BP: blood pressure (including hypertension, mean arterial pressure, systolic blood pressure, use of antihypertensive drugs, left ventricular hypertrophy, ankle-to-arm index); HL: hyperlipidemia; AF: atrial fibrillation; PVD: peripheral vascular disease (including peripheral artery disease, coronary artery disease, cardiac disease, congestive heart failure, ECG changes); ICD: ischaemic cerebrovascular disease (including TIA, stroke, leukoaraiosis, white matter lesions, ultrasound examination of carotids or intracranial arteries)

††For each study the power (1-β) to detect a statistically significant difference between the DM and the control group was estimated, assuming an OR for infarcts of 2.0 in the diabetic group and an α=0.05 with two-sided testing (http://calculators.stat.ucla.edu/powercalc/)

We calculated the power for each study to detect statistically significant differences between DM and non-DM subjects, assuming a relative risk of 2.0 for infarcts in the DM group. Despite the rather high contrast between the groups in this assumption, the estimated power of the majority of studies was around 0.5, while it is common to require a power between 0.8 and 0.9.

All studies on lacunar infarcts could be included in the meta-analysis (***table 4***). There was a significant association between DM and lacunar infarcts in all

Table 2. *Continued*

Outcome and results‡	p-value	Adjustments/matching§	Estimated power††
Silent: OR 1.1 (0.8-1.5)	0.6	Age, sex, BP, HL, smoking, PVD, creatinine	1.0
Symptomatic: OR 2.2 (1.1-4.5)	0.02		
Silent: OR 0.7 (0.4-1.5)	NS	Age, sex, BP, smoking	0.8
Symptomatic: OR 2.5 (1.0-5.9)	<0.05		
Silent: OR 1.4 (0.7-2.7)m	0.3	Sex, age, edu, BP, smoking, BMI, HL, PVD	0.6
Silent: OR 1.4 (0.9-2.4)m	0.2	No	0.8
Silent: OR 0.8	NS	Age, sex, BP, HL	0.5
Symptomatic: OR 2.5	NS		
Symptomatic: OR 12.5 (3.1-57.6)	<0.05	No	0.3
Silent: OR 1.9 (0.9-3.9)	0.1	No	0.5
Symptomatic: OR 5.4 (1.5-18.9)	0.008	Age, sex, BP, HL, smoking,	0.4
Silent: OR 3.0 (1.3-7.0)	0.03	Age, sex, BP, HL, smoking, alcohol, PVD	0.5
Silent: OR 2.0 (0.9-4.1)m	0.07	No	0.5
Silent: OR 1.4 (0.7-2.8)m	0.4	No	0.5
Symptomatic: OR 1.8 (1.3-3.8)	0.009	Sex, smoking, HL	1.0
Symptomatic: OR 2.6 (1.8-3.9)	<0.05	No	0.9
Silent and symptomatic: OR 2.3 (0.6-8.0)	NS	Age, sex, BP	0.2
Symptomatic: OR 0.7 (0.3-1.6)	0.35	Age, sex, smoking	0.5
Silent: OR = 1.0 (0.7-1.4)m	NS	No	1.0
Silent: OR 2.4 (1.2-4.9)	0.01	Age, sex, BP, alcohol,, PVD	0.5
Silent LI white matter: OR 2.3 (0.98-5.6)	0.06	Age, sex, BP, HL, smoking, PVD	0.5
Silent LI in BG: OR 0.7 (0.2-2.1)	0.6		
Silent: OR 2.3 (0.9-5.6)	NS	Age, sex	0.3

cohort types (general cohorts OR 1.3 (95% CI 1.1-1.6); vascular cohorts 2.2 (95% CI 1.9-2.5); outpatient cohorts 1.4 (95% CI 1.1-1.8))

*Diabetes Mellitus and cerebral atrophy (**table 3, see page 48/49**)*
Ten studies addressed the relation between DM and atrophy, with marked heterogeneity in the methods for atrophy assessment. Some studies measured only cortical atrophy or hippocampal atrophy[12,21,32,33], others mea-sured only subcortical atrophy[34], while others assessed both[10,11,13,35,36].

All 4 studies categorized as "general cohorts" [12,13,33,36], one of the 2 studies categorized as "vascular cohorts" [10] and all 4 studies belonging to the "outpatient's cohorts" [11,21,32,35] showed associations between DM and cerebral atrophy, i.e. amygdalar atrophy, cortical atrophy or subcortical atrophy.
The outcome measures on atrophy were too heterogeneous to perform a meta-analysis.

Relation of CT and MRI findings to cognition and other disease variables.
Only 3 studies compared cognition between DM and non-DM patients[11,16,36]. One study, classified as a "general cohort" showed modest impairments of cognitive performance in DM1-patients[36], whereas a study classified as a "vascular

Table 3. *Relation diabetes mellitus and cerebral atrophy*

No	Study population*	Subjects total/DM	Mean age (years)	DM type	Imaging	Rating scale†
General cohorts:						
Longstreth 2000[33]	Population-based	3253 /?	>65	2¶	MRI	Ord (0 - 9)
Den Heijer 2003[12]	Population-based	506/41	>60	2¶	MRI	Int
Schmidt 2004[13]	Population-based	1252/114	69	2¶	MRI	Ord (0 - 15) ventricle-to-brain ratio
Musen 2006[36]	Case-control	118/82	33	1	MRI	volumetry
Vascular cohorts:						
Manolio 1994[10]	Stroke and control	303/76	>65	2¶	MRI	Ord (0 - 9)
Padovani 1997[34]	Stroke and control	100/20	>60	2¶	MRI	Int
Outpatient cohorts:						
Pirttila 1992[32]	CT for any indication	416/46	>15	ND	CT	Dich
Soininen 1992[35]	Elderly volunteers	84/25	>70	2	CT	Int
Araki 1994[21]	MRI for any indication	2725/159	60	2¶	MRI	Dich
Biessels 2005[11]	Memory clinic	347/29	73	2¶	MRI	Ord

Studies are listed in chronological order

* Study populations: general cohorts: population-based or case-control studies; vascular cohorts: cohort with stroke or other cardiovascular risk factors; outpatient cohorts: neurological outpatients.

DM type: 2¶: population classified as predominantly DM2, see methods. ND = not determined

†Rating scales: Dich: dichotomous scale; Ord: ordinal scale; Int: interval scale

‡Outcome and results. Odds ratio's (OR) are presented with 95% CI within brackets. ה where possible we calculated ORs or effect sizes (d) if they were not provided in the original paper. Mean differences (mean diff; with 95% CI within brackets), d, β and t values > 0 reflect more severe atrophy in the DM group relative to controls.

p-value: NS= not significant, ? = not specified

§Adjustments/matching: Edu: education; BP: blood pressure (including hypertension, mean arterial pressure, systolic blood pressure, use of antihypertensive drugs, left ventricular hypertrophy, ankle-to-arm index); HL: hyperlipidemia; AF: atrial fibrillation; PVD: peripheral vascular disease (including peripheral artery disease, coronary artery disease, cardiac disease, congestive heart failure, ECG changes); ICD: ischaemic cerebrovascular disease (including TIA, stroke, leukoaraiosis, white matter lesions, ultrasound examination of carotids or intracranial arteries)

cohort"[16] and a study of patients attending a memory clinic reported no difference between DM and non-DM patients[11]. None of these studies presented analyses on the association between cognition and MRI findings in the DM population.

From the 46 articles 3 study populations included only DM1 patients, 2 only DM2, 32 study populations were classified as "predominantly DM2" and 9 study populations were classified as "DM of unknown type" (***tables 1-3***). The diagnosis of DM was based on history or medication use in 20 studies[7,8,14,18,20,21,24,24,26,28,31-33,37-44], while in the other studies active screening was done by fasting glucose levels, random glucose levels or an oral glucose tolerance test. Only 2 studies included data on metabolic control[16,36]. Two studies on DM2 patients specified which glucose lowering therapy was used[11,27]. The duration of DM was mentioned in 2 studies[16,36].

Table 3. *Continued*

Outcome and results‡	p-value	Adjustments/matching§
Increase in cortical atrophy grade:	?	Age, race, edu, BP, PVD, alcohol
Men: 0.6 (0.2-0.9) Women: 0.2 (0 - 0.4)		
Hippocampal volume: -4% (0 - 9)ת	0.04	Age, sex, PVD
Amygdalar volume: -7% (-2 to12)ת	0.004	
Cortical atrophy d = 0.3	0.001	Sex, age, edu, BP, PVD, smoking, BMI, HL
Subcortical atrophy d = 0.3ת	0.03	
Cortical density loss: range 4.3 - 5.0%	<0.001	Age, sex, edu,
Subcortical density loss: 5.2%	<0.001	
Sulcal widening: mean diff -0.3	0.3	No
Ventricular enlargement: mean diff 0.5	<0.03	
Ventricular enlargement: NS	NS	No
Any cerebral atrophy: OR 3.4 (1.8 - 6.5)ת	?	No
Cortical atrophy: d = range -0.2 to 0.7 (right temporal horn)ת	NS	Age, head size
Subcortical atrophy: d = range 0.2 to 0.4ת	NS	
Any cerebral atrophy: OR 3.2 (2.3 - 4.4)ת	<0.05	No
Cortical atrophy: mean diff 1.5 (0 - 2.5)	?	
Subcortical atrophy: mean diff 0 (-1.5 to 2)	NS	Age, sex
Medial temporal lobe atrophy: mean diff 0.5 (-0.5 to 0.5)	NS	

Few studies presented detailed data on relevant disease variables in relation to brain imaging. One study indicated that higher levels of glycosylated haemoglobin, longer duration of DM1, severe hypoglycaemic events and severity of retinopathy were associated with cortical and/or subcortical gray matter atrophy[36]. Although several studies collected data on for example hypertension and vascular morbidity (see ***tables 1 to 3***), these data were generally only entered as co-variates in the analysis of the between group difference of the population with and without DM. Data on the effects of these variables on lesion severity within the DM population were not provided.

MRS studies

Three studies examined cerebral metabolism in DM with ^{1}H-MRS. One study, which included 6 DM1 and 24 DM2 patients reported increased myo-inositol-to-creatine ratios in the gray and white matter, but did not observe significant changes in N-acetylaspartate ratios[45]. Another study that included 17 DM1 (of which 9 were recovering from diabetic ketoacidosis) and 4 DM2 patients reported increased myo-inositol-to-creatine ratios and decreased N-acetyl-aspartate-to-creatine ratios[46]. The third study only included DM2 patients with hypertension and hypertensive controls, and also showed decreased N-acetyl-aspartate-to-creatine ratios[47]. The latter is regarded as an indicator of reduced neuronal viability[48].

Table 4. *Meta-analyses white matter lesions and lacunar infarcts*

	Imaging measure*	Studies (n)	Subjects		OR†
			Control (n)	DM (n)	
White matter lesions					
Vascular cohorts	CT	5	2129	604	1.1 (0.9-1.4)
Outpatient cohorts	MRI – PVH	2	1024	86	1.8 (0.9-3.6)
	MRI – DWML	2	1024	86	1.7 (0.9-3.5)
	MRI - any WML	2	4071	246	2.4 (1.7-3.4)
Lacunar infarcts					
General cohorts	MRI	3	5281	708	1.3 (1.1-1.6)
Vascular cohorts	CT	5	1349	338	2.3 (1.8-3.0)
	MRI	7	4389	888	2.1 (1.8-2.5)
	Total (CT + MRI)	12	5738	1226	2.2 (1.9-2.5)
Outpatient cohorts	MRI	4	3934	291	1.4 (1.1-1.8)

Analyses were performed on the crude, unadjusted data.

* DWML = deep white matter lesions, PVH = periventricular hyperintensities, "any WML" includes studies that did not distinguish between DWML and PVH.

† Odds ratios (OR) are presented with 95% CI within brackets.

For WML, all studies that could be included in the meta-analysis are marked in table 1. The analysis on lacunar infarcts includes all studies listed in table 2.

PET and SPECT studies

Four studies examined cerebral perfusion in DM with SPECT[49-52]. Three of these studies involved patients with DM1 (mean ages 30-40 years; population sizes 20-65)[49-51] observing both modest regional hypo- and hyperperfusion in the DM patients relative to controls, particularly in patients with longstanding DM and with a history of severe hypoglycaemic episodes. The fourth study that predominantly involved patients with DM2 observed 25% to 30% reductions in mean cerebral blood flow in all cortical areas studied, and the cerebellum, in a group of 27 patients (mean age 64 years) relative to age-matched controls[52]. The abnormalities were most pronounced in patients that were treated with insulin[52]. A study in DM1 patients with Xenon-enhanced CT reported CBF to be in the normal range in most patients, but did observe reduced flow with increased duration of DM[53].

One study on 21 patients with DM1 and 12 controls reported a 15-20% reduction in cerebral glucose metabolism in DM1 with PET, but only in a subgroup of patients with longstanding DM and microvascular complications (neuropathy, retinopathy)[54]. No abnormalities in glucose metabolism were observed in patients with newly diagnosed DM[54].

Discussion

The CT and MRI studies reviewed herein show a relation between DM and cerebral atrophy and lacunar infarcts, but no consistent relation with WML. The MRS studies report elevated myo-inositol-to-creatine ratios and reduced N-acetylaspartate-to-creatine ratios in DM patients. The PET and SPECT studies reveal regional alterations in cerebral blood flow. None of the studies assessed the relation between imaging findings and cognition, and data on the relation between imaging findings and disease variables were scarce.

Methodological limitations were observed in a considerable proportion of studies. Study design and methodology were markedly heterogeneous, involving issues such as sample selection, DM assessment, imaging rating methods and data analyses. The majority of the studies based their results on relatively small populations. This leads to low statistical power, as illustrated by the power calculations in ***table 2***. The findings from negative studies may therefore reflect lack of power instead of lack of associations. Selective recruitment may also have confounded the results. For example, patients with more severe brain lesions are less likely to participate in imaging studies. Moreover, the results of the studies belonging to the "vascular" or "outpatient cohorts" have a low external validity and cannot readily be generalized to the DM population at large. The results of the meta-analysis support this point: the risk estimates for lacunar infarction, for example, clearly differ between the studies from the "vascular cohorts" and the "general and outpatient cohorts". All but one study had a cross-sectional design. A longitudinal design with repeated brain imaging could detect progression of brain abnormalities and would provide a better indication of their relation with DM. A high response rate on follow-up is needed to overcome selective (related to both the determinant and the outcome) participation.

The methodology for the diagnosis and classification of DM was suboptimal in the majority of the studies. Undiagnosed cases of DM will therefore have been erroneously assigned to the non-diabetic group, which can lead to an underestimation of the effect of DM. A distinction into DM type was usually not made. The majority of the CT and MRI studies are likely to have predominantly included DM2 patients, based on the age of the study populations. PET and SPECT studies, in contrast, mainly involved DM1 patients. The relevance of the PET and SPECT findings for the CT and MRI abnormalities can therefore be questioned (and vice versa). It should be considered that DM1 and DM2 may have different effects on the brain. DM2, for example, is closely linked to the so-called metabolic syndrome, which refers to a cluster of vascular risk factors, including hypertension, obesity, insulin resistance and dyslipid-

aemia, which may each affect the brain[55]. Hypoglycaemic episodes, on the other hand, are more common in DM1 patients and may also have detrimental effects, albeit through entirely different pathophysiological mechanisms.

Limitations concerning the rating methods for the imaging data were also noted, in particular in studies on WML. The majority of the WML scales that were applied were originally developed for patients with cerebrovascular disease or vascular dementia, and are relatively crude and insensitive. Although these scales adequately distinguish between patients with or without severe WML, they could be too insensitive to detect differences in WML between patients with DM and controls. True volumetric scales should be used in future studies[56]. The same applies to measurement of cerebral atrophy, but apparently the association between DM and atrophy is more robust and has therefore been more consistently detected even with relatively crude techniques. A possible methodological limitation of the PET and SPECT studies is failure to account for cerebral atrophy, which may have confounded the assessment of tracer uptake due to partial volume effects[57].

The included studies herein provide leads on the pathogenesis, but do leave many questions unanswered. The MRI and CT studies clearly identify DM as a risk factor for vascular brain pathology, in particular infarctions. The mechanisms underlying cerebral atrophy, however, cannot be readily determined from cross-sectional imaging studies. Along these lines, specific causative mechanisms cannot be derived from elevated myo-inositol levels and decreased N-acetylaspartate levels on ^{1}H-MRS studies[48]. PET and SPECT studies point at disturbances of both cerebral blood flow and glucose metabolism. However, blood flow changes were regional, included both hypo- and hyperperfusion, and were mostly limited to subgroups of patients. It is still uncertain whether these changes are cause or consequence of alterations in cerebral function in DM.

The lack of information on risk factors for brain imaging abnormalities also hampers the identification of underlying mechanisms. Only a minority of the studies included in this review took the effects of vascular risk factors, such as hypertension or atherosclerosis, into account, which should be regarded as an important omission. In the general population, hypertension, atherosclerosis and markers of inflammation are established risk factors for WML and lacunar infarcts[58-60]. Although cerebral atrophy is generally assumed to be due to neurodegenerative processes, it is also associated with vascular risk factors[33,61]. It could therefore be argued that vascular (co)morbidity is the driving force in the association between DM and brain imaging abnormalities, but this appears to be an oversimplification. A recent population based study (proportion of DM

patients <10%) indicated that increased HbA1c levels are associated with accelerated cerebral atrophy, while taking into account vascular risk factors[62]. This is in line with observation from studies on cognitive functioning in DM patients, which also indicate that chronic hyperglycaemia may have detrimental effects on the brain[3-5].

In conclusion, there is convincing evidence for an association between DM and cerebral atrophy and lacunar infarcts, but the risk factors for these brain imaging abnormalities have not yet been identified, and the relation with impaired cognition has not been addressed. In addition, the issue on the association between DM and WML is not yet settled, as the methodology of available studies was not sufficiently sensitive to detect subtle alterations. Future studies should have a longitudinal design and include sufficiently large groups of well defined DM patients preferably at an early stage of the disease in order to detect incident structural brain changes. MRI is the preferred imaging modality, because the abnormalities are subtle, and rating methods should be sensitive and quantitative (e.g. 3D volumetry). Patients should be without cognitive impairment at study entry to assess causality with cognitive function. Standardized neuropsychological examinations should be performed at regular intervals and data on relevant disease variables and co-morbidity should be carefully recorded in order to identify the risk factors for structural brain changes. PET, SPECT and MRS may help to identify underlying metabolic and vascular mechanisms.

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Chapter 5

Brain Lesions on MRI in the Elderly Patients with Type 2 Diabetes Mellitus

European Neurology; accepted for publication

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Abstract

Background and purpose:

Diabetes Mellitus (DM) type 2 has been associated with poor cognitive performance and dementia, particularly in the elderly patients. The exact mechanisms underlying the cognitive dysfunction in DM remain unclear. Imaging studies of the brain could be helpful to give more insight into possible structural brain lesions underlying this cognitive dysfunction. Therefore, we performed a study in independently living patients with DM type 2 in order to investigate the association between DM and brain imaging abnormalities.

Methods:

The study population consisted of 45 patients with DM type 2 without hypertension (mean age 73.2±5.1 years, mean duration 16.7±11.4 years), 45 patients with DM type 2 and hypertension (mean age 73.3±5.9 years, mean duration 11.3±9.1 years) and 44 control subjects (mean age 73.0±5.3 years). All patients and control subjects underwent an MRI of the brain. White matter lesions (WML), cerebral atrophy and medial temporal lobe atrophy (MTA) were rated by a standardized visual rating scale. Lacunar infarcts were defined as focal hypointensities on FLAIR sequences with a hyperintense rim around it.

Results:

WML occurred more frequently in diabetic patients with hypertension as well as without hypertension. Significantly more deep white matter lesions (DWML) were found in DM patients with and without hypertension when compared to control subjects, whereas no difference was found in the occurrence of periventricular hyperintensities (PVH). In all 3 groups lacunar infarcts occurred sporadically. A trend towards higher atrophy scores was seen in patients with DM compared to control subjects.

Conclusions:

The data of this cross-sectional study suggest that type 2 DM is an independent risk factor for deep WML in the independently living elderly patients.

Introduction

Diabetes Mellitus (DM) has been associated with cognitive impairment and dementia, particularly in the elderly[1]. The exact cerebral mechanisms underlying these cognitive deficits remain unclear but brain atrophy and vascular changes have both been assumed. Although a significant relation between DM and cortical or subcortical atrophy has been found in several studies, the results with regard to the relation of DM and white matter lesions (WML) or lacunar infarcts are conflicting[2-10]. Reasons for these inconsistencies are methodological problems, like the number of patients studied, the use of insensitive rating scales to assess WML and patient selection. Moreover, most studies were not specifically designed to assess the effects of DM on structural brain lesions, but were performed in a group of selected patients who already suffered from a stroke[2,5,7,9]. In addition, a distinction into type 1 or type 2 DM was usually not made in most studies, while they may have different effects on the brain. Often type 2 DM typically develops in the context of a cluster of vascular and metabolic risk factors, like hypertension, dyslipidaemia and obesity, also called the "metabolic syndrome", which each could lead to brain damage itself. Hypertension, indeed, is the most consistent risk factor associated with WML and has been reported to increase the risk for WML approximately two fold[11-13]. More detailed insight into structural brain abnormalities that may underlie changes in cognition in diabetic patients could provide important clues into the pathogenesis.
Therefore, we performed a study in a well-defined group of independently living elderly patients with type 2 DM to investigate the association between type 2 DM, WML, lacunar infarcts and brain atrophy. Furthermore we compared diabetic patients with and without hypertension to assess if concomitant hypertension could be defined as a relevant disease variable in DM patients or if DM is an independent risk factor.

Methods

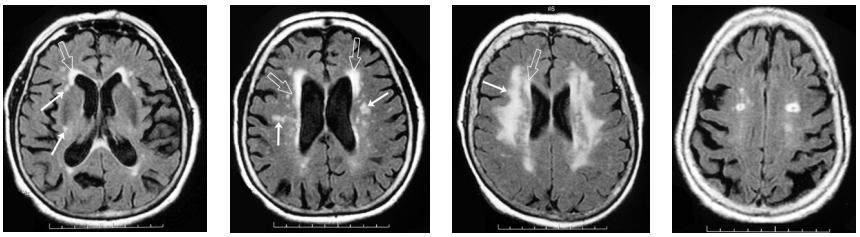
The study population consisted of 45 type 2 DM patients with hypertension, 45 type 2 DM without hypertension, and 44 control subjects without DM and without hypertension. DM patients were recruited from the department internal medicine in the Sint Lucas Andreas hospital during a time period from 2001 to 2004. The diagnosis of DM was made according to the WHO criteria[14].

Control subjects were age-matched healthy partners or neurological outpatients, visiting the hospital for low back pain or a peripheral nerve problem. Control subjects were without cardiovascular or metabolic disorder. All were recruited

by the same neurologist (BvH). Exclusion criteria for patients as well as control subjects were cerebrovascular accidents, intracranial tumours, neurodegenerative diseases and alcohol intake of >3 units/day.

Information on current health status, medical history, drug prescriptions, smoking behaviour and level of education was obtained by means of interview. Educational attainment was rated on an ordinal scale ranging from 1 (incomplete primary) to 7 (university). Total serum cholesterol, high-density lipoprotein (HDL), glucose and glycosylated haemoglobin (glyco-Hb) were determined. Blood pressure was measured in upright sitting position using an aneroid Sphygmomanometer. Measurements were done on two different occasions with a minimal interval of 4 weeks. The diagnosis of hypertension was based on history or if the mean of at least two measurements was systolic ≥160 mmHg or diastolic ≥ 95 mmHg.

Brain MRIs were obtained with a 1.5 Tesla scan (General Electric, Milwaukee, USA). Whole brain axial and coronal fluid attenuated inversion recovery (FLAIR) and axial T2-weighted were acquired to allow detailed visualization of WML and lacunar infarcts. Coronal FLAIR images and sagittal T1-weighted images were acquired to allow measurement of medial temporal lobe atrophy (MTA) and whole brain volume. The MRI scans were analyzed by an experienced rater (PhS) who was blinded to all clinical information. The Scheltens' scale was used to assess periventricular hyperintensities (PVH), white matter hyperintensities (WMH), basal ganglia hyperintensities (BGH) and infratentorial foci of hyperintensities (IFH)[15]. The PVH were examined in three regions, frontal and occipital gaps and periventricular bands, which were rated as follows: none (score 0); 5 mm or less (score 1); 6 mm or greater (score 2). The WMH were examined in four regions of the brain, the temporal, frontal, parietal, and occipital lobes, which were rated as follows: none (score 0); 3 mm and less and five or less lesions (score 1); 3 mm or less and six ore more lesions (score 2); 4 to 10 mm and five or less lesions (score 3); 4 to 10 mm and six or more lesions (score 4); 11 mm or greater and one or more lesions (score 5); and large confluent lesions (score 6). The BHG were examined in five regions of the basal ganglia, the head of the caudate, putamen, globus pallidus, thalamus, and internal and external capsule (scores similar to the WMH). The IFH were examined in four regions of the infratentorial structures, the cerebellum, mesencephalon, pons and medulla with scores similar to the WMH. Total scores and subscores were used for analysis, whereby a total of deep white matter lesions (DWML) was derived by summing WMH and BGH scores. The presence of PVH and DWML is illustrated in ***figure 1***.



1a. 1b. 1c 1d.

Figure 1 *Examples of periventricular hyperintensities (open arrows), deep white matter lesions (white arrows) (a,b,c) and lacunar infarcts (d) on axial fluid attenuated inversion recovery (FLAIR) sequences.*

Cerebral atrophy and MTA were measured by a five point visual rating scale[16,17]. Mean scores of left and right MTA were used for analysis. Lacunar infarcts were defined as focal hypointensities corresponding on FLAIR sequences with a hyperintense rim around it (***figure 1d***). Distinction from dilated perivascular spaces was made on the basis of location, size and shape of the hypointense abnormalities. The number of patients with lacunar infarcts ($n \geq 1$) was used for analysis.

Statistical analysis:

Data were analyzed with SPSS for Windows statistical package (release 12.0, SPSS, Chicago, IL). Baseline differences between groups were assessed using independent samples t-tests and $[Chi]^2$ tests as appropriate. Non-parametric tests were used for comparison of WML, lacunar infarcts, MTA and cerebral atrophy. Correlations were computed with the Spearman's correlation coefficient. All statistical tests were two-tailed and significance was accepted at a level of $p<0.05$.

Results

The groups were comparable with regard to sociodemographic factors and lipoprotein levels (***table 1, see page 64)***. The mean systolic pressure was significantly higher in the DM group with hypertension. The mean duration of DM was significantly longer in patients without hypertension. MRI data were inconclusive in 2 patients due to claustrophobia. The total WML score was statistically significantly higher in DM patients compared to control subjects ($p=0.02$) (***table 2, see page 64)***. DWML occurred more frequently in patients with DM ($p=0.007$), whereas the occurrence of PVH did not ($p=0.3$). The total amount of WML and DWML showed higher scores in DM patients with hypertension compared to those without, but significance was not reached ($p=0.74$ and $p=0.91$ respectively).

Table 1. *Characteristics of the study population*

	DM with hypertension	DM without hypertension	Control subjects
Number	45	45	44
Age	73.5 (6.1)	73.4 (5.1)	73.1 (5.4)
Sex m/v	19/26	21/24	21/23
Duration of DM	11.9 (9.2)#	16.5 (11.5)	-
Education, median	4.0	4.0	4.5
Smoking behaviour (yes/no)	3/42	7/38	7/38
Atrial fibrillation (N)	4	4	0
RR systolic	155 (19)*#	136 (12)	144 (14.9)
RR diastolic	80 (10)#	75 (7)*	83 (8)
Cholesterol/HDL	4.8 (1.3)	4.2 (1.4)	4.5 (1.4)
Glyco-Hb	7.7 (1.0)*	7.8 (1.0)*	5.8 (1.1)
OAD/insulin	9/36	14/31	--

DM = Diabetes Mellitus, OAD = oral anti-diabetics, BP = blood pressure, HDL = high density lipoprotein

Data are expressed as means (SD), analyses were done with ANOVA with posthoc Bonferroni tests, Chi square tests or Kruskal-Wallis tests when appropriate; * signifies $p<0.05$ compared to the control group; # signifies $p<0.05$ compared to the other patient group; OAD signifies oral anti-diabetics

Table 2*. Prevalence of WML, lacunar infarcts and atrophy between the different groups.*

	DM with hypertension	DM without hypertension	Control subjects
Total WML score	5.9 (5.6)*	5.4 (3.7)*	3.3 (2.4)
PVH	2.5 (1.5)	2.8 (1.6)	2.2 (1.4)
DWML	3.3 (4.4)*	2.6 (2.5)*	1.2 (1.4)
IFH	0.1 (0.4)	0.0 (0.1)	0 (0)
Lacunar infarcts (N patients)	5	3	3
MTA	0.38 (0.56)	0.44 (0.70)	0.28 (0.55)
Global atrophy	1.0 (0.5)	1.2 (0.7)	0.9 (0.6)

PVH = periventricular hyperintensities, DWML = deep white matter lesions, IFH = infrantentorial foci of hyperintensities.

Values of the WML total score, subscores, medial temporal lobe atrophy (MTA) and global atrophy scores are expressed as means (SD).

The lacunar infarcts are expressed as the number of patients with lacunar infarcts;

Kruskal-Wallis tests were performed for the analysis of WML and atrophy, Chi-square tests for the differences of lacunar infarcts; * signifies $p<0.05$ compared to control group.

The prevalence of lacunar infarcts in all 3 groups was low without significant differences (p=0.68) (***table 2***). Although atrophy scores tended to be higher in the DM group a statistically significant association was not found for MTA (p=0.48) or global atrophy (p=0.25) (***table 2***). A significant positive correlation was found between the value of glyco-Hb and total WML score (r = 0.25, p = 0.02) as well as DWML score (r = 0.25, p = 0.02). The correlation of glyco-Hb with PVH was not significant. The duration of DM correlated significantly with PVH (r=0.24, p=0.03), DWML (r=0.28, p=0.01) and total WML score (r=0.29, p=0.008).

Discussion

We found more DWML in a group of independently living elderly patients with type 2 DM compared to healthy control subjects. A relation between DM and lacunar infarcts and DM and atrophy was not found. No significant differences were found between the DM groups with and without hypertension. The significantly positive correlation between the duration of DM and WML may explain the non-significant differences in findings between diabetic patients with and without hypertension. To strengthen the association between type 2 DM and DWML we found significantly positive correlations between the severity of DWML and the value of glyco-Hb and the duration of DM respectively.

A number of studies addressing the association between DM and WML have been published previously with inconsistent results. We have chosen a case-control study design consisting of independently living elderly outpatients with type 2 DM, which may have implications for these specific patients. Our results with regard to DWML are in line with a recently published study in a group of patients with type 2 DM recruited from general practioners, but in contrast to our study differences in atrophy scores were also significant[18]. Two other relatively small case-control studies have shown conflicting results with regard to DM and WML, but only patients with type 1 DM were included[19,20]. Two population-based studies demonstrated a relation of DM with cerebral atrophy, whereas an association with WML was not found[3,6]. Most other studies used dichotomous or ordinal rating scales, which may be not sensitive enough in the discrimination between various degrees of WML[2,7-10]. This might be important, because the consistently reported modest cognitive deficits in DM patients do not suggest severe lesions and the used scales may therefore underestimate WML in DM patients[1]. The Scheltens' scale, on the contrary, which was used in the present study, is able to detect small amount of WML[15]. Furthermore, other studies were not designed to specifically assess the effects of DM on neuroimaging modalities, but assessed the effect of DM in selected patients with stroke or other cardiovascular riskfactors[2,5,7,9]. The results of these studies

have low external validity and do not allow to generalize to the DM population, which are visiting an outpatient clinic.

The difference between the association of DM with DWML versus PVH supports the hypothesis that DWML and PVH are pathologically different. It has already been suggested that PVH is more associated with atrophic processes involving ventricular enlargement whereas DWML is associated with cerebrovascular risk factors[21,22].

The results of the present study may be important to provide clues for the pathogenesis of cognitive impairment in DM patients. To our knowledge only one study analyzed cognitive function and brain imaging within a type 2 DM population and found some associations between cognitive function and brain MRI abnormalities[18].

Among the limitations of the present study is firstly the use of a visual rating scale for assessing atrophy. Although visual rating of MTA is a clinically useful method for differentiating Alzheimer's disease from controls and is quicker and more accurate than volumetry[23], volumetric scales may be more sensitive in our study population without clinically diagnosed dementia. This may explain the non-significant trend towards higher atrophy scores in DM patients compared to controls. Secondly, actual volumetric assessments may be more sensitive to assess WML, but in fact a significant agreement of the Scheltens' scale with quantitative volumetric measurements has been shown, so results are not expected to differ much when volumetry had been used [24]. Finally, the prevalence of lacunar infarcts was low and may therefore explain the non-significant differences in the DM patients with hypertension compared to those without as well as the control subjects due to lack of statistical power.

In conclusion, the data of this cross-sectional study show that type 2 DM is an independent risk factor for DWML in the independently living elderly patients. The significantly positive correlation between the value of glyco-Hb and the severity of WML may have important therapeutical implications suggesting that better metabolic control in the elderly patients with type 2 DM could prevent worsening of WML. Further studies are needed to investigate the relations between MRI measures and cognitive decline in DM patients.

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Chapter 6

Cognitive Impairment and MRI Correlates in the Elderly Patients with Type 2 Diabetes Mellitus

Submitted

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Abstract

Background:
Exact mechanisms underlying cognitive dysfunction in Diabetes Mellitus (DM) remain unclear. Imaging studies of the brain could help to identify possible structural brain lesions underlying cognitive dysfunction.

Objective:
To describe a detailed neuropsychological profile in patients functioning independently with type 2 DM. Secondly, correlations were studied between cognitive impairment and brain lesions on magnetic resonance imaging (MRI), i.e. periventricular hyperintensities (PVH), deep white matter lesions (DWML), medial temporal lobe atrophy (MTA), cerebral atrophy and lacunar infarcts. In addition, the influence of relevant disease variables of DM was studied.

Methods:
92 patients with type 2 DM (mean age 73.2±5.7 years, mean duration 13.8±10.8 years) and 44 control subjects (mean age 72.9±5.3 years) were included and underwent an extensive neuropsychological test battery and an MRI of the brain.

Results:
Neuropsychological scores were worse for each cognitive domain except for memory functions after adjustment for hypertension in a group of elderly patients with type 2 DM compared to healthy control subjects. Only PVH were independently associated with motor speed, whereas all other MRI measures were not independently associated with cognitive impairment. Interactions between the different MRI measures were not present. Glycosylated haemoglobin ($HbA_{1c)}$ and duration of DM were significantly associated with cognitive dysfunction.

Conclusions:
The data of this cross-sectional study show that type 2 DM is associated with diminished cognitive function in different cognitive domains, while memory is less affected after adjustment for hypertension. The association of cognitive impairment with MRI measures is equivocal, whereas HbA_{1c} and duration of DM were significantly associated with cognitive dysfunction.

Introduction

Type 2 Diabetes Mellitus (DM) is a common condition in the elderly and has been associated with cognitive impairment and dementia[1-4]. The majority of studies investigating cognitive impairment associated with type 2 DM had a case-control design and indicated that older DM patients perform worse than controls on a variety of cognitive function tests. Cognitive impairment may be particularly affect verbal memory or complex information processing in type 2 DM[1,3]. However, study populations were mostly small and studies did not take into account possible differences in educational level and usually did not adjust for age, sex and comorbid hypertension[3]. In addition, most studies did not perform an extensive neuropsychological test battery and population studies more often used global cognitive screening tests like the mini mental state examination (MMSE)[3,5].

The cerebral mechanisms underlying these cognitive deficits and the responsible brain structures remain to be delineated and are subject of intense research, but brain atrophy and vascular changes have both been assumed[6,7]. Although a significant relation between DM and cortical or subcortical atrophy has been found in several studies, the results with regard to the relation of DM and white matter lesions (WML) or lacunar infarcts are conflicting[8-16]. These inconsis-tencies may be due to methodological problems, like the number of patients studied, the use of insensitive rating scales to assess WML or patient selection. In all studies no associations were investigated between cognitive impairment and brain imaging abnormalities in diabetic patients.
Therefore, we performed a cross-sectional case-control study in a well-defined group of elderly type 2 DM patients living independently at home to describe the neuropsychological profile in detail. Secondly, we investigated the relationship of cognitive performance to MRI measures and DM related determinants (e.g. glycosylated haemoglobin (HbA_{1c}), DM duration, insulin treatment, hypertension, hypercholesterolemia and diabetic polyneuropathy).

Patients and methods

The study population consisted of 92 patients with type 2 DM, which were recruited from the department internal medicine in the Sint Lucas Andreas hospital during a time period from 2001 to 2004 and 44 control subjects. For inclusion all patients and control subjects had to be 60 years or older and diabetic patients had to have a diabetic duration of at least 1 year. Patients were recruited irrespective of the presence of cognitive complaints. Control subjects were age-matched healthy spouses or neurological outpatients, visiting the

hospital for low back pain or a peripheral nerve problem. Control subjects were without a history of cardiovascular or metabolic disorder. All were recruited by the same neurologist (BvH). Exclusion criteria for patients as well as control subjects were a psychiatric or neurologic disorder (unrelated to type 2 DM) that could influence cognitive function, cerebrovascular accidents, a history of alcohol or substance abuse and dementia. Control subjects were excluded if they had a blood glucose of $\geq$ 7.0 mmol/l. All participants were functioning independently at home and had intact comprehension of the Dutch language. The study was approved by the local Medical Ethical Committee. All subjects gave informed consent.
Information on current health status, medical history, drug prescriptions, smoking behaviour and level of education was obtained by means of interview. Information on the presence or absence of hypertension in the diabetic population was obtained by studying the medical records. Educational attainment was rated on an ordinal scale ranging from 1 (incomplete primary school) to 7 (university degree). Total serum cholesterol/high-density lipoprotein (HDL) ratio, glucose and HbA_{1c} were determined. Blood pressure was measured in upright sitting position using an aneroid sphygmomanometer, which was calibrated regularly. Measurements were done on two different occasions with a minimal interval of 4 weeks. The diagnosis of hypertension in all patients and control subjects was based either on history and the use of antihypertensive medication or if the mean of at least two measurements was systolic $\geq$160 mmHg or diastolic $\geq$ 95 mmHg[17,18]. A diagnosis of polyneuropathy was based on history and physical exam.

Cognitive assessment

A subjective memory questionnaire consisting of 24 questions based on the Memory Assessment Clinic rating scales (MAC) was used to obtain information on subjective cognitive function[19,20]. All information was collected without the help of a proxy.
Objective cognitive assessment included global cognitive screening tests and an extensive neuropsychological test battery. Global cognitive functioning was assessed using the HIV Dementia Scale (HDS)[21], the Cognitive part of the Cambridge Examination for Mental Disorders of the Elderly[22], which incorporates the Cambridge Cognitive Examination (CAMCOG) and the Mini Mental State Examination (MMSE)[23]. In addition, a battery of standardized neuropsychological tests was administered in order to further characterize the nature of cognitive dysfunction. The examiner was blind to the status (diabetic or non-diabetic) of the patients. Tests of executive functioning included Controlled Oral Word Association Test (COWAT), category fluency (animals, jobs)[24], Trail making test B[25] and Stroop color/word test part III, including the errors[26]. The score of trailmaking test B divided by trailmaking A and the subtraction score of Stroop colour/word test part III-part II were used for analysis. Memory

was evaluated using Rey Auditory Verbal Learning Test (RAVLT, immediate and delayed recall)[27] and Rivermead Behavioural Memory Test (RBMT) Logical Memory test (immediate and delayed recall)[28]. Speed of mental processing was assessed with the Trail making test part A, Stroop colour/word test part I and II. Tests of motor functions included Grooved Pegboard test (GP dominant and non-dominant hand[29]) and the binary choice reaction time of the FEPSY[30]. In order to reduce the number of variables, four composite scores were constituted by calculating the mean of the standardized z-scores across the whole study sample in each domain. The scales were first reversed to correspond with each other. A negative score always represented a lower performance. The validity of this test classification was found to be satisfactory (Cronbach's alpha > 0.6 for each cognitive domain).

Brain imaging

Brain MRIs were obtained with a 1.5 Tesla scan (1.5 Tesla, General Electric, Milwaukee, USA). Whole brain axial and coronal fluid attenuated inversion recovery (FLAIR) and axial T2-weighted were acquired to allow detailed visualization of WML and lacunar infarcts. Coronal FLAIR images and sagittal T1-weighted images were acquired to allow measurement of medial temporal lobe atrophy (MTA) and cerebral atrophy. The MRI scans were analyzed by an experienced rater (PhS) who was blinded to all clinical information. The Scheltens' scale was used to assess periventricular hyperintensities (PVH), white matter hyperintensities (WMH), basal ganglia hyperintensities (BGH) and infratentorial foci of hyperintensities[31]. Total scores and subscores were used for analysis, whereby a total of deep WML (DWML) was derived by summing WMH and BGH scores.

Cerebral atrophy and MTA were measured by a five point visual rating scale[32,33]. Mean scores of left and right MTA were used for analysis. Lacunar infarcts were defined as focal hyperintensities corresponding to cerebrospinal fluid on FLAIR and T2 sequences (<5mm). The number of patients with lacunar infarcts ($n \geq 1$) was used for analysis.

Statistical analysis

Data were analyzed with SPSS for Windows statistical package (release 12.0, SPSS, Chicago, IL). Baseline differences between groups were assessed using independent samples t-tests, Mann-Whitney U tests and $[Chi]^2$ tests as appropriate. Neuropsychological test performance was studied using analysis of variance (ANOVA) with sex, age, education and hypertension as covariates. Magnitude of effect size (Cohen's d) for each cognitive domain and individual neuropsychological test was calculated as the mean group difference divided by the pooled standard deviation[34]; a negligible effect is defined if $d \leq 0.2$, a small effect if $0.2 < d \leq 0.5$, a medium effect if $0.5 < d \leq 0.8$ and a large effect if $d > 0.8$.

Multiple linear regression analyses were performed to examine independent associations between MRI measures and cognitive impairment in the diabetic

population. The different cognitive domains were used as the dependent variables and the MRI measures were the independent variables. In addition, age, sex, education and hypertension were entered as covariates. WML (low/high) and atrophy scores (low/high) were dichotomized at the respective sample medians. Interactions between the different MRI lesions were tested with ANOVA. A second linear regression analysis was performed to investigate relationships between the cognitive domains and DM disease variables. All statistical tests were two-tailed and significance was accepted at a level of $p<0.05$.

Results

Table 1. *Characteristics of the study population*

	Type 2 DM	Control subjects
Number	92	44
Age (years (s.d.))	73.2 (5.7)	72.9 (5.3)
Sex m/v	40/52	20/24
Duration of DM(years (s.d.))	13.8 (10.8)	-
Education (median)	4.0 (1.6)	4.5 (1.5)
Current smokers (yes/no)	9/83	6/38
Hypertension (N)	49*	4
Systolic BP mmHg	147 (18)	143 (15)
Diastolic BP mmHg	79 (9)*	83 (8)
Cholesterol/HDL	4.4 (1.4)	4.6 (1.4)
HbA_{1c}	7.7 (1.0)*	5.7 (1.1)
DM treatment:		
OAD (N)	24	
Insulin (N)	66	
Diet (N)	1	

DM = Diabetes Mellitus, OAD = oral anti-diabetics, BP = blood pressure, HDL = high density lipoprotein. Data are expressed as means (SD) unless otherwise mentioned, analyses were done with ANOVA, Chi square tests or Kruskal-Wallis tests when appropriate; * signifies $p<0.05$ compared to the control group

The groups were comparable with regard to sociodemographic factors, systolic blood pressure and cholesterol/HDL (***table 1***). Diastolic blood pressure was lower in DM patients compared to control subjects. Due to technical problems data for the motor tests were not available in 16 patients. The neuropsychological test results are presented in ***table 2***. MRI data were inconclusive in 2 patients due to claustrophobia and 8 patients withdrew from MRI study. No differences were detected in the subjective memory scale between both groups and the composite z score of the memory functions, whereas all global test scores and other composite z scores differed significantly in the diabetes group compared to control patients with small to medium effect sizes. When hypertension was not controlled the patient group also differed significantly in memory functions (results not shown). The results were also analysed by using the raw scores of the neuropsychological tests. ANOVA with age, sex, education and hypertension as covariates revealed lower scores in diabetic patients on all tests with small to medium effect sizes. Significance was reached on verbal fluency (jobs category), letter fluency, delayed recall of RBMT, GP dominant hand and GP nondominant hand (***table 2)***.

Table 2. *Results of the subjective memory questionnaire, global cognitive functioning tests, different cognitive domains and individual neuropsychological tests*

	Type 2 DM	Control subjects	p-value	d
MAC	3.28 (0.40)	3.32 (0.48)	0.719	
HDS	10.2 (3.7)	13.0 (3.2)	0.001	0.84
MMSE	27.2 (2.1)	28.3 (1.5)	0.026	0.65
CAMCOG	93.0 (7.5)	98.1 (9.2)	0.008	0.59
Cognitive domains:				
Z executive functioning	-0.106 (0.68)	0.268 (0.60)	0.014	0.37
Z memory	-0.118 (0.82)	0.273 (0.83)	0.092	0.39
Z mental speed	-0.133 (0.88)	0.294 (0.78)	0.035	0.43
Z motor speed	-0.027 (0.77)	0.290 (0.51)	0.001	0.32
Individual tests:				
Executive functions				
Trailmaking test B division score (B time/ A time)	2.9 (1.3)	2.5 (0.8)	0.37	0.35
Stroop III, subtraction score (Stroop III time -Stroop II time)	88.3 (48.8)	76.1 (58.1)	0.26	0.23
Stroop III errors	4.1 (7.7)	3.1 (8.7)	0.45	0.13
Verbal fluency, animals	17.6 (5.5)	20.1 (4.8)	0.08	0.48
Verbal fluency, jobs	12.2 (4.2)	14.4 (3.2)	0.02	0.57
Letter fluency	24.8 (11.4)	32.1 (11.3)	0.01	0.65
Memory				
RAVLT immediate recall	9.6 (2.8)	10.6 (2.9)	0.52	0.36
RAVLT delayed recall	7.2 (3.2)	8.6 (3.6)	0.30	0.42
RBMT immediate recall	14.9 (6.2)	17.7 (6.0)	0.06	0.46
RBMT delayed recall	10.9 (5.9)	13.7 (6.2)	0.03	0.47
Speed of mental processing				
Trailmaking test A, sec	57.1 (22.5)	46.5 (21.2)	0.12	0.48
Stroop I, sec	51.9 (12.1)	47.2 (11.4)	0.05	0.40
Stroop II, sec	65.5 (16.3)	58.7 (12.3)	0.06	0.45
Speed of motor functions				
Grooved Pegboard (dominant hand), sec	105.1 (35.2)	85.1 (22.8)	0.001	0.63
Grooved Pegboard (non-dominant hand), sec	114.3 (41.6)	99.1 (27.3)	0.004	0.41
Binary choice (FEPSY), ms	653.5 (200.3)	601.4 (105.8)	0.12	0.30

MAC = Memory Assessment Clinic rating scale, HDS = HIV dementia scale, MMSE = Mini Mental State Examination, CAMCOG = Cambridge Cognitive Examination, d = effect size estimate, sec = seconds, ms = milliseconds..Data for the MAC and for the global cognitive functioning tests are expressed as means (s.d.); analyses were done with Mann Whitney U tests; .Data for the different cognitive domains are expressed as mean standardized values or z scores (s.d.), negative values always represented lower performance, data for the different individual neuropsychological tests are expressed as mean (s.d.); ANOVA was used for analyses with age, sex, education and hypertension as covariates. Effect sizes were expressed as Cohen's d.

Multiple linear regression analyses were performed to investigate the independent contribution of PVH, DWML, MTA, global atrophy and lacunar infarcts to impairment in several cognitive domains (***table 3, see page 76***). In addition, age, sex, education and hypertension were entered as covariates in all analyses. Only PVH was independently associated with motor speed (β=-0.269, p=0.04), whereas all other MRI measures were not associated with cognitive decline.

There were no interactions between PVH, DWML, global atrophy, MTA and lacunar infarcts.
In addition, a second linear regression analysis was performed to predict cognitive deterioration in DM patients with DM related determinants (e.g. duration of the disease, HbA_{1c}, insulin therapy, hypertension, cholesterol/HDL and polyneuropathy) as the independent variables. Only the duration of DM was independently associated with the domain motor speed (standardized β = -0.226; p=0.04) and HbA_{1c} with the HDS score (standardized β = -0.217; p=0.015), whereas all other variables were not.

Table 3. *Associations between medial temporal lobe atrophy, global atrophy, deep white matter lesions and periventricular hyperintensities and cognitive domains in type 2 DM patients*

	Adjusted R^2	β pvh	β dwml	β MTA	β global atrophy	β lacunar infarcts
MMSE	0.828	0	0.105	0.072	-0.058	-0.124
CAMCOG	0.164	0.076	0.204	-0.019	-0.112	-0.107
HDS	0.368	0.036	0.061	0.023	-0.034	0.049
Executive functions	0.268	-0.167	0.117	-0.100	-0.164	0.091
Memory	0.210	-0.037	0.195	-0.069	0.013	-0.004
Mental speed	0.177	-0.185	0.220	0.011	-0.199 (p=0.086)	-0.033
Motor speed	0.335	-0.269*	0.238	-0.080	-0.103	0.122

MMSE = Mini Mental State Examination, CAMCOG = Cambridge Cognitive Examination, HDS = HIV dementia scale. Linear regression analyses with cognitive domains as dependent variables were performed. PVH, DWMH, MTA, cerebral atrophy, lacunar infarcts, age, sex, education and hypertension were entered as independent variables. Regression coefficients were standardized to enable direct comparison of their effects on cognitive functions. * p<0.05.

Discussion

Despite the fact the patients did not express cognitive complaints we demonstrated that global cognitive test scores and neuropsychological scores were worse for each cognitive domain except for memory functions after adjustment for hypertension in a group of elderly independently living patients with type 2 DM compared to healthy control subjects. The contribution of MRI measures to cognitive impairment, however, was equivocal. Only PVH were independently associated with motor speed, whereas all other MRI measures were not associated with cognitive performance in the diabetic population. Interactions between the different MRI measures were not present. HbA_{1c} and the duration of DM were significantly associated with some cognitive dysfunction whereas the other DM related determinants were not.

Other studies showed different results with regard to neuropsychological test scores between subjects with type 2 DM and controls[3,5]. Important reasons

could be the use of different cognitive batteries and a different way of analyzing the results of these tests. In our study we used two analytical approaches to assess neuropsychological performance of DM patients, including comparison to healthy controls on composite measures of specific cognitive domains and comparison of the magnitude of deficits on individual measures.

Although a critical review published in 1997[1] reported that the most commonly affected cognitive ability in subjects with type DM was verbal memory, our finding of a non-significant difference in memory functions after adjustment for hypertension is consistent with results of other studies[3]. Some studies found also non-significant differences and small or negligible effect sizes after controlling for hypertension, but in general their overall cognitive assessment was relatively brief[3,5].

Recently Manschot et al. reported the results of their study on cognitive testing and MRI correlates in type 2 DM in patients recruited from general practioners[35]. Our results on cognitive performance in a different population were in line with their results. They also found impaired cognitive performance in all cognitive domains in DM patients but statistically significant changes only in the domains executive functioning, information processing speed and memory. After adjustment for hypertension their results were not affected, but we showed that after adjustment for hypertension no statistically significant difference was found for the memory domain. Although our study population was older, had a longer DM duration and worse metabolic control, no associations were found between cognitive impairment and MRI abnormalities in the diabetic population except for PVH. This could be due to the fact that they included patients with a history of stroke, which may implicate that their study population had more advanced cerebrovascular disease than our patients. Moreover, Prins et al. reported in a prospective study that white matter lesions, brain infarcts and generalized brain atrophy were associated with decline in information processing speed and executive function. After exclusion of participants with an incident stroke some of the associations were no longer significant, which may indicate that stroke plays an intermediate role in the relationship between cerebral small vessel disease and cognitive decline[36].

We only found an independent association of PVH with motor speed. This finding is supported by other studies, which also found an association between cognitive dysfunction and PVH, but not with DWML, although analyses were not performed in DM patients[37,38]. However, it is important to realize that the definition of PVH differed in the studies[39]. In the present study PVH was defined as hyperintensities adjacent to the ventricles and not exceeding 10 mm.

A non-significant trend towards an association between mental speed with global atrophy was found, while other studies reported associations with white matter disease for this particular cognitive domain[40,41]. Our results confirm the suggestion that cognitive impairment in elderly subjects with type 2 DM is due to more complex pathology and not just cerebrovascular disease or cerebral atrophy[7].

No significant differences were detected in a subjective memory questionnaire between DM patients and controls. This illustrates that objective testing is important in diabetic patients to detect cognitive dysfunction. Global cognitive screening tests may be sufficient for detecting cognitive dysfunction and the HDS seems to be the most clinically relevant test.

Associations between global cognitive function and HbA_{1c} may suggest that optimal glycaemic control is necessary even in the elderly patients. Furthermore duration of the disease seems to be important in diminished motor speed tasks, whereas our results show that insulin treatment, diabetic polyneuropathy, hypertension and cholesterol/HDL were not independently associated with cognitive performance in type 2 DM patients.

Among the limitations of our study is the lack of data on known vascular complications of DM. It would have been interesting to associate cognitive decline with other long-term complications as retinopathy, nephropathy and peripheral vascular disease, since some studies show a relation of retinopathy with vascular brain lesions and cognitive impairment. One study reported an association between background diabetic retinopathy and small focal white matter hyperintensities in the basal ganglia and significant cognitive disadvantage[42]. Another study showed that retinopathy is independently associated with poor cognitive function, suggesting that cerebral microvascular disease may contribute to the development of cognitive impairment[43]. While we used visual rating scales more sophisticated MRI analyses, like volumetry, may reveal significant correlations with structural brain changes and cognitive impairment in DM patients. Another possible limitation is that our findings are based on selected outpatients. Therefore we cannot extrapolate our findings to the general population of type 2 DM patients. Finally, the number of DM patients is relatively small and these findings need to be replicated in a larger group preferably with a longitudinal design.

In conclusion, the data of this cross-sectional study show that patients with type 2 DM have diminished cognitive function in different cognitive domains, while memory is less affected after adjustment for hypertension. The association of cognitive impairment with MRI measures is equivocal, but may support a dual

pathology involving vascular disease as well as cerebral atrophy and probably yet unknown factors. Metabolic control of DM as well as the duration of DM seems to be important disease variables in the impaired cognitive performance. Regular assessment of cognitive function should be performed as part of the routine review of diabetic patients.

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Chapter 7

Summary and general discussion

Summary and general discussion

This final chapter provides a summary and discussion of the main findings of the studies that have been described in this thesis, with reference to results from other studies. The chapter concludes with a discussion of the possible implications of our findings and recommendations for future research.

Summary

Subcortical ischaemic vascular disease (SIVD) is an important cause of cognitive impairment in elderly patients. Screening and diagnostic tests are needed to identify these patients. The HIV dementia scale (HDS) is a reliable and quantitative scale for identifying HIV dementia[1]. The cognitive profile of HIV dementia has subcortical features that resemble subcortical ischaemic vascular disease (SIVD). The clinical syndrome is characterized by early impairment of attention and executive function, accompanied by a slowing of motor performance and information processing, while memory functions remain relatively intact[2].

Chapter 2 reported the results of an attempt to validate the HDS for elderly SIVD patients. The primary hypotheses were that the HDS could be used as a screening test in SIVD patients and that it could be used as a screening test for patients who have vascular risk factors. The HDS consists of four items and is easy to administer. All items of the HDS represent characteristics of subcortical cognitive functions, (i.e. psychomotor speed, concentration, executive functions and memory skills). Because the neuropsychological profiles of patients with normal pressure hydrocephalus (NPH) are identical to those of SIVD patients, NPH patients were also included in the study population[2,3]. The results of the study indicated that the HDS is capable of discriminating between patients with cognitive impairments due to SIVD or a NPH and normal control subjects in an older population. Patients had HDS scores of 5.1 ± 3.5 (maximum score 16), and control subjects had scores of 13.0± 2.4 ($p < 0.0001$). The results further showed that the HDS is of additional value for subjects whose Mini Mental State Examination (MMSE) scores fall within the normal range. The results of this study suggest that the HDS is capable of detecting cognitive impairment in SIVD patients and may therefore be used in clinical trials in SIVD patients or those who are at risk for SIVD.

The central hypothesis of Chapter 3 was that a clinical neurophysiological test could be helpful for detecting cognitive impairment in SIVD patients. The late responses that are elicited by the auditory oddball paradigm are considered to

be related to cognitive processing[4]. It has been shown that the latency of the N2 complex and the P3 is prolonged in patients with Alzheimer's disease, Parkinson's disease, Huntington's disease, Binswanger's disease and depression[5-7]. Several studies have investigated the auditory oddball paradigm in patients with vascular white matter disease (i.e. leukoaraiosis or lacunar infarcts)[6,8-11]. These studies, however, used either a definition of cognitive decline that was based on DSM-IV criteria for Alzheimer's dementia[12] or tests of cognitive function that were not described in detail. In addition, these studies analyzed only the P3 wave. We attempted to determine whether the various deflections of the event-related potential (N1, N2 complex and P3) that are evoked by the auditory oddball paradigm could differentiate between patients who have vascular cognitive impairment (VCI) caused by SIVD in an early phase of the disease and age-matched control subjects. We demonstrated that N2 latency was significantly longer in patients with VCI (254.6 ± 25.1 milliseconds) than it was in age-matched control subjects (235 ± 28.6 milliseconds) ($p = 0.001$), whereas the latencies of P3 and N1 were not significantly different. The peak-to-peak amplitude of the N2 complex to the P3 wave was significantly lower in the patient group (patients 11.5 ± 7.0 microvolt vs. controls 15.4 ± 9.4 microvolt, $p = 0.02$). White-matter lesions revealed by MRI were not correlated with N2 latency ($r = -0.255$, $p = 0.3$). These data show that the latency of the N2 complex is longer and the peak-to-peak amplitude of the N2 to P3 wave is lower for a well-defined group of VCI patients than it is for healthy control subjects.

Subcortical ischaemic vascular disease incorporates both white-matter lesions and lacunar infarcts. While hypertension is the most important and consistent risk factor for white-matter lesions and lacunar infarcts, the data on the relation between these lesions and diabetes mellitus (DM) are not consistent. Because of the frequency of both SIVD and DM among elderly subjects we investigated the relation between DM and SIVD.

Chapter 4 reports the result of a systematic review addressing the association between DM and structural brain-imaging abnormalities. It is known that DM increases the risk of cerebral large-vessel disease two to threefold. Whether DM is a risk factor for SIVD, including white-matter lesions and lacunar infarcts, remains unclear. Our systematic review addressed available data on brain-imaging changes in diabetic patients, as revealed by computer tomography (CT) and magnetic resonance imaging (MRI); it also analysed studies that use magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single-photon emission computer tomography (SPECT) to investigate the relationship between DM and abnormalities. We also assessed the relationship of these cerebral changes to cognition, and related disease

variables, including DM subtype, age and hypertension, DM duration, medication use and glycaemic control. Eligible studies were evaluated according to predefined inclusion criteria (i.e. clear imaging-outcome measures, a clear definition of DM and a sample size of at least 20 DM patients). Data on study design, DM type, treatment and associated comorbidity, imaging modality (MRI, MRS, CT, SPECT or PET) and imaging findings were extracted from the fifty-five articles that were included in the review. The methodology of these studies with regard to population selection, DM assessment, neuroimaging rating methods and data analyses were heterogeneous. DM was associated with cerebral atrophy in eight out of ten studies that investigated this relationship. Eight of nineteen studies reported an association between DM and lacunar infarcts. We found little evidence of an association with white-matter lesions. Studies that used PET and SPECT reported regional abnormalities of cerebral blood flow and cerebral glucose metabolism. None of the studies assessed the relationship between imaging findings and cognition. Data on the relationship between imaging findings and disease variables (e.g. age, hypertension, medication use, glycaemic control) were scarce as well. We concluded that DM is associated with cerebral atrophy and lacunar infarcts, but that the association with white-matter lesions is equivocal.

Chapter 5 elaborated on the conclusions that were drawn in Chapter 4 by reporting results from a cross-sectional study that compared a well-defined population of independently living elderly patients with Type 2 DM to healthy control subjects in order to investigate the association between DM, white-matter lesions, lacunar infarcts and brain atrophy. We also compared DM patients who had hypertension to those who did not, in order to determine whether concomitant hypertension could be defined as a relevant disease variable in DM patients. In addition, we investigated the relationship of DM to other disease determinants. The study population consisted of forty-five patients who suffered from Type 2 DM without hypertension (mean age 73.2 ± 5.1 years, mean duration of DM 16.7 ± 11.4 years), forty-five patients with type 2 DM and hypertension (mean age 73.3 ± 5.9 years, mean duration of DM 11.3 ± 9.1 years) and forty-four control subjects (mean age 73.0 ± 5.3 years). All patients and control subjects underwent MRI brain scans. White-matter lesions (WML), cerebral atrophy and medial temporal lobe atrophy (MTA) were rated using a standardized visual rating scale. WML occurred more frequently among DM patients (both with hypertension and without hypertension) than it did among healthy control subjects. Significantly more DWML (deep white-matter lesions) were found among DM patients (with and without hypertension) than were found among control subjects, although no difference was found in the occurrence of periventricular hyperintensities (PVH). Although higher atrophy scores were seen among DM patients than among control subjects, this result

was not significant. The association between Type 2 DM and DWML is supported by significant positive correlations between the severity of DWML and the value of glycosylated haemoglobin (HbA_{1c}) and the duration of DM. Data from this cross-sectional study suggest that Type 2 DM is an independent risk factor for DWML in independently living elderly patients.

Chapter 6 addressed the detailed neuropsychological profiles of independently functioning patients who have Type 2 DM. It also examined correlations between cognitive impairment and brain lesions (i.e. SIVD, atrophy and lacunar infarcts) that were revealed by MRI. The chapter discusses the influence of relevant disease variables. After adjusting for hypertension neuro-psychological scores for each cognitive domain except for memory functions were worse for a group of elderly patients with Type 2 DM than they were for healthy control subjects. Periventricular hyperintensities (PVH) were an inde-pendent predictor of motor speed, while none of the other MRI measures was independently associated with cognitive impairment. No interactions between the various MRI measures were found. HbA_{1c} and duration of DM were both significantly associated with cognitive dysfunction. Data from this cross-sectional study show that Type 2 DM is associated with diminished cognitive functioning in various cognitive domains, while memory is less affected, after adjusting for hypertension. The association of cognitive impairment with MRI measures is equivocal, although HbA_{1c} and duration of DM were significantly associated with cognitive dysfunction.

General discussion

Four major conclusions can be drawn from this thesis. First, we demonstrated that the HIV dementia scale (HDS) is a sensitive screening test for detecting cognitive impairment in patients with SIVD, and it may be useful as a screening test for a population of patients who have vascular risk factors. Second, we investigated the auditory oddball paradigm in SIVD patients, showing that the latency of the N2 complex is longer and the peak-to-peak amplitude of the N2 to P3 wave is lower among a well-defined group of VCI patients than among healthy control subjects. Third, Type 2 DM is an indepen-ent risk factor for deep white-matter lesions in independently living elderly patients who visit an outpatient clinic. Fourth, although patients with Type 2 DM exhibit global cognitive deterioration with memory function being less affected after adjustment for hypertension, independent correlations with SIVD or atrophy are equivocal.

The concept of SIVD was introduced as a homogeneous subtype of vascular cognitive impairment. This condition is a frequent cause of vascular cognitive impairment, and it is caused by small-vessel disease, which includes cerebral white-matter lesions (WML) and lacunar infarcts in subcortical white and grey matter[13-15]. Vascular cognitive impairment due to SIVD covers a wide spectrum of cognitive dysfunction, ranging from subtle and clinically often undetected deficits to overt dementia[16]. The neuropsychological profile is characterized by early impairment of attention and executive function, with a slowing of motor performance and information processing. Episodic memory is believed to be relatively unaffected[13]. Subtle clinical symptoms are often neglected by physicians and both patients and physicians often consider these symptoms as normal signs of ageing.

Most screening tests, such as the Mini Mental State Examination (MMSE), are not sensitive enough to detect cognitive impairment in such patients, as they were designed to identify cognitive symptoms, as in Alzheimer's disease (AD)[17]. Because of the frequency with which SIVD is identified as a cause of vascular cognitive impairment, a brief and simple cognitive screening test should enable physicians to make early diagnoses and should facilitate the recognition of cognitive problems in patients who are at risk for SIVD. We demonstrated that the HIV dementia scale (HDS) discriminates between elderly patients with subcortical cognitive impairment due to SIVD and normal control subjects. The difference was still significant in a sub-analysis of patients who had MMSE scores of 27 or higher (Chapter 2). Nonetheless, we cannot exclude the possibility that the cognitive deficits in these patients were caused by concomitant AD. Patients with AD present with a different clinical picture, however, and they generally have lower MMSE scores. Our findings suggest that the HDS may be useful as a screening test for SIVD and that it is of additional value for subjects whose MMSE scores fall within the normal range.

Second, the auditory oddball paradigm is a neurophysiological method for eliciting an event-related potential (ERP); it contains different deflections with the highest amplitude, usually measured at about 300 milliseconds (P3)[4]. The late responses elicited by the auditory oddball paradigm are considered related to cognitive processing[4]. Although several studies have evaluated the diagnostic value of the ERP for patients with dementia, these studies primarily investigated patients with advanced disease, even though early diagnosis is needed to provide adequate care and therapy[5-7,18,19]. In the present thesis, we showed that the latency of the N2 complex is prolonged and the peak-to-peak amplitude of the N2 complex to P3 wave is lowered in patients who suffer from VCI caused by SIVD (Chapter 3). One of the limitations of this study was that we did not include patients with Alzheimer's disease. Although Goodin and

Aminoff reported that the N1 latency is prolonged in subcortical dementia as compared to cortical dementia, we found no prolonged N1 wave in our patients, as compared to the control subjects[20]. The patients in the study by Goodin and Aminoff were already suffering from advanced disease, while the patients in our study were clinically characterized by cognitive impairment and not dementia. Further studies are therefore necessary to compare the ERP that it evoked by the auditory oddball paradigm in patients with early Alzheimer's disease to that which is evoked in patients who suffer from cognitive impairment due to SIVD. We could not demonstrate a significant positive correlation between the severity of white-matter abnormalities, the presence of lacunar infarcts and the N2 latency in a subgroup of our study population who underwent MRI. Although this result may be explained by the small sample size, it may also suggest that the functional difference in N2 complex between the two groups is not accompanied by anatomical changes that are revealed by MRI. The lack of correlation is not completely surprising, as the clinical impact of the severity of WML on cognition is also a subject of discussion[21].

Third, age and hypertension have been shown to be clearly associated with WML on MRI. The association of WML with DM, however, is much weaker than its association with any of the other risk factors. Chapter 4 presented a review of the literature on the association between DM and brain-imaging changes. Studies using CT and MRI provide evidence of a relationship between DM and cerebral atrophy, and they suggest that lacunar infarcts are more common in DM patients, although the association with WML is equivocal. Many of these studies, however, have major methodological limitations, including small sample size, inability to adjust for confounding factors, unclear operationalization of DM and insensitive rating scales for structural brain changes[22-26].

Because of these inconsistencies and methodological shortcomings, we investigated MRI abnormalities in independently living elderly patients with Type 2 DM who were visiting an outpatient clinic. The results presented in this thesis confirm that Type 2 DM in elderly patients is an independent risk factor for deep WML (Chapter 5). In contrast to other studies, our study population consisted of a well-defined patient group with Type 2 DM, taking comorbid hypertension into account as well. In addition, we used a semi-quantitative rating scale to assess WML; this scale is more sensitive for detecting small amounts of WML than are the rating scales that have been used in many previous studies. Most of the WML scales that have been applied in previous studies were originally developed for patients with cerebrovascular disease or vascular dementia, and they are relatively crude and insensitive. Although these scales discriminates adequately between patients with severe WML and those

with modest or subtle abnormalities, they may not be sensitive enough to detect the modest differences in WML that are expected between patients with DM and control subjects (especially in small study populations). Nonetheless, although true volumetric scales claimed higher sensitivity, very few studies have used these techniques[27,28]. Furthermore, these studies revealed no more WML in DM patients than they did for control subjects. These studies also suffer from other methodological shortcomings (e.g. undefined DM subtype, no adjustment for other disease variables)[27,28]. Results regarding the association between DM and atrophy are more consistent in the literature[23,26,29,30]. We also found more atrophy among the DM group, but this difference was not statistically signi-ficant. Although this lack of difference may be due to the visual rating scale that was used, a comparative study between visual rating and volumetry concluded that visual rating is as clinically useful and sometimes even more accurate than volumetry[31]. Lacunar infarcts occurred sporadically in both DM patients and control subjects. This finding may be attributable to the fact that we investigated independently living patients who were visiting an outpatient clinic in the early phase of vascular disease.

Fourth, Type 2 DM is common among the elderly, and it has been associated with cognitive impairment and dementia[32-35]. Study populations tend to be small, however, and they do not take into account possible differences in educational level. They also do not usually adjust for age, sex and co-morbid hypertension[32]. In addition, most studies do not include extensive neuropsychological test batteries, and most population studies use global cognitive screenings tests, such as the MMSE. We investigated neuropsychological profiles in a well-defined group of elderly patients with Type 2 DM, as well as correlations with brain-imaging abnormalities. In particular, we hypothesized that cognitive impairment in Type 2 DM was caused by SIVD (Chapter 6). When we started our study, the association between cognition and MRI findings in the DM population was not known. We administered an extensive neuropsychological test battery to Type 2 DM patients and investigated associations with MRI lesions, in order to clarify the pathological mechanisms of cognitive impairment among these patients. We demonstrated that global cognitive test scores and neuropsychological scores for each cognitive domain except for memory functions after adjustment for hypertension were worse for a group of independently living elderly patients with Type 2 DM than they were for healthy control subjects. This result has been confirmed by other studies[32]. Nonetheless, although we have demonstrated that Type 2 DM is an independent risk factor for deep WML, these lesions are not independently associated with cognitive impairment in the diabetic population. Only PVH was an independent predictor for motor speed: none of the other MRI measures was associated with cognitive impairment. Interactions between the various MRI

measures were also not present. One of the limitations of this study was that we used a semi-quantitative visual rating scale to assess WML and a visual rating scale to determine atrophy. More sophisticated MRI analyses (e.g. volumetrics) may reveal significant correlations with structural brain changes and cognitive impairment in DM patients. We concluded that the association of cognitive impairment with MRI measures is equivocal in Type 2 DM, but that it may support a dual pathology involving both vascular disease and cerebral atrophy. It is possible that other factors that are not yet known play a role in cognitive impairment in patients with Type 2 DM.

Clinical implications

1. *The HIV dementia scale could be used as a screening test for patients who are at risk for SIVD.*

Subcortical ischaemic vascular disease (SIVD) is a frequent cause of cognitive impairment. Most screening tests, such as the MMSE, are not sensitive enough to detect cognitive impairment in these patients, because they were designed to identify cognitive symptoms, as in AD. The results of this thesis show that the HIV dementia scale may be useful as a screening test for SIVD in elderly patients.

2. *Assessment of cognitive function should be performed routinely in diabetic patients.*

Polyneuropathy, retinopathy, nephropathy and peripheral vascular disease are important complications of DM, and patients with DM are routinely evaluated to assess the occurrence of these complications. The results of this study show that Type 2 DM in elderly patients is also associated with cognitive impairment in various cognitive domains. Regular assessment of cognitive function should be performed as part of the routine review of DM patients by skilled clinicians.

Recommendations for future research

1. The HIV dementia scale (HDS) is able to detect cognitive impairment in patients with SIVD; it may therefore be used in clinical trials involving SIVD patients or those who are at risk for SIVD. We did not include patients with mild cognitive impairment (MCI), however, or patients with early clinical symptoms of Alzheimer's disease (AD). Patients with AD usually present a different clinical picture and tend to have lower MMSE scores. Patients with MCI and normal MMSE scores, however, may fail the HDS. Further research could evaluate the HDS for use with patients with MCI or early AD (with and

without vascular risk factors), in order to differentiate between MCI and AD, and subcortical vascular cognitive impairment.

2. The latency of the N2 complex is longer and the peak-to-peak amplitude of the N2 to P3 wave is lower in a well-defined group of patients with VCI than it is in healthy control subjects. Correlations with WML on MRI could not be assessed. Further research is needed to clarify the pathophysiological mechanism underlying the prolonged latency of the N2 complex in patients with cognitive impairment due to SIVD and to compare the ERP responses of these patients to those of patients who are suffering from early Alzheimer's disease.

3. The findings on the correlations between Type 2 DM, cognitive impairment and SIVD were based on selected outpatients. Although these results may be true for an outpatient population, we cannot extrapolate our findings to the general population of Type 2 DM patients. The study was also based on a cross-sectional design. To assess the causality of brain imaging abnormalities with cognitive function, patients with Type 2 DM should preferably have no cognitive impairment at study entry, and they should be followed regularly using standardized neuropsychological examinations at pre-defined intervals. Future research should be prospective in nature and should include large groups of well-defined DM patients, preferably in an early stage of the disease, in order to detect incidental structural brain changes. Given the fact that cerebral changes in DM patients are relatively subtle, MRI rating methods should be sensitive and quantitative (e.g. 3D volumetry).

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Chapter 8

Samenvatting en discussie

Samenvatting en discussie

De belangrijkste resultaten van de studies worden samengevat en in breder perspectief geplaatst. Implicaties worden besproken en aanbevelingen voor toekomstig onderzoek worden gedaan.

Samenvatting

De aanwezigheid van witte stofafwijkingen en lacunaire infarcten is een belangrijke oorzaak voor cognitieve achteruitgang bij de oudere patiënt. Er is behoefte aan screeningstesten en diagnostische testen om deze patiënten te kunnen detecteren. De HIV dementie schaal (HDS) is een betrouwbare en sensitieve test om patiënten met HIV dementie te kunnen identificeren[1]. Het cognitieve profiel van patiënten met HIV dementie is vergelijkbaar met dat van patiënten met ischemische veranderingen in de witte stof. De klinische presentatie wordt gekenmerkt door stoornissen in aandacht en uitvoerende functies, psychomotore traagheid en geheugenstoornissen, waarbij de herkenning grotendeels intact is[2].

In hoofdstuk 2 wordt de HDS gevalideerd als een screeningstest in een oudere patiëntenpopulatie met cognitieve stoornissen ten gevolge van witte stofafwijkingen. De HDS bestaat uit 4 items en is makkelijk uitvoerbaar. Deze test onderzoekt kenmerken van cognitieve functies met een subcorticaal karakter, te weten pychomotore snelheid, aandacht en concentratie, uitvoerende functies en geheugentaken, waarbij ook de herkenning wordt getest. Patiënten met een "normal pressure hydrocephalus" (NPH) vertonen een identiek cognitief profiel en zijn derhalve ook geïncludeerd in de studie[2,3]. We hebben aangetoond dat de HDS in staat is oudere patiënten met cognitieve achteruitgang veroorzaakt door witte stofafwijkingen of een NPH te onderscheiden van gezonde controlepersonen. De gemiddelde HDS score in de patiëntengroep was 5.1 ± 3.5 (maximum score 16) en in de controlegroep 13.0 ± 2.4 ($p< 0.0001$). Tevens concludeerden we dat de HDS van aanvullende waarde is bij patiënten met een normale Mini Mental State Examination (MMSE) score.

In hoofdstuk 3 testten we de hypothese dat een klinische neurofysiologische test behulpzaam zou kunnen zijn om patiënten met witte stofafwijkingen op te sporen. De late responsies die worden opgewekt door het zogenoemde "Auditieve Oddball paradigma" zijn gerelateerd aan cognitieve processen[4]. Het is reeds aangetoond dat de latentietijden van de N2 en van de P3 verlengd zijn bij patiënten met de ziekte van Alzheimer, de ziekte van Parkinson, de ziekte van Huntington, de ziekte van Binswanger en een depressieve stoornis[5-7]. Een beperkt aantal studies heeft het Auditieve Oddball paradigma onderzocht in pati-

enten met subcorticale ischemische veranderingen als leukoaraiosis en lacunaire infarcten[6,8-11]. Deze studies gebruikten echter, óf een definitie van cognitieve achteruitgang die gebaseerd was op de DSM-IV criteria voor de ziekte van Alzheimer[12] óf cognitieve testen die niet nader werden besproken. Bovendien werd alleen de P3 potentiaal in deze studies geanalyseerd. Wij onderzochten of de verschillende deflecties van de "event-related" (gebeurtenis-gerelateerde) potentiaal opgewekt door het Auditieve Oddball paradigma patiënten met cognitieve achteruitgang ten gevolge van witte stofafwijkingen kunnen onderscheiden van gezonde controlepersonen in een vroege fase van de ziekte. Wij toonden aan dat de N2 latentietijd statistisch significant verlengd is in de patientengroep in vergelijking met de controlegroep (254.6 ± 25.1 ms versus 235 ± 28.6 ms, p = 0.001), terwijl de latentietijden van de P3 potentiaal niet statistisch significant verschillend waren. De piek-piek amplitude gemeten van de N2 naar de P3 potentiaal was statistisch significant verlaagd in de patiëntengroep vergeleken met de controlegroep (11.5 ± 7.0 μV versus 15.4 ± 9.4 μV, p = 0.02). Aangetoonde witte stofafwijkingen met MRI zijn niet gecorreleerd aan de N2 latentietijden (r = -0.255, p=0.3). De resultaten tonen aan dat de latentietijd van het N2 complex langer is en de piek-piek amplitude van de N2 naar de P3 potentiaal lager is in patiënten met cognitieve achteruitgang ten gevolge van witte stofafwijkingen vergeleken met gezonde controlepersonen.

Aantasting van de kleine cerebrale vaten ("small-vessel disease") resulteert in witte stofafwijkingen en lacunaire infarcten. Hypertensie is de belangrijkste risicofactor voor deze afwijkingen, terwijl de relatie met diabetes mellitus (DM) veel minder duidelijk is. Vanwege de hoge prevalentie van zowel DM als witte stofafwijkingen bij de oudere patiënt onderzochten wij de relatie tussen DM en deze vasculaire afwijkingen.

In hoofdstuk 4 verrichtten wij een systematisch onderzoek van studies die de relatie tussen DM en structurele afwijkingen middels beeldvorming van de hersenen hebben onderzocht. Het is bekend dat DM een risicofactor is voor een beroerte in het verzorgingsgebied van de grote bloedvaten en dat het risico bij patiënten met DM verdubbeld tot verdrievoudigd is. Het is onduidelijk of DM een risicofactor is voor aantasting van de kleine cerebrale bloedvaten, wat leidt tot witte stof afwijkingen en lacunaire infarcten. In dit systematisch onderzoek werden de beschikbare data geanalyseerd met betrekking tot cerebrale afwijkingen bij patiënten met DM die zichtbaar zijn op computer tomography (CT) of magnetic resonance imaging (MRI), zoals witte stofafwijkingen, atrofie en lacunaire infarcten. Ook werd gekeken naar de relatie tussen DM en cerebrale afwijkingen aangetoond met technieken als magnetic resonance spectroscopy (MRS), positron emission tomography (PET) en single-photon emission computer tomography (SPECT). Vervolgens werd het verband onderzocht tussen de

cerebrale afwijkingen en cognitieve prestaties, en tussen de cerebrale afwijkingen en relevante ziekte variabelen, zoals DM type, DM duur, leeftijd, bloeddruk, antidiabetische therapie en metabole controle. Beschikbare studies moesten voldoen aan tevoren gedefinieerde inclusie criteria: goed gedefinieerde uitkomstmaten, definitie van de vaststelling van DM en een populatiegrootte van tenminste 20 DM patiënten. Van de 55 geïncludeerde studies werden data verzameld over studie-opzet, DM type, medicamenteuze behandeling, geassocieerde comorbiditeit en de gebruikte beeldvorming met bevindingen. De methodologie van de studies met betrekking tot populatieselectie, het vaststellen van DM, schalen om afwijkingen op de beeldvormende technieken weer te geven en statistische analyses waren erg heterogeen. DM was geassocieerd met cerebrale atrofie in 8 van de 10 studies. In 8 van de 19 studies werd een associatie tussen DM en lacunaire infarcten gevonden. Wij vonden weinig aanwijzingen voor een relatie tussen DM en witte stofafwijkingen. PET en SPECT studies vonden regionale stoornissen in de cerebrale doorbloeding en in het cerebrale glucosemetabolisme. Geen van de studies heeft gekeken naar de relatie tussen cerebrale afwijkingen op de beeldvorming en cognitie, en gegevens over de relatie tussen ziektevariabelen (leeftijd, hypertensie, medicatie en DM instelling) en cerebrale afwijkingen waren beperkt. Wij concludeerden dat DM geassocieerd is met cerebrale atrofie en lacunaire infarcten, maar dat de associatie met witte stofafwijkingen onduidelijk is.

Hoofdstuk 5 beschrijft de resultaten van een cross-sectionele studie waarbij de studiepopulatie bestond uit een groep oudere DM type 2 patiënten, die onafhankelijk functioneren en een controlegroep. Associaties tussen DM met respectievelijk witte stofafwijkingen, lacunaire infarcten en cerebrale atrofie werden onderzocht. De DM patiënten werden onderverdeeld in patiënten met en zonder hypertensie om te beoordelen of hypertensie een belangrijke ziektevariabele is. Ook werden relaties met andere ziektevariabelen onderzocht. De studiepopulatie bestond uit 45 DM type 2 patiënten zonder hypertensie (gemiddelde leeftijd 73.2 ± 5.1 jaar, gemiddelde DM duur 16.7 ± 11.4 jaar), 45 DM type 2 patiënten met hypertensie (gemiddelde leeftijd 73.3 ± 5.9 jaar, gemiddelde DM duur 11.3 ± 9.1 jaar) en 44 controlepersonen (gemiddelde leeftijd 73.0 ± 5.3 jaar). Alle patiënten en controlepersonen ondergingen een MRI hersenen. Witte stofafwijkingen, cerebrale atrofie en mediotemporale atrofie werden gescoord met behulp van een gestandaardiseerde visuele schaal. Witte stofafwijkingen kwamen vaker voor in alle DM patiënten. Er was, echter, alleen een statistisch significant verschil met betrekking tot de diepe witte stofafwijkingen, terwijl er geen verschil werd gevonden voor periventriculaire witte stofafwijkingen. De atrofie scores waren hoger in de DM groep dan in de controlegroep, maar dit verschil was niet statistisch significant. De associatie tussen DM type 2 en diepe witte stofafwijkingen werd verder gesteund door statistisch signifi-

cante positieve correlatie coëfficiënten tussen ernst van de diepe witte stofafwijkingen en respectievelijk geglycosyleerd hemoglobine en DM duur. De resultaten van deze studie suggereren dat DM type 2 een onafhankelijke risicofactor is voor diepe witte stofafwijkingen in oudere patiënten.

Hoofdstuk 6 richt zich op het neuropsychologische profiel in DM type 2 patiënten die zelfstandig functioneren. Tevens werden correlaties onderzocht tussen cognitieve stoornissen en afwijkingen op de MRI hersenen, i.e. witte stofafwijkingen, lacunaire infarcten en atrofie. De DM type 2 patiënten hadden ten opzichte van de controlegroep beperkingen in alle cognitieve domeinen, behalve in het geheugendomein na correctie voor hypertensie. De aanwezigheid van periventriculaire witte stofafwijkingen was een onafhankelijke voorspeller voor het domein motorische snelheid, terwijl alle andere MRI maten niet onafhankelijk geassocieerd waren met cognitieve stoornissen. Er bestonden geen interacties tussen de verschillende MRI maten. Geglycosyleerd hemoglobine en DM duur waren significant geassocieerd met cognitieve stoornissen. De data van deze cross-sectionele studie tonen aan dat DM type 2 geassocieerd is met stoornissen in verschillende cognitieve domeinen, terwijl na controle voor hypertensie het geheugendomein niet meer statistisch significant verschillend was. Associaties tussen cognitieve stoornissen en MRI maten waren niet duidelijk, terwijl geglycosyleerd hemoglobine en DM duur wel statistisch significant geassocieerd waren met cognitieve stoornissen.

Discussie

Op basis van dit proefschrift kunnen 4 belangrijke conclusies worden getrokken. Ten eerste hebben we aangetoond dat de HIV dementie schaal (HDS) een sensitieve screeningstest is voor de detectie van cognitieve achteruitgang bij patiënten met witte stofafwijkingen, en behulpzaam zou kunnen zijn als screeningstest bij patiënten met vasculaire risicofactoren. Ten tweede hebben wij het Auditieve Oddball paradigma onderzocht in patiënten met cognitieve stoornissen door witte stofafwijkingen en hebben wij aangetoond dat de N2 latentietijd langer is en de piek-piek amplitude van de N2-P3 golf lager is in de patiëntengroep vergeleken met een gezonde controlegroep. Ten derde hebben we laten zien dat DM type 2 een onafhankelijke risicofactor is voor diepe witte stofafwijkingen in oudere zelfstandig functionerende DM type 2 patiënten. Tenslotte konden wij aantonen dat DM type 2 patiënten een globale cognitieve achteruitgang vertonen, waarbij het geheugendomein het minst is aangedaan, terwijl de correlaties van deze cognitieve stoornissen met witte stofafwijkingen, lacunaire infarcten en atrofie niet duidelijk is.

Aantasting van de kleine cerebrale vaten wordt beschouwd als een homogeen subtype van vasculair veroorzaakte cognitieve achteruitgang ("subcortical ischaemic vascular disease"). Deze conditie blijkt een frequente oorzaak te zijn voor cognitieve achteruitgang en wordt veroorzaakt door aantasting van de kleine arteriolen leidend tot witte stofafwijkingen en lacunaire infarcten in de subcorticale witte en grijze stof[13-15].

Cognitieve stoornissen veroorzaakt door witte stofafwijkingen en lacunaire infarcten beslaan een breed spectrum aan cognitieve disfunctie dat varieert van geringe, vaak onopgemerkte stoornissen tot een ernstig dementiesyndroom[16]. Het neuropsychologische profiel wordt gekenmerkt door vroege achteruitgang in de aandachts- en uitvoerende functies met psychomotore traagheid. Het episodische geheugen is relatief gespaard gebleven[13]. De subtiele klinische symptomen worden vaak niet herkend en worden door zowel patiënt als arts beschouwd als verschijnselen van normale veroudering. De meeste cognitieve screeningstesten, zoals de Mini Mental State Examination (MMSE), zijn niet sensitief genoeg om cognitieve stoornissen bij deze patiënten vast te stellen, omdat zij gericht zijn op herkenning van cognitieve achteruitgang zoals die voorkomt bij de ziekte van Alzheimer[17]. Vanwege het feit dat de aanwezigheid van witte stofafwijkingen een frequente oorzaak is van cognitieve stoornissen is behoefte aan een cognitieve screeningstest die de arts in staat stelt om herkenning van deze cognitieve stoornissen te vergemakkelijken.

Wij hebben aangetoond dat de HIV dementie schaal (HDS) de oudere patiënt met cognitieve achteruitgang ten gevolge van witte stofafwijkingen goed kan onderscheiden van normale controles. Ook was het verschil statistisch significant in een subanalyse bij patiënten met een MMSE score van 27 of hoger (normale score) (hoofdstuk 2). We kunnen echter niet uitsluiten dat de cognitieve stoornissen veroorzaakt waren in het kader van bijvoorbeeld de ziekte van Alzheimer. Patiënten met de ziekte van Alzheimer hebben doorgaans een andere klinische presentatie met vaak ook een lagere MMSE score. Onze bevindingen suggereren dat de HDS gebruikt kan worden als een cognitieve screeningstest bij patiënten met witte stofafwijkingen en van aanvullende waarde kan zijn bij patiënten met een normale MMSE score.

Het Auditieve Oddball paradigma is een klinisch neurofysiologische methode die een event-related potentiaal (ERP) creëert. Deze potentiaal bevat verschillende deflecties waarbij de hoogste amplitude gewoonlijk gemeten wordt bij ongeveer 300 milliseconden (P3)[4]. Deze late responsies zijn gerelateerd aan cognitieve processen[4]. De diagnostische waarde van deze ERP is in verscheidene studies onderzocht bij patiënten met dementie. Het dementiesyndroom was bij de meeste patiënten echter al in een vergevorderd stadium, terwijl juist een

vroege diagnose van belang is om de patiënt adequate zorg en therapie te kunnen bieden[5-7,18,19]. In dit proefschrift hebben we aangetoond dat de N2 latentietijd verlengd is en de piek-piek amplitude (N2-P3) verlaagd is bij patiënten met cognitieve stoornissen ten gevolge van witte stofafwijkingen (hoofdstuk 3). Eén van de studiebeperkingen is dat we geen patiënten met de ziekte van Alzheimer hebben geïncludeerd. Hoewel Goodin en Aminoff concludeerden dat de N1 latentietijd verlengd is bij patiënten met subcorticale dementie vergeleken met corticale dementie hebben wij geen verlengde N1 latentietijd gevonden in de patiëntengroep in vergelijking met de controlegroep[20]. De ziekte van de patiënten in de studie van Goodin en Aminoff was echter al ver voortgeschreden, terwijl in onze studie de patiënten cognitieve stoornissen vertoonden zonder te voldoen aan de criteria van een dementiesyndroom. Verdere studies zijn daarom ook noodzakelijk om de ERP van patiënten die zich bevinden in een vroeg stadium van de ziekte van Alzheimer te vergelijken met de ERP van patiënten met cognitieve stoornissen ten gevolge van witte stofafwijkingen. In een subgroep van patiënten bij wie een MRI was verricht konden wij geen relatie aantonen tussen de N2 latentietijd en de ernst van de witte stofafwijkingen of de aanwezigheid van lacunaire infarcten. Hoewel dit resultaat verklaard zou kunnen worden door een te kleine studiepopulatie, kan het ook suggereren dat het functionele verschil tussen de groepen niet veroorzaakt wordt door de MRI afwijkingen. Het ontbreken van een relatie is niet onverwacht, daar de klinische impact van de mate van witte stofafwijkingen eveneens onduidelijk is[21].

Het is bekend dat leeftijd en hypertensie geassocieerd zijn met witte stofafwijkingen in de hersenen. De associatie van diabetes mellitus (DM) met deze afwijkingen is echter veel minder duidelijk. In hoofdstuk 4 wordt een overzicht van de literatuur gegeven met betrekking tot de associatie van DM en stucturele cerebrale afwijkingen. CT en MRI studies tonen een associatie tussen DM en cerebrale atrofie en tussen DM en lacunaire infarcten. De associatie met witte stofafwijkingen is echter onduidelijk. Veel studies vertonen belangrijke methodologische tekortkomingen, zoals kleine studiepopulaties, onvermogen te corrigeren voor confounders, onduidelijke definities van DM type en DM vaststelling en het gebruik van methoden om afwijkingen te scoren die niet sensitief zijn[22-26].

Vanwege de inconsistenties en de methodologische tekortkomingen hebben wij een studie verricht die MRI afwijkingen bestudeert in een groep van oudere zelfstandig functionerende DM type 2 patiënten, gerekruteerd op de polikliniek interne geneeskunde (hoofdstuk 5). De resultaten die worden gepresenteerd in dit proefschrift tonen aan dat DM type 2 een onafhankelijke risicofactor is voor diepe witte stofafwijkingen. In tegenstelling tot veel andere studies bestaat onze studiepopulatie wel uit een goed gedefinieerde groep DM type 2 patiënten. Te-

vens is ook rekening gehouden met hypertensie daar dit een bekende vasculaire risicofactor is voor witte stofafwijkingen. Bovendien hebben wij voor het beoordelen van afwijkingen een semi-kwantitatieve schaal gebruikt. De meerderheid van de witte stof schalen die zijn gebruikt in voorgaande studies zijn eigenlijk ontwikkeld voor patiënten met cerebrovasculaire aandoeningen of vasculaire dementie. Deze schalen zijn relatief grof en ongevoelig. Hoewel deze schalen een adequaat onderscheid kunnen maken tussen patiënten met ernstige witte stofafwijkingen en subtiele afwijkingen zijn zij mogelijk niet sensitief genoeg om de kleinere verschillen in witte stofafwijkingen tussen DM patiënten en controlepersonen vast te stellen. Hoewel volumetrische schalen de meest gevoelige scoringsmethoden zijn werden deze in slechts enkele studies toegepast en werden in deze studies niet meer witte stofafwijkingen gevonden[27,28]. Methodologische tekortkomingen zijn eveneens aan te wijzen in deze studies, zoals geen onderscheid in DM type en geen vaststelling van confounders[27,28]. De resultaten met betrekking tot de associatie tussen DM en atrofie zijn redelijk consistent in de literatuur[23,26,29,30]. Ook wij vonden meer atrofie, maar dit verschil was niet statistisch significant. Dit kan het gevolg zijn van de gebruikte visuele scoringsmethode. Echter een studie die visuele schalen heeft vergeleken met volumetrie concludeerde dat visuele schalen klinisch bruikbaar zijn en nauwkeuriger kunnen zijn dan volumetrie[31]. De prevalentie van lacunaire infarcten was laag in onze studiepopulatie. Deze bevinding kan het gevolg zijn van het feit dat wij poliklinische patiënten hebben onderzocht die nog zelfstandig functioneren en een polikliniek bezoeken, m.a.w. deze patiënten kunnen zich bevinden in een vroeg stadium van cerebrovasculaire ziekte.

Tenslotte, DM type 2 is een veel voorkomende aandoening bij de oudere patient en is geassocieerd met cognitieve stoornissen en dementie[32-35]. De studiepopulaties waren echter meestal klein en vaak werd er geen rekening gehouden met verschillen in opleiding, leeftijd, geslacht en de aanwezigheid van hypertensie[32]. Bovendien waren de cognitieve testen in de studies veelal beperkt en werden in populatie studies meestal globale cognitieve testen gebruikt, zoals de MMSE. Wij hebben het neuropsychologische profiel onderzocht in een groep oudere DM type 2 patiënten en hebben correlaties van cognitieve stoornissen met MRI afwijkingen onderzocht (hoofdstuk 6). De hypothese werd getoetst dat cognitieve achteruitgang in DM type 2 patiënten voornamelijk wordt veroorzaakt door witte stofafwijkingen en lacunaire infarcten. Toen wij onze studie begonnen was de associatie tussen cognitieve stoornissen en MRI bevindingen bij DM type 2 onbekend en nooit eerder beschreven. Wij hebben een uitvoerige neuropsychologische testbatterij gebruikt en hebben associaties met MRI afwijkingen onderzocht om het pathologische mechanisme dat ten grondslag ligt aan de cognitieve stoornissen nader te onderzoeken. Wij hebben aangetoond dat alle scores op screeningstesten en neuropsychologische testen

slechter waren in DM type 2 patiënten vergeleken met controlepersonen, maar dat na correctie voor hypertensie de verschillen voor het geheugen domein niet meer statistisch significant verschillend waren. Dit resultaat werd ook gevonden in andere studies[32]. Hoewel we aangetoond hebben dat DM type 2 een onafhankelijke risicofactor is voor diepe witte stofafwijkingen vonden we echter geen onafhankelijke relatie tussen diepe witte stofafwijkingen en cognitieve stoornissen in de DM populatie. Alleen periventriculaire witte stof afwijkingen waren geassocieerd met het domein motorische snelheid, terwijl geen van de andere MRI maten geassocieerd was met cognitieve stoornissen. Interacties tussen de verschillende MRI maten waren ook niet aanwezig. Eén van de beperkingen van deze studie is dat we visuele schalen hebben gebruikt om witte stofafwijkingen en atrofie te scoren. Volumetrische technieken zouden misschien wel significante correlaties hebben aangetoond. Wij hebben geconcludeerd dat de associatie van cognitieve achteruitgang met MRI afwijkingen onduidelijk is bij DM type 2 patiënten. De cognitieve stoornissen bij DM type 2 patiënten kunnen verklaard worden door zowel vasculaire afwijkingen als atrofie en mogelijk spelen andere nog onbekende factoren ook een rol.

Klinische implicaties

1. *De HIV dementie schaal kan worden gebruikt als screeningstest bij patiënten met risicofactoren voor witte stofafwijkingen.*

De aanwezigheid van witte stofafwijkingen en lacunaire infarcten is een frequente oorzaak voor cognitieve achteruitgang. De veelvuldig gebruikte Mini Mental State Examination (MMSE) als meetinstrument is niet sensitief genoeg om cognitieve stoornissen in deze patiënten te detecteren, omdat zij gericht is op herkenning van cognitieve stoornissen zoals die voorkomen bij de ziekte van Alzheimer. De resultaten van dit proefschrift tonen dat de HIV dementie schaal bruikbaar kan zijn als screeningstest voor cognitieve stoornissen ten gevolge van witte stofafwijkingen bij oudere patiënten.

2. *Onderzoek van cognitieve functies zou standaard moeten worden uitgevoerd bij diabetes patiënten*

Polyneuropathie, retinopathie, nefropathie en perifere vaatziekte zijn belangrijke complicaties van diabetes mellitus. Patiënten worden routinematig gecontroleerd op het voorkomen van deze lange termijn complicaties. De resultaten van dit proefschrift tonen aan dat diabetes mellitus type 2 ook een risicofactor is voor cognitieve functiestoornissen. Regelmatig onderzoek naar het cognitief functioneren zou dan ook onderdeel moeten zijn van het screeningsprogramma om lange termijn complicaties op te sporen.

Aanbevelingen voor toekomstig onderzoek

1. De HIV dementie schaal (HDS) is in staat om cognitieve stoornissen te detecteren in patiënten met witte stofafwijkingen en zou daarom gebruikt kunnen worden in klinische trials of bij patiënten met een verhoogd risico. Patiënten met "mild cognitive impairment" (MCI) of met vroege symptomen van de ziekte van Alzheimer zijn echter niet geïncludeerd. Gewoonlijk vertonen deze patienten een andere klinische presentatie en hebben zij lagere MMSE scores. Patienten met MCI en een normale MMSE zouden theoretisch gezien slecht kunnen scoren op de HDS. De HDS moet nader onderzocht worden bij patiënten met MCI en de ziekte van Alzheimer met en zonder vasculaire risicofactoren.

2. De N2 latentietijd is langer en de piek-piek amplitude van de N2 –P3 golf is lager van de auditief opgewekte event-related potentiaal bij een patiëntenpopulatie met cognitieve achteruitgang ten gevolge van witte stofafwijkingen vergeleken met gezonde controlepersonen. Correlaties met witte stofafwijkingen konden echter niet worden aangetoond. Verder onderzoek is nodig om het onderliggende pathofysiologisch mechanisme te ontrafelen van de verlengde N2 latentietijd. Tevens is het belangrijk om de bevindingen te vergelijken met patienten met de ziekte van Alzheimer.

3. De bevindingen met betrekking tot de correlaties tussen DM type 2, cognitieve stoornissen en MRI afwijkingen zijn gebaseerd op een geselecteerde populatie. Hoewel de resultaten gelden voor een poliklinische populatie kunnen we deze bevindingen niet extrapoleren naar de algemene DM type 2 populatie. Bovendien gaat het om een cross-sectionele studie. Om causaliteit aan te tonen tussen MRI afwijkingen en cognitieve stoornissen zou de opzet van de studie een longitudinaal karakter moeten hebben en zouden de DM patiënten bij aanvang van de studie geen cognitieve stoornissen moeten hebben. Vervolgens zouden ze regelmatig onderzocht moeten worden met gestandaardiseerde neuropsychologische testbatterijen en een MRI. Vanwege het feit dat de MRI afwijkingen relatief subtiel zijn in DM patiënten zouden sensitieve schalen moeten worden gebruikt om afwijkingen weer te geven.

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