MRI correlates of vascular cerebral lesions and cognitive impairment

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and cognitive impairment

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List of abbreviations

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General introduction

1.1 Vascular dementia

Dementia is a decline in cognitive function to such extent that daily living is impaired. Vascular lesions in the cerebrum can lead to this syndrome (vascular dementia, VaD) and is believed to be the most prevalent form after Alzheimer’s disease (AD). The incidence rates of VaD are highly dependent on age and vary between 1.5 and 3.3 per 1000 person-years in elderly populations. Typically, the clinical course is described by a stepwise progression. Cognitive deficits vary according to the site of the lesions but memory dysfunction is not the most prominent feature in most cases. Mental slowing and executive function disturbances are more pronounced. Focal neurological deficits, such as motor and sensory disturbances, can accompany the cognitive deficits. Ischemic vascular lesions leading to VaD are large vessel infarctions, lacunar infarctions and white matter hyperintensities (WMH).

A.  B.  C.

Figure 1. A. FLAIR image of a left medial temporal lobe infarction. B. T1-weighted image of lacunar infarctions. C. FLAIR image of confluent WMH.

1.2 White Matter Hyperintensities

WMH are located in the subcortical white matter, where myelated fibers form connecting tracts between cortical and subcortical gray matter structures. Subtotal ischemic damage can lead to dysfunction of the fibers and cognitive decline. The exact mechanisms are still unknown but disease of the small perforating vessels has been recognized as a causative factor. Older age and hypertension are among the most reported risk factors for small vessel disease. The dementia syndrome is of subcortical type and WMH can be visualized by computed tomography (CT) and especially magnetic resonance imaging (MRI). The use of cerebral MRI scanning has become more available, and has lead to more knowledge on the
Chapter 1

incidence, radiological features, risk factors, and clinical implications of WMH. Not much is known at this time on the progression of the disease. However, longitudinal data are now becoming available.\textsuperscript{13}

1.3 Aim of thesis

The aim of this thesis was twofold. First, in the last decade of the previous century a renewed interest in VaD rose among researchers. This was partly due to the fact that neuroimaging became more widely available and vascular lesions were visualized with high resolution. At first, relationship of the lesions with clinical features was hard to establish and only advancing age and hypertension were consistently found to be correlated. Among the reasons could be the heterogeneity of the lesions (cortical infarcts, lacunar infarcts, and WMH) and the fact that the vascular lesions can occur in any part of the brain, leading to a variety of (cognitive) symptoms. In general, dementia is considered a slowly progressive disease due to degeneration of neuronal cells, with several possible causes. VaD is not necessary slowly progressive (but can show a stepwise decline in cognitive function), and this might influence outcome of studies to the relationship between vascular disease and dementia. In this thesis, we set out to describe and discuss the different radiological appearances of vascular brain disease, and their relationship to vascular dementia and general vascular risk factors.

Second, we focus on WMH, the subcortical subtotal vascular lesion type. They are a common observation in the elderly. A review published in 1995 on this subject reported an association with age, selective cognitive dysfunction and future stroke.\textsuperscript{14} Pathogenesis, pathological substrate and clinical significance were not completely understood. Furthermore, data on progression of the lesions over time were not yet available and prognostic value was unclear.\textsuperscript{15} Later, the profile of the cognitive deficits became more clear with mainly attention, executive functions, and visuospatial skills affected but again, longitudinal data were lacking.\textsuperscript{16} We set out to establish some methodological issues of WMH assessment (the correlation of WMH, as assessed with several methods, with clinical information and measurement of lesion change in time with different visual scales and a volumetric method) and correlation of WMH with longitudinal data (conversion from mild cognitive impairment (MCI) to AD).

1.4 Outline of thesis

Chapter 2.1 is an overview of the possible applications of neuroimaging in VaD. Also, different lesions and underlying diseases are discussed. In chapter 2.2 the radiological part of the NINDS-AIREN criteria and its interobserver variability are investigated. Use of different MRI
General introduction

sequences for the detection of lesions in the thalamus, known for their effect on cognition, is evaluated in chapter 2.3.

Chapter 3 focuses on the radiological features of WMH. Impact of scoring method on correlations with clinical characteristics (chapter 3.1) and on the detection of WMH progression in time (chapter 3.2) is described.

In chapter 4, the radiologically assessed vascular lesions are correlated with vascular risk factors, symptoms and signs. Chapter 4.1 describes the role of WMH in the conversion from amnestic mild cognitive impairment (MCI) to Alzheimer’s disease and in chapter 4.2 risk factor profiles for large- and small vessel disease are assessed. Interpretation and discussion of the results of this thesis, as well as future directions, are presented in chapter 5. Chapter 6 consists of a brief summary.
Chapter 1

References

Chapter 2

Characteristics of vascular dementia on imaging
Chapter 2.1

MRI and CT in the Diagnosis of Vascular Dementia

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Chapter 2

Abstract

Neuroimaging is necessary to demonstrate cerebrovascular disease (CVD) and is therefore an important examination in vascular dementia (VaD) and vascular cognitive impairment (VCI). MRI is preferred over CT because multiple planes and sequences are needed to assess various types of pathology in relevant regions. These protocols allow differentiation of VaD from other forms of dementia and sometimes identify specific underlying disorders. Different diagnostic criteria for VaD exist but the NINDS-AIREN criteria are widely used in controlled clinical trials in VaD. These criteria have relatively low sensitivity but are highly specific and include radiological requirements. The radiological criteria have poor interobserver agreement. In general, the radiological portion of the diagnostic criteria for VaD needs revision and refinement to include bone fide cases of VaD not currently accepted by imaging rules, and for the early detection of patients with VCI.
Characteristics of vascular dementia on imaging

Introduction

Dementia is rapidly becoming a major health care problem. Despite progress in the treatment of dementia, broader knowledge is needed for the development of more effective agents. Significant effort has resulted in clinical trials to investigate possible therapeutic agents on different groups of dementia patients.\textsuperscript{1-3} It is, therefore, important to be able to differentiate well between the different causes of dementia.

In the past, brain imaging—computerized tomography (CT) and magnetic resonance imaging (MRI)—was regarded as an optional examination in patients with cognitive decline. It was used mainly to exclude surgically treatable causes of cognitive impairment, such as subdural hematoma, hydrocephalus and mass lesions. Recently, the focus has shifted from its use to rule out certain aetiologies, towards a supporting role for the clinical diagnosis with positive imaging findings.\textsuperscript{4} For all of the above reasons, it now appears desirable to obtain a structural brain scan at least once during the work-up of patients with cognitive decline.

CT or MRI

In the setting of a patient with cognitive decline, CT will generally suffice to rule out surgically treatable disorders. However, MRI is preferred to demonstrate specific types of pathologies, such as regionally specific atrophy, e.g. of the hippocampus in Alzheimer’s disease (AD), and presence of relevant vascular lesions. Reasons include its ability to reveal more detail and the greater capabilities to show subtle lesions in regions that are difficult to image with CT, such as the temporal lobe, but also the possibility to scan in different directions (e.g. coronal and sagittal).

MRI protocols

When the MRI scan is performed in a patient suspected of dementia, application of contrast material is not routinely indicated. The scanning protocol should include a coronal (3D) T1-weighted series for the evaluation of the medial temporal lobe (MTL) and other regional patterns of atrophy. If cortical infarctions and lacunes are present, these can be seen using this sequence. In addition, axial Fluid-Attenuated Inversion Recovery (FLAIR) or dual-echo Turbo Spin Echo
(TSE) images will reveal cortical infarcts and hypoxic/ischemic pathology (white matter hyperintensities or WMH).

Figure 1. A. Infarction of the medial temporal lobe in the left hemisphere, FLAIR image. B. Infarction in the parieto-temporal association area, FLAIR image.

Figure 2. A. Severe white matter hyperintensities in a patient with vascular dementia on FLAIR image. B. Extensive widened perivascular spaces, seen on FLAIR image.

The use of FLAIR has the advantage of suppressing cerebrospinal fluid (CSF) signal, allowing a simple distinction of lacunes and perivascular spaces from WMH, both of which are
Characteristics of vascular dementia on imaging

bright on standard T2-weighted (T)SE images. However, the reduced sensitivity of FLAIR in infratentorial lesions appears to extent to the diencephalon, and FLAIR should not be used in isolation since thalamic lesions may easily be missed. It may replace a proton-density type of image. Finally, axial T2* gradient echo images are useful to detect hemorrhages (microbleeds) and calcifications.

Vascular dementia

In vascular dementia (VaD), brain imaging can greatly add to the accuracy of the diagnosis and is the only way to determine the vascular cause of the dementia with certainty in vivo. Following the successful medication trials for AD, a number of controlled clinical trials were also completed for patients with VaD. A renewed interest in assuring a diagnosis of certainty has therefore developed. The most commonly used criteria for VaD in clinical trials require demonstration of lesions of cerebrovascular disease (CVD) with brain imaging; MRI being preferred over CT in patients with suspected VaD. It distinguishes better between ‘pure’ VaD and other forms of dementia, such as ‘mixed’ dementia (AD+CVD), as well as distinguishing between the different causes of VaD (e.g. CADASIL). Subcortical vascular lesions can be seen with higher sensitivity and therefore the severity of WMH can be better assessed. MRI is also superior in detecting the presence of microbleeds.

Overview of diagnostic criteria for VaD

Numerous sets of criteria for VaD have been proposed. The most widely used criteria are: DSM-IV, ADDTC, NINDS-AIREN, HIS and ICD-10. The DSM IV and the ICD-10 criteria do not require brain imaging, whereas the ADDTC and NINDS-AIREN do require such direct evidence. The DSM-IV criteria are the most liberal, leading to high sensitivity but low specificity. On the other hand, the NINDS-AIREN are most specific but are not as sensitive. The ADDTC and HIS have intermediate sensitivity and specificity. The NINDS-AIREN criteria for VaD are the most recent and are widely used in randomized clinical trial on VaD at this time.
Chapter 2

Characteristics of NINDS-AIREN criteria for vascular dementia

The NINDS-AIREN criteria for VaD have three main features: a patient must be demented, have evidence of CVD on clinical examination and imaging, and fulfil a temporal relationship between onset of dementia relevant CVD. In order to assess the presence of CVD on the brain scan, a number of radiological features have been listed. In short, this radiological part of the criteria prescribes that vascular lesions should fulfil criteria for topography as well as severity. In case of large vessel stroke, the locations that meet criteria are: bilateral anterior cerebral artery, paramedian thalamic, inferior medial temporal lobe, parietotemporal and temporo-occipital association areas and angular gyrus, superior frontal and parietal watershed areas, as long as they involve the dominant hemisphere. In case of small vessel disease, lesions that fulfil criteria are: WMH more than 25% of the total white matter, multiple basal ganglia and frontal white matter lacunes and bilateral thalamic lesions. However, further specifications are missing and interobserver agreement is low, even after operationalization; further work is needed to increase the applicability of these criteria.12

Territorial infarctions

In VaD, cognitive impairment may result from large or small vessel disease. Following stroke localized in eloquent brain areas, dementia may emerge, especially when located in the dominant hemisphere. The clinical characteristics may indicate the location, but MRI and CT provide in vivo evidence for infarction, for example, in the medial temporal lobe. Criteria for VaD require stroke(s) in specific areas that can be easily depicted using neuroimaging. In selected cases, MR angiography (MRA) can be useful in the diagnosis in case of large vessel stroke.

Findings in CADASIL

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) can be diagnosed when a mutation in the NOTCH 3 gene on chromosome 19 is demonstrated. The diagnosis can also be made with typical pathological findings in skin or brain biopsies. When this information is not available, radiological criteria for
probable CADASIL have been shown to be quite sensitive and accurate. Early MRI findings include extensive symmetrical WMH involving the U-fibers at the vertex and the temporal pole; in later stages, involvement of the corpus callosum, external capsule, and development of multiple small lacunes and microbleeds may develop.\textsuperscript{13}

**Findings in amyloid angiopathy**

Dementia is present in approximately 40% of cases of cerebral amyloid angiopathy (CAA). The clinical presentation of CAA is often with a lobar hemorrhage. The radiological key feature of CAA is the presence of microbleeds that can best be evaluated with gradient-echo scanning. This sequence may show multiple residues of petechial hemorrhages throughout the brain.\textsuperscript{14}

**Conclusions**

Brain imaging is a crucial component in the evaluation of patients with VaD and VCI. MRI has a number of advantages over CT and currently is the examination of choice. The radiological portion of the NINDS-AIREN criteria has poor interobserver agreement and excludes some cases. Therefore, these radiological criteria need revision and refinement to include bone fide cases of VaD not currently accepted by imaging rules, and for the early detection of cases (e.g. vascular cognitive impairment).
Chapter 2

References

Chapter 2.2

Operational Definitions for the NINDS-AIREN Criteria for Vascular Dementia
An Interobserver Study

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Abstract

Vascular dementia (VaD) is thought to be the most common cause of dementia after Alzheimer’s disease. The commonly used International Workshop of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria for VaD necessitate evidence of vascular disease on CT or MRI of the brain. The purposes of our study were to operationalize the radiological part of the NINDS-AIREN criteria and to assess the effect of this operationalization on interobserver agreement.

Six experienced and 4 inexperienced observers rated a set of 40 MRI studies of patients with clinically suspected VaD twice using the NINDS-AIREN set of radiological criteria. After the first reading session, operational definitions were conceived which were subsequently used in the second reading session. Interobserver reproducibility was measured by Cohen’s $\kappa$.

Overall agreement at the first reading session was poor ($\kappa=0.29$) and improved slightly after application of the additional definitions ($\kappa=0.38$). Raters in the experienced group improved their agreement from almost moderate ($\kappa=0.39$) to good (0.62). The inexperienced group started out with poor agreement ($\kappa=0.17$) and did not improve ($\kappa=0.18$). The experienced group improved in both the large- and small-vessel categories, whereas the inexperienced group improved generally in the extensive white matter hyperintensities categories.

Considerable interobserver variability exists for the assessment of the radiological part of the NINDSAIREN criteria. Use of operational definitions improves agreement but only for already experienced observers.
Introduction

Vascular dementia (VaD) is thought to be the most common cause of dementia after Alzheimer’s disease. The reported incidence rates of VaD vary between 1.5 and 3.3 per 1000 person-years in elderly populations. Incidence rates are highly dependent on age. The prevalence of VaD ranges from 1.0% in a population cohort \( \geq 55 \) years of age to 4.2% in a cohort of subjects \( \geq 71 \) years of age. Differences in diagnostic criteria may partly explain this variability. In 1993, the International Workshop of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) reported diagnostic criteria for the diagnosis of VaD for research studies. Criteria were formulated for the different parts of the diagnostic process (history and physical, radiological, and pathological examination) to classify patients as having possible, probable, and definite VaD. The NINDS-AIREN criteria state that the diagnosis of probable VaD cannot be made without some form of radiological assessment. Consequently, a list of lesions associated with VaD was included in the NINDSAIREN criteria. Recently, a vast interest in clinical trials on the efficacy of cholinesterase inhibitors and other drugs for VaD has emerged, and the NINDS-AIREN criteria with their radiological definitions are being used on a large scale in these trials. However, clear operational definitions on how to use and interpret the radiological criteria are lacking. Only a few interobserver studies of the NINDS-AIREN criteria have been published. In 2 of these studies, both clinical and radiological diagnoses were studied together. The agreement between raters was moderate to good (\( \kappa = 0.42 \) in the first study mentioned, 0.46 < \( \kappa < 0.72 \) in the second study). It was suggested that a cause of the disappointing results could have been the difference in interpretation of the radiological criteria by the different raters. In this study, we examined the interobserver agreement of the radiological part of the NINDS-AIREN criteria and the effect of subsequently formulated operational definitions on the level of agreement in patients with clinical signs of VaD. Second, we investigated whether experienced and inexperienced raters would benefit equally from such definitions.

Methods

MRI Studies

For this study, we selected MRI studies of patients with dementia and clinical signs of cerebrovascular disease. The selection was done to get 10 cases of large-vessel disease and 30
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cases of small-vessel disease, reflecting the distribution in a recently completed trial on VaD.9
Two authors who did not participate in the interobserver studies (E.C.W. van S., F.B.) performed
the selection by applying the NINDS-AIREN criteria to the MRI scans. Based on the experience
of an ~50% rejection rate in the above-mentioned trial and to have a balanced distribution in the
study sample, MRI studies were selected in a way that we expected half of the scans to be rated
as having sufficient abnormalities to fulfil the NINDS-AIREN criteria. It should be noted that the
percentage of cases fulfilling such criteria is not reflective of the general population of patients
clinically suspected of having VaD. In addition to the 40 scans, we selected 10 scans to be scored
during the first assessment and to be used for consensus reading and formulation of definitions.
All MRI studies consisted of axial T2, axial fluid-attenuated inversion recovery, and axial and
coronal T1 series using 5-mm slices and 1x1-mm pixel size.

Study Design

Ten raters with different levels of experience evaluated the 40 selected MRI studies in
2 consecutive reading sessions. The decision to use the same data set twice (rather than having 2
independent data sets) was based on the expectation that this would preclude variability to be
introduced by unbalanced matching in the distribution of cases over the various subcategories of
the NINDS-AIREN criteria. On the other hand, we expected no bias from a learning effect when
the same samples were rated twice because the second rating was done with a set of operational
criteria developed from the additional training set of 10 scans; if any, this design would tend to
maintain rather than to reduce interobserver variability and therefore is slightly conservative. The
team of raters consisted of 10 physicians (2 radiologists, 4 neurologists, 3 research fellows, 1
neurology resident). Six had extensive experience in the evaluation of vascular lesions on MRI
scans in clinical settings or in population-based studies on aging and dementia. The other 4 had
experience in assessing MRI scans of the brain, but they had never assessed vascular lesions
systematically on a large scale. The raters were blinded to all clinical and personal information.
During the first reading session, all raters individually assessed the scans
### Characteristics of vascular dementia on imaging

**Table 1.** Scoring form of brain imaging lesions associated with VaD

<table>
<thead>
<tr>
<th>1. TOPOGRAPHY</th>
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<th>both</th>
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<tbody>
<tr>
<td><strong>Radiologic lesions associated with dementia</strong></td>
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<td><em>include ANY of the following or combinations thereof:</em></td>
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<tr>
<td>A. Large vessel strokes in the following territories:</td>
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<td>Anterior cerebral artery</td>
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<td>Posterior cerebral artery, including:</td>
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<td>Paramedian thalamic infarctions</td>
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<td>Inferior medial temporal lobe lesions</td>
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<td>Association areas:</td>
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<tr>
<td>Parietotemporal</td>
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<td>Temporo-occipital</td>
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<td>Angular gyrus</td>
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<td>Watershed carotid territories:</td>
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<tr>
<td>Superior frontal</td>
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<tr>
<td>Parietal region</td>
<td></td>
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<tr>
<td>B. Small vessel disease:</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
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<tr>
<td>Multiple basal ganglia and frontal white matter lacunae</td>
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<tr>
<td>Extensive periventricular white matter lesions</td>
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<tr>
<td>Bilateral thalamic lesions</td>
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| 2. SEVERITY | | | | |
| *In addition to the above, relevant radiologic lesions associated with dementia include:* | yes | no |
| Large vessel lesions of the dominant hemisphere | | | | |
| Bilateral large-vessel hemispheric strokes | | | | |
| Leukoencephalopathy involving at least ¼ of the total white matter | | | | |

Do the radiological findings fulfil the radiological criteria for VaD? | yes | no |
Table 2. Operational definitions of the imaging guidelines of the NINDS-AIREN criteria for Vascular Dementia

TOPOGRAPHY

*Large vessel stroke:* Large vessel stroke is an infarction, defined as a parenchymal defect in an arterial territory, involving the cortical gray matter

1) Anterior cerebral artery (ACA): Only bilateral ACA infarcts are sufficient to meet the NINDS-AIREN criteria
2) Posterior cerebral artery (PCA): Infarcts in the PCA territory can only be included when they involve the following regions:
   a. Paramedian thalamic infarction: the infarct includes the cortical gray matter of the temporal/occipital lobe AND extends into the paramedian part (defined as extending to the third ventricle) of the thalamus; the extension may be limited to the gliotic rim of the infarct that surrounds the parenchymal defect
   b. Inferior medial temporal lobe lesions
3) Association areas: a medial cerebral artery (MCA) infarction needs to involve the following regions:
   a. Parietotemporal: the infarct involves both the parietal and temporal lobe (e.g. angular gyrus)
   b. Temporo-occipital: the infarct involves both the temporal and occipital lobe
4) Watershed carotid territories: A watershed infarction is defined as an infarct in the watershed area between MCA and PCA or between MCA and ACA, in the following regions:
   a. Superior frontal region
   b. Parietal region

*Small vessel disease:* Ischemic pathology resulting from occlusion of small perforating arteries may manifest itself as lacunes or white matter lesions. A lacune is defined as a lesion with CSF-like intensity on all sequences on MRI (water density on CT), surrounded by white matter or subcortical gray matter, larger than 2 mm. Care should be taken not to include Virchow-Robin spaces, which typically occur at the vertex and around the anterior commissure near the substantia perforata. Ischemic white matter lesions are defined as circumscribed abnormalities with high signal on T2-weighted images not following CSF signal (mildly hypodens compared to surrounding tissue on CT), with a minimum diameter of 2 mm.

1) Multiple basal ganglia and frontal white matter lacunes: The criteria are met when at least two lacunes in the basal ganglia region (including thalamus and internal capsule) AND at least two lacunes in the frontal white matter are present.
2) Extensive periventricular white matter lesions: lesions in the white matter, abutting the ventricles and extending irregularly into the deep white matter, or deep/subcortical white matter lesions. Smooth caps and bands by themselves are not sufficient. Gliotic areas surrounding large vessel strokes should not be included here
3) Bilateral thalamic lesions: To meet the criteria, at least one lesion in each thalamus should be present.
Characteristics of vascular dementia on imaging

SEVERITY

1) **Large vessel disease of the dominant hemisphere**: If there is a large vessel infarct as defined above, to meet the criteria it has to be in the dominant hemisphere. In the absence of clinical information, the left hemisphere is considered the dominant one.

2) **Bilateral large vessel hemispheric strokes**: One of the infarcts should involve an area listed under topography but is in the non-dominant hemisphere, while the one in the dominant hemisphere does not meet the topography criteria.

3) **Leukencephalopathy involving at least ¼ of the total white matter**: Extensive white matter lesions are considered to involve ¼ of the total white matter when they are confluent (grade 3 in the ARWMC scale) in at least two regions of the ARWMC scale and beginning confluent (grade 2 in the ARWMC scale) in two other regions.

Note: a lesion is considered confluent when larger than 20 mm or consists of two or more smaller lesions that are fused by more than connecting bridges.

**FULFILMENT OF RADIOLOGICAL CRITERIA FOR PROBABLE VaD**

1) **Large vessel disease**: both the “topography” and “severity” criteria should be met (a lesion must be scored in at least one subsection of both “topography” and “severity” category).

2) **Small vessel disease**: for white matter lesions, both the topography and severity criteria should be met (a lesion must be scored in at least one subsection of both “topography” and “severity” category); for multiple lacunes and bilateral thalamic lesions, only the topography criterion is sufficient.

in random order with only the aid of the table of radiological findings of the NINDS-AIREN criteria for VaD as stated in the original article. All images were presented to the readers on identical personal computers using a digital viewing program, allowing window and level adjustment. The readers were able to browse through the scans as often as they wanted; no time limits were set. Scoring consisted of 2 stages. First, lesions had to be identified and classified topographically on a scoring form (Table 1), divided into a section on large-vessel disease (strategic infarcts in certain anterior, middle, or posterior cerebral artery territories) and a section on small-vessel disease (lacunes, white matter hyperintensities, bilateral thalamic lesions).

Second, the topographical information had to be combined with severity criteria to decide whether the scan met the radiological criteria for VaD (final diagnosis). Subsequently, a joint consensus reading of the additional 10 scans was held, and operational definitions for scoring vascular lesions according to the NINDS-AIREN criteria were discussed. After consensus on a set of definitions was reached, a second reading of the 40 scans was performed the next day, again in random order, according to the newly formulated operational definitions (Table 2).

**Statistical Analysis**

We determined agreement between raters for the 2 reading sessions separately by Cohen’s κ for >2 raters. The weighted κ was not used because most scorings were
dichotomous and the different categories were not ordered. We did this using AGREE software (ProGAMMA), which also calculated standard error values. We determined $\kappa$ for presence of radiological evidence for probable VaD, presence of large-vessel disease, and presence of small-vessel disease. To test whether agreement between the first and second readings differed statistically, we determined $z$ values for the difference in $\kappa$ and used the corresponding probability value for testing. All scores were calculated for 3 groups: the whole group of raters ($n=10$), the group of experienced raters ($n=6$), and the group of inexperienced raters ($n=4$). A $\kappa$ between 0 and 0.2 refers to poor agreement; 0.2 to 0.4, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, good agreement; and 0.81 to 1.00, very good agreement.

### Results

Table 3 shows the results of the baseline readings. In 35.8% of all cases, a large-vessel infarction was scored; in 60.3% of cases, small-vessel disease was scored. This distribution was roughly as we expected. The percentage of cases in which the raters found vascular lesions that met the radiological criteria of the NINDS-AIREN was 41.3%, which again is in line with what we had anticipated. In Table 4, $\kappa$ is given for the various sections of the scoring separately.

At the first reading session, agreement in the group of inexperienced raters was generally less than the agreement in the group of experienced raters. This is also true for the assessment of the final diagnosis (Table 5). At the first reading session, mean $\kappa$ for the final diagnosis for all raters signifies fair agreement. After the first scoring, operational definitions were formulated in consensus (Table 2). During this consensus meeting, we identified the problems that had risen with the interpretation of the criteria. The meaning, exact location, and borders of a paramedian thalamic infarction were uncertain in our opinion. We had trouble interpreting the term “multiple basal ganglia and frontal white matter lacunes.” Questions that arose included, Are lacunes needed in both areas to meet the criteria? How many lacunes is “multiple” exactly? How big should an extensive periventricular white matter lesion be, and is a lesion considered only when directly abutting the ventricles? Should strokes in any area be considered in the bilateral large-vessel hemispheric strokes category, or only those strokes that are scored previously in the topography section? How can we approximate one fourth of the total white matter? We tried to address these questions in the operational criteria, leaving the original set of criteria fundamentally intact. Definitions were laid out for the different radiological types of vascular pathology, different regions of relevant strokes were defined, and for small-vessel...
Characteristics of vascular dementia on imaging

Table 3. Average number of times a lesion was scored by region (baseline scoring)

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Mean number of times a lesion was scored</th>
<th>SD</th>
<th>% of all scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA infarction</td>
<td>1.3</td>
<td>1.3</td>
<td>3.3</td>
</tr>
<tr>
<td>PCA infarction</td>
<td>7.3</td>
<td>7.9</td>
<td>18.3</td>
</tr>
<tr>
<td>MCA association area infarction</td>
<td>7.6</td>
<td>2.0</td>
<td>19.0</td>
</tr>
<tr>
<td>WSH infarction</td>
<td>5.8</td>
<td>2.9</td>
<td>14.5</td>
</tr>
<tr>
<td>Total large vessel stroke</td>
<td>14.3</td>
<td>6.9</td>
<td>35.8*</td>
</tr>
<tr>
<td>SVD1</td>
<td>16.6</td>
<td>11.0</td>
<td>41.5</td>
</tr>
<tr>
<td>SVD2</td>
<td>18.4</td>
<td>7.2</td>
<td>46.0</td>
</tr>
<tr>
<td>SVD3</td>
<td>3.9</td>
<td>2.9</td>
<td>9.8</td>
</tr>
<tr>
<td>Total small vessel disease</td>
<td>24.1</td>
<td>10.1</td>
<td>60.3*</td>
</tr>
<tr>
<td>SEV1</td>
<td>6.7</td>
<td>4.0</td>
<td>16.8</td>
</tr>
<tr>
<td>SEV2</td>
<td>0.4</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>SEV3</td>
<td>8.6</td>
<td>7.1</td>
<td>21.5</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td>16.5</td>
<td>8.5</td>
<td>41.3*</td>
</tr>
</tbody>
</table>

ACa: anterior cerebral artery, PCA: posterior cerebral artery, MCA: medial cerebral artery, WSH: watershed region, SVD1: multiple basal ganglia and frontal white matter lacunes, SVD2: extensive periventricular white matter lesions, SVD3: bilateral thalamic lesions, SEV1: large vessel lesion in dominant hemisphere, SEV2: bilateral large vessel strokes, SEV3: leukencephalopathy involving at least ¼ of the total white matter. *: Due to overlap in scores this figure is not just a summation of the sub-categories above.

Disease, numeric definitions were adopted. With respect to the leukencephalopathy, we agreed on quantification with the use of the age-related white matter changes (ARWMC) rating scale. In the severity section, we discussed dominance of hemispheres, and for practical reasons, the left hemisphere was considered dominant. In addition to describing the different parts of the diagnostic criteria, rules on how to combine these parts were added because we noticed differences in opinion during consensus reading. We agreed that a scan would meet the final diagnosis of VaD if both severity and topography criteria were met, with the exception of the bilateral thalamic lesions and multiple lacunes subcategories, which have no related severity criterion.

Table 4 shows that agreement generally increases, especially in the small-vessel category. To calculate significance of change in $\kappa$, $z$ values were calculated. For appreciation of
Table 4. Mean κ scores for first and second reading session by sub-category

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Reading session</th>
<th>κ of all raters (n = 10)</th>
<th>κ of experienced raters (n = 6)</th>
<th>κ of inexperienced raters (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>1</td>
<td>0.43</td>
<td>0.29</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.24</td>
<td>0.19</td>
<td>0.21</td>
</tr>
<tr>
<td>PCA</td>
<td>1</td>
<td>0.11</td>
<td>0.35</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.08</td>
<td>0.69</td>
<td>0.06</td>
</tr>
<tr>
<td>MCA</td>
<td>1</td>
<td>0.28</td>
<td>0.40</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.42</td>
<td>0.53</td>
<td>0.31</td>
</tr>
<tr>
<td>WSH</td>
<td>1</td>
<td>0.39</td>
<td>0.44</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.38</td>
<td>0.47</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean large vessel stroke</td>
<td>1</td>
<td>0.30</td>
<td>0.37</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.28</td>
<td>0.47</td>
<td>0.18</td>
</tr>
<tr>
<td>SVD1</td>
<td>1</td>
<td>0.13</td>
<td>0.30</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.21</td>
<td>0.46</td>
<td>0.04</td>
</tr>
<tr>
<td>SVD2</td>
<td>1</td>
<td>0.47</td>
<td>0.51</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.67</td>
<td>0.64</td>
<td>0.74</td>
</tr>
<tr>
<td>SVD3</td>
<td>1</td>
<td>0.38</td>
<td>0.56</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.25</td>
<td>0.56</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean small vessel disease</td>
<td>1</td>
<td>0.33</td>
<td>0.46</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.38</td>
<td>0.55</td>
<td>0.29</td>
</tr>
<tr>
<td>SEV1</td>
<td>1</td>
<td>0.48</td>
<td>0.48</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.37</td>
<td>0.68</td>
<td>0.13</td>
</tr>
<tr>
<td>SEV2</td>
<td>1</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.12</td>
<td>0.59</td>
<td>0.08</td>
</tr>
<tr>
<td>SEV3</td>
<td>1</td>
<td>0.36</td>
<td>0.53</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.62</td>
<td>0.69</td>
<td>0.55</td>
</tr>
</tbody>
</table>

ACA: anterior cerebral artery, PCA: posterior cerebral artery, MCA: medial cerebral artery, WSH: watershed region, SVD: small vessel disease, SVD1: multiple basal ganglia and frontal white matter lacunes, SVD2: extensive periventricular white matter lesions, SVD3: bilateral thalamic lesions, SEV1: large vessel lesion in dominant hemisphere, SEV2: bilateral large vessel strokes, SEV3: leukencephalopathy involving at least ¼ of the total white matter
Characteristics of vascular dementia on imaging

Table 5. Mean κ (standard error) and differences in mean κ of the final diagnosis

<table>
<thead>
<tr>
<th></th>
<th>All raters</th>
<th>Experienced raters</th>
<th>Inexperienced raters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean κ reading session 1 (SE)</td>
<td>0.29 (0.05)</td>
<td>0.39 (0.05)</td>
<td>0.17 (0.06)</td>
</tr>
<tr>
<td>Mean κ reading session 2 (SE)</td>
<td>0.38 (0.05)</td>
<td>0.62 (0.07)</td>
<td>0.18 (0.05)</td>
</tr>
<tr>
<td>Difference κ reading sessions 1 and 2</td>
<td>0.09</td>
<td>0.22</td>
<td>0.01</td>
</tr>
<tr>
<td>z-value</td>
<td>1.27</td>
<td>2.51</td>
<td>0.04</td>
</tr>
<tr>
<td>p-value</td>
<td>0.20</td>
<td>0.01</td>
<td>0.97</td>
</tr>
</tbody>
</table>

SE=standard error

large-vessel disease, z values indicated that none of these differences are statistically significant. For small-vessel disease, only the difference in scoring of the inexperienced raters in the small-vessel category showed statistically significant improvement (p=0.04). The mean κ for the final diagnosis for all raters at the second reading was slightly greater than at the first reading session (Table 5). For the experienced group, agreement rose to κ=0.62, but in the inexperienced group, it remained low. Only in the experienced group of raters did agreement improve significantly.

Discussion

We examined the interobserver agreement for the radiological assessment of the NINDS-AIREN criteria and quantified the added value of operational definitions. We found that overall agreement on the final diagnosis of VaD was only fair without guidelines, especially for inexperienced raters; this was true for the agreement in both the large- and small-vessel pathology categories. The large variability we found is in agreement with earlier studies on the
total set of criteria for VaD of the NINDS-AIREN and is in part the result of a lack of operational
definitions for the radiological criteria. Already at the first scoring, several problems with the
interpretation of those criteria arose. The weakest parts of the radiological criteria are those
related to small-vessel disease, for which the original publication provides no details. This is
especially unfortunate because these are the most prevalent types of pathology in patients with
VaD. The raters also experienced difficulties in combining the individual parts of the criteria to
make the final decision of VaD or not. Confusingly, the original criteria by the NINDS-AIREN
list some of the topography characteristics in the severity section and vice versa. Additional
definitions will not solve this problem because they do not actually change the original criteria.
Taking this into consideration, we can explain low agreement. Our results suggest that a revision
of the original criteria might be needed in this respect. After the application of operational
definitions, agreement on the final diagnosis of VaD improved. However, stratified analysis
showed that this improvement in agreement was confined to the group of experienced raters with
a $\kappa$ of 0.62, indicating good agreement. This was due to improvements in both the large- and
small-vessel categories. In the group of inexperienced raters, agreement worsened in the large-
vessel category but improved in the small-vessel category. The latter was due mainly to an
increase in $\kappa$ by 0.35 to good agreement in the extensive white matter lesions subcategory.

The design of this study has some limitations. We did not have a gold standard. The
operational definitions were not validated against pathology or clinical findings but had the sole
purpose of being practical, usable, and able to improve standardization. In addition, the raters did
not have clinical information that could have contributed to the final diagnosis. In large clinical
trials in which the MRI scans are rated centrally, this information is also not available, but
agreement can be expected to improve in a clinical setting because previous studies show higher
$\kappa$ when this information is accessible by the readers. Another limitation of the study might have
been the use of $\kappa$. In some cases, expected agreement was high because of the very low
prevalence of some lesions, especially some stroke types (e.g., anterior cerebral artery,
paramedian thalamic infarctions). This results in low $\kappa$ even when agreement is high. Finally, the
operational definitions formulated are, of course, arbitrary and may be subject to further
amendments. However, the raters who formulated the criteria were the same raters who were
going to apply them in the second reading session. It can therefore be expected that they were
optimal for use in this interobserver study.

In conclusion, we found that the radiological criteria for the NINDS-AIREN criteria for
VaD are very complex. This makes these criteria less suitable for inexperienced raters and not
appropriate for routine diagnosis on the basis of a standard radiological report only. The
radiological criteria for the NINDS-AIREN criteria for VaD have suboptimal reproducibility.
Characteristics of vascular dementia on imaging

Use of operational criteria improves agreement to acceptable levels, but only in experienced readers. Because operational definitions essentially do not change the original criteria, a critical reappraisal of the NINDS-AIREN radiological criteria seems to be needed to further improve the quality of the criteria and interobserver agreement. We hope that our results set the stage for such an endeavour.
References

Chapter 2.3

Thalamic Lesions in Vascular Dementia

Low Sensitivity of Fluid-Attenuated Inversion Recovery (FLAIR) Imaging

A.J. Bastos Leite
E.C.W. van Straaten
P. Scheltens
G. Lycklama
F. Barkhof

Stroke 2004;35:415-419
Chapter 2

Abstract

The criteria of the National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) include thalamic lesions for the diagnosis of vascular dementia (VaD). Although studies concerning VaD and brain aging advocate the use of fluid-attenuated inversion recovery (FLAIR) or T2-weighted images (T2-WI) to detect ischemic lesions, none compared the sensitivity of these sequences to depict thalamic lesions.

We performed a blinded review of T2-WI and FLAIR images in 73 patients fulfilling the radiological part of the NINDS-AIREN criteria (mean age, 71 years; range, 49 to 83 years). This sample was drawn from a large multicenter trial on VaD and was expected to have a high prevalence of thalamic lesions. In a side-by-side review, including T1-weighted images as well, lesions were classified according to presumed underlying pathology.

The total number of thalamic lesions was 214. Two hundred eight (97%) were detected on T2-WI, but only 117 (55%) were detected on FLAIR ($\chi^2=5.1; P<0.05$). Although the mean size of lesions detected on T2-WI and not on FLAIR (4.4 mm) was significantly lower than the mean size of lesions detected on both sequences (6.7 mm) ($P<0.001$), 5 of the 29 lesions >10 mm on T2-WI were not visible on FLAIR. FLAIR detected only 81 (51%) of the 158 probable ischemic lesions and 30 (60%) of the 50 probable microbleeds.

FLAIR should not be used as the only T2-weighted sequence to detect thalamic lesions in patients suspected of having VaD.
Characteristics of vascular dementia on imaging

Introduction

In 1937, Papez\(^1\) described an anatomic circuit beginning and ending in the hippocampal formation possibly related to emotional experience. The projections of the Papez circuit involve the fornix, mammillary bodies, mamillothalamic tracts, anterior thalami, cingulate cortex, and cingulate bundles. The early notion that the Papez circuit subserves emotion has been abandoned and replaced by the proposal it is primarily involved in mnemonic functions. Lesions of the major components of this circuit have been shown to disrupt memory in humans, particularly those localized in the anterior group of thalamic nuclei.\(^2-6\) However, lesions affecting other thalamic components or connections not considered in the circuit, such as the mediodorsal (dorsomedial), intralaminar, and pulvinar nuclei or the thalamofrontal networks, may also cause cognitive deficits and marked behavioral changes.\(^2,7-11\) MRI and CT are crucial for the diagnosis of cerebrovascular diseases. The first studies using CT for the evaluation of brain lesions in patients with ischemic stroke confirmed the importance of thalamic infarctions as a cause of dementia.\(^12,13\) Therefore, the criteria of the National Institute of Neurological Disorders and Stroke (NINDS–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) include radiological evidence of thalamic lesions for the diagnosis of probable vascular dementia (VaD).\(^14\) Moreover, a single thalamic infarction may induce VaD.\(^15\) MRI studies concerning VaD and brain aging advocate the use of fluid-attenuated inversion recovery (FLAIR) or T2-weighted images (T2-WI) to detect and characterize brain abnormalities.\(^16-18\) However, to our knowledge no comparative study was performed to assess which MRI sequence yields the highest sensitivity for thalamic lesions. In this study we sought to compare the sensitivity of each of these sequences to depict thalamic lesions in patients with VaD.

Subjects and Methods

Patients

The subjects were derived from cases belonging to the VantagE study, a multicenter, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with VaD. For the present study we selected a sample of 73 patients (mean age, 71 years; range, 49 to 83 years) fulfilling the radiological part of the NINDS-AIREN criteria.\(^14\) On the basis of earlier central reading of the images for trial inclusion, we knew that approximately
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75% of the current sample might be expected to have either unilateral or bilateral focal thalamic lesions. To avoid any clinical bias, we were blinded to all clinical and center data of the patients.

MRI Technique

The patients were scanned on different scanners operating from 0.5 to 1.5 T. Axial T2 spin-echo weighted images (echo time [TE] 80 to 120 ms, repetition time [TR] 3000 to 4000 ms, slice thickness 5 mm); axial FLAIR (TE 110 to 150 ms, TR 9000 to 10000 ms, inversion time 2000 to 2200 ms, slice thickness 5 mm); and axial, sagittal, and coronal T1 spin-echo weighted images (TE 11 to 20 ms, TR 500 to 700 ms, slice thickness 5 mm) were acquired. To maintain blinding, we were restricted from access to information about the type of the scanner used for each particular patient as well as the location of the imaging center.

Image Assessment

The initial assessment was performed in a blinded way, in which the T2-WI and FLAIR images were evaluated in pseudorandom order, with the use of 16-bit digital imaging files. All lesions were marked and numbered with digital overlays. We included only focal thalamic abnormalities >1 mm and excluded those suggestive of perivascular spaces. Perivascular spaces were defined as sharply demarcated areas with a signal isointensity relative to cerebrospinal fluid (CSF), following the course of a perforating vessel on sagittal or coronal images. Care was also taken to avoid the inclusion of pulsation artifacts, recognizable by linear patterns of signal banding due to phase misregistration. For further subtyping and analysis, T2-WI, FLAIR, and T1-weighted images (T1-WI) were evaluated side by side. The greatest dimension of each focal abnormality was measured, and all were classified on each of the 3 imaging sequences in the following categories: hyperintense, hypointense, predominantly hypointense (hypointense with a small hyperintense component), and hypointense with a peripheral rim of hyperintensity.

Statistical Evaluation

Statistical analysis was performed with the use of SPSS 11.0. We used χ² statistics to compare categorical data, such as proportions of lesions detected by each sequence. For comparisons of continuous variables, Student’s t test was applied because the data were normally distributed.
Characteristics of vascular dementia on imaging

Results

The total number of focal thalamic lesions detected was 214. One hundred twenty-four (58%) of the 214 measured <5 mm, 61 (29%) between 5 and 10 mm, and 29 (14%) >10 mm. One hundred nine (51%) were localized in the right thalamus and 105 (49%) on the left. Two hundred eight (97%) of the 214 lesions were identified on T2-WI, but only 117 (55%) were detected on FLAIR ($\chi^2=5.1; P<0.05$). Almost half (47%) of the lesions found on T2-WI were not detected on FLAIR (Table 1).

Although the mean size of lesions detected on T2-WI and not on FLAIR (4.4 mm) was significantly lower than the mean size of lesions detected on both sequences (6.7 mm) ($P<0.001$), 5 of the 29 lesions >10 mm on T2-WI were not visible on FLAIR (Table 2).

One hundred eight (50%) of the lesions were hyperintense on T2-WI and hypointense on T1-WI and probably correspond to infarctions. Fifty lesions (23%) were hyperintense on T2-WI and isointense on T1-WI and may correspond to areas of myelin pallor. Fifty lesions (23%) were hypointense on T2-WI and T1-WI and probably represent microbleeds (hemorrhagic lacunae).

FLAIR detected 61 (56%) of the 108 probable infarctions, 30 (60%) of the 50 probable microbleeds, and 20 (40%) of the 50 probable areas of myelin pallor. Thirty-two of the probable infarctions were hyperintense on FLAIR (incomplete or non-cystic infarctions), and 29 were totally or partially hypointense (cystic and partially cystic infarctions). The vast majority (79%) of the 97 lesions not detected on FLAIR were hyperintense on T2-WI (Table 3).

Discussion

Our study shows that FLAIR imaging is not very sensitive in detecting focal thalamic lesions and is therefore not well suited as a stand-alone sequence in the evaluation of patients suspected of VaD. FLAIR sequences employ a long inversion time that suppresses the signal from CSF and a long TE that provides heavy T2 weighting.
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### Table 1. Lesions on T2-WI and FLAIR

<table>
<thead>
<tr>
<th>Signal on FLAIR</th>
<th>Not detected</th>
<th>Hyperintense</th>
<th>Hypointense</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Detected</td>
<td>0</td>
<td>77</td>
<td>20</td>
<td>97</td>
</tr>
<tr>
<td>Hyperintense</td>
<td>3</td>
<td>49</td>
<td>0</td>
<td>52</td>
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<tr>
<td>Hypointense</td>
<td>3</td>
<td>14</td>
<td>30</td>
<td>47</td>
</tr>
<tr>
<td>Predominantly hypointense</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Hypointense with hyperintense rim</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>158</td>
<td>50</td>
<td>214</td>
</tr>
</tbody>
</table>

### Table 2. Detection on FLAIR and Distribution by Size of Focal Lesions on T2-WI

<table>
<thead>
<tr>
<th>Size on T2-WI</th>
<th>Not Detected</th>
<th>Detected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5 mm</td>
<td>66</td>
<td>53</td>
<td>119</td>
</tr>
<tr>
<td>5–10 mm</td>
<td>26</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>5</td>
<td>24</td>
<td>29</td>
</tr>
</tbody>
</table>

### Table 3. Detection on FLAIR and Signal on T2 and T1-WI

<table>
<thead>
<tr>
<th>Signal on T2-WI</th>
<th>Not Detected on FLAIR</th>
<th>Hyperintense on T2-WI</th>
<th>Hypointense on T2-WI</th>
<th>Total</th>
<th>X=0.079</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isointense on T1-WI</td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>13</td>
<td>P=0.079</td>
</tr>
<tr>
<td>Hypointense on T1-WI</td>
<td>61</td>
<td>20</td>
<td>47</td>
<td>7</td>
<td>P=0.095</td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>30</td>
<td>77</td>
<td>20</td>
<td>X=1.164</td>
</tr>
</tbody>
</table>
Therefore, the major interest of FLAIR is to detect and characterize brain lesions around CSF spaces. Most studies advocate superiority of FLAIR over conventional spin-echo imaging in a wide range of pathologies. FLAIR images also have the advantage of easily identifying CSF-like lesions. Some studies showed that FLAIR was more often associated with image artifacts or could not corroborate the aforementioned superiority of FLAIR. Disadvantages of FLAIR include a reduced sensitivity to detect infratentorial or spinal cord lesions. The reason for this is unknown but most likely reflects different relaxation characteristics in those regions, both in normal-appearing tissue and in lesions. For example, T1 and T2 relaxation times of infratentorial lesions in patients with multiple sclerosis are closer to the relaxation times of local normal-appearing white matter than those of supratentorial lesions, resulting in reduced contrast between posterior fossa lesions and the background. Age-related increases in T1 relaxation times of human brain also have been shown, particularly in the thalami, and may serve to explain the lack of sensitivity of FLAIR for thalamic lesions in elderly patients with VaD. Alternatively, the occurrence of cystic changes in lacunar infarctions will lead to a prolongation of T1 relaxation time, and the signal from these lesions may be suppressed, as in CSF spaces. MRI-pathological correlation studies performed to determine the background of age-related subcortical gray and white matter hyperintensities on T2-WI found different types of pathology: infarctions, gliosis, myelin and axonal loss, breakdown of the ependymal lining, and enlarged perivascular spaces. Areas of myelin pallor can be hyperintense on T2-WI but isointense on T1-WI, and it seems possible that differences in type of pathology can also influence detection on FLAIR. Although the proposed neuropathological classification of lacunae includes both ischemic (type I) and hemorrhagic (type II) vascular abnormalities and enlarged perivascular spaces (type III), in VaD it is important to differentiate the vascular lesions. MRI-pathological correlation studies found that the great majority of enlarged perivascular (Virchow-Robin) spaces normally surround perforating arteries that enter the striatum in the anterior perforated substance, just above the internal carotid artery bifurcation and lateral to the anterior commissure. They are responsible for the so-called état criblé of the basal ganglia and are much less frequently located in the thalami. Therefore, it is unlikely that those lesions classified as cystic infarctions on the basis of MRI are in fact Virchow-Robin spaces or could account for the greater number of lesions detected on T2-WI. Actually, FLAIR performed more poorly for all types of presumed pathology. A limitation of our study is that we used images acquired on a wide range of scanners and sequences, not all of which may be optimally tuned. On the other hand, this reflects the normal variability of vendor-supported
sequences, and given the more complex contrast mechanisms in FLAIR, these may be less stable than for T2-WI. For the detection of type II hemorrhagic lacunae, both spin-echo and FLAIR are insensitive compared with T2*-WI gradient-echo sequences, but these were not available in the context of this trial. Nevertheless, we detected a fair amount of probable microbleeds. In conclusion, the accuracy of T2-WI for the detection of thalamic lesions in patients with probable VaD is far superior to FLAIR. Given the great clinical importance of these lesions, FLAIR should not be used as the only T2-weighted sequence in patients suspected of having VaD. In addition to the posterior fossa and spinal cord, the diencephalon seems to represent another region not suitable for evaluation by FLAIR MRI.
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References

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Chapter 3

Characteristics of White Matter

Hyperintensities on imaging
Chapter 3
Chapter 3.1

Impact of White Matter Hyperintensities Scoring Method on Correlations With Clinical Data

The LADIS Study

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Abstract

White matter hyperintensities (WMH) are associated with decline in cognition, gait, mood, and urinary continence. Associations may depend on the method used for measuring WMH. We investigated the ability of different WMH scoring methods to detect differences in WMH load between groups with and without symptoms.

We used data of 618 independently living elderly with WMH collected in the Leukoaraiosis And DISability (LADIS) study. Subjects with and without symptoms of depression, gait disturbances, urinary incontinence, and memory decline were compared with respect to WMH load measured qualitatively using 3 widely used visual rating scales (Fazekas, Scheltens, and Age-Related White Matter Changes scales) and quantitatively with a semiautomated volumetric technique and an automatic lesion count. Statistical significance between groups was assessed with the $\chi^2$ and Mann–Whitney tests. In addition, the punctate and confluent lesion type with comparable WMH volume were compared with respect to the clinical data using Student $t$ test and $\chi^2$ test. Direct comparison of visual ratings with volumetry was done using curve fitting.

Visual and volumetric assessment detected differences in WMH between groups with respect to gait disturbances and age. WMH volume measurement was more sensitive than visual scores with respect to memory symptoms. Number of lesions nor lesion type correlated with any of the clinical data. For all rating scales, a clear but nonlinear relationship was established with WMH volume.

Visual rating scales display ceiling effects and poor discrimination of absolute lesion volumes. Consequently, they may be less sensitive in differentiating clinical groups.
Introduction

White matter hyperintensities (WMH) on MRI are associated with cognitive dysfunction, gait abnormalities, falls, and depression and contribute to disability in the elderly population.\(^1\)\(^-\)\(^5\) Lesion load on MRI may serve as surrogate marker of disease burden and may ultimately guide treatment. For the measurement of WMH extent, different methods can be used, ranging from visual rating to fully computerized techniques. Visual rating of WMH is easy, and several scales are available with good reproducibility.\(^6\) The visual scales often do not detail size and location, and most are not linear. Scores from different rating scales are not directly comparable.\(^7\) Most volumetric studies use supervised semiautomated methods that may provide more information on location and size, as well as continuous data, but are time consuming.\(^8,\)\(^9\) Both methods have been used to correlate WMH with clinical data and have rendered varying results.\(^10,\)\(^11\) Subjective memory symptoms, although difficult to define, are associated with higher risk of dementia and WMH and may be used for the early detection of subjects at risk.\(^12\) Number of lesions and lesion pattern (punctate versus confluent) may also be correlated to clinical data. WMH burden might be caused by a large number of punctate lesions or few confluent lesions, possibly leading to different clinical signs.

In this study, we aimed to establish cross-sectionally the sensitivity of several visual WMH scales, volumetric WMH measurement, as well as WMH lesion count and pattern, to symptoms of cognitive decline, gait abnormalities, urinary incontinence, and depression. The relationship between visual and volumetric methods was characterized by establishing the mathematical function that best fitted the data. The study group consisted of elderly independently living individuals recruited on the basis of WMH and stratified by lesion severity into 3 groups.

Materials and Methods

Subjects

Data were drawn from the multinational multicenter longitudinal Leukoaraiosis And DISability (LADIS) study among 639 elderly, described previously.\(^13\) Inclusion criteria were 65 to 85 years of age and no or mild disability in everyday life (as established with the Instrumental Activities of Daily Living scale).\(^14\) Subjects were required to have at least some degree of WMH, demonstrated on MRI. Participants presented for evaluation in various settings: stroke unit, memory clinic, neurological or geriatric wards/clinic, population studies on aging, controls in
other studies. The study was approved by the local ethics committees, and all subjects gave informed consent. At baseline, subjects underwent a standardized evaluation (including global functioning, cognitive, motor, and psychiatric assessment), and, together with their informants, filled in questionnaires on medical history. The data used in this study are age, gender, presence of depression requiring therapy, symptoms of urinary incontinence, gait disturbances, and memory problems, as expressed by the participants or their informants.

MRI Scans

All subjects underwent magnetic resonance scanning following a standard protocol, during which 0.5-T or 1.5-T scanners were used and series included axial T2-weighted images (echo time [TE] 100 to 120 ms; repetition time [TR] 4000 to 6000 ms; voxel size 1x1x5 to 7.5 mm³; 19 to 24 slices), axial fluid-attenuated inversion recovery (FLAIR) images (TE 100 to 140 ms; TR 6000 to 10 000 ms; inversion time 2000 to 2400 ms; voxel size 1x1x5 to 7.5 mm³; 19 to 24 slices), and coronal or sagittal 3D T₁ sequence (TE 4 to 7 ms; TR 10 to 25 ms; flip angle 15 to 30°; voxel size 1x1x1 to 1.5 mm³). All scans were checked and stored at the Image Analysis Center of the VU Medical Center, Amsterdam, the Netherlands. Postprocessing and data analysis for this study was performed in Amsterdam and Copenhagen. Of the 639 scans, 21 could not be used because of insufficient quality for the volumetric assessment.

Visual Rating

On the FLAIR images, we applied the visual rating scales of Fazekas (range 0 to 3), Scheltens (range 0 to 84), and the Age-Related White Matter Changes (ARWMC) scale (range 0 to 30).15-17 All ratings were performed by an experienced rater (E.vS.) blind to the clinical data.

Volumetric Assessment

Volumetric analysis of WMH was performed by a single rater on the same axial FLAIR images, including the infratentorial region, using a Sparc 5 workstation (SUN). Lesions were marked and borders were set using local thresholding (home-developed software Show_Images, version 3.6.1) on each slice. No distinction was made between subcortical and periventricular hyperintensities. Areas of hyperintensity on T2-weighted images around infarctions and lacunes were disregarded.
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Lesion Count
An automated assessment of the number of lesions was performed by defining each lesion that was generated with the volumetric method, as a cluster of 3D connected voxels, and counting the number of such clusters (26-connectivity).

Reliability Assessment
To test reproducibility of the different methods, 18 scans, with a mean volume (SD) of 26.3 (19.0) mL, were assessed twice with an interval of >2 months.

Statistical Analysis
Sensitivity of WMH measurements to detect clinical group differences was tested with $\chi^2$ for trend (Fazekas scale) and Mann–Whitney test (Scheltens scale, ARWMC scale, volumetric measurement, and lesion count). Nonparametric testing was used for the WMH volumes because of the nonnormal distribution. Differences in lesion volume and number between Fazekas groups were tested using ANOVA with Bonferroni correction. To test the hypothesis that lesion type (punctate, defined as Fazekas score 1, versus confluent, defined as Fazekas score 3, with comparable lesion volumes) was associated with clinical characteristics, we selected all subjects with WMH volume between 15 and 30 mL. In this volume range, both Fazekas scores 1 and 3 were represented. These groups were compared with respect to the clinical data, using the Student $t$ test and $\chi^2$ test. Visual rating scales were correlated with the volumetric method using Spearman rank correlation method. To test the hypothesis of a nonlinear relationship between the visual methods and the volumetric method, we fitted a linear and a quadratic function to the plot using a linear regression with a correction factor based on the local variance.18

Results

WMH Load and Clinical Data
Table 1 shows mean WMH volumes and scores for different subject groups. Mean WMH volumes, but not visual ratings, were significantly greater in men than in women. Both visual and volumetric assessments showed group differences in WMH load between the older and younger subjects. No significant differences in WMH load could be found between the groups with and without a history of depression or symptoms of urinary incontinence. The mean WMH load of subjects with symptoms of gait disturbance was only significantly larger when measured volumetrically or with the ARWMC and Scheltens scales. With the volumetric
### Table 1. Mean WMH scores

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean WMH volume (SD)†</th>
<th>Mean Fazekas score ‡</th>
<th>Mean ARWMC score (SD)†</th>
<th>Mean Scheltens score (SD)†</th>
<th>Mean number of lesions †</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>278</td>
<td>25.0 (26.6)</td>
<td>1.9 (0.8)</td>
<td>9.9 (5.9)</td>
<td>18.4 (9.4)</td>
<td>43.0 (23.1)</td>
</tr>
<tr>
<td>Female</td>
<td>340</td>
<td>18.1 (18.2)**</td>
<td>1.7 (0.8)</td>
<td>9.6 (5.5)</td>
<td>18.0 (8.9)</td>
<td>44.5 (24.5)</td>
</tr>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 years</td>
<td>315</td>
<td>17.6 (19.4)</td>
<td>1.7 (0.8)</td>
<td>9.1 (5.5)</td>
<td>17.0 (9.0)</td>
<td>42.8 (23.8)</td>
</tr>
<tr>
<td>75-85 years</td>
<td>303</td>
<td>24.9 (25.1)**</td>
<td>1.9 (0.8)**</td>
<td>10.5 (5.8)**</td>
<td>19.3 (9.1)**</td>
<td>44.8 (23.9)</td>
</tr>
<tr>
<td><strong>History of</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>depression</td>
<td>Yes</td>
<td>170</td>
<td>21.5 (22.8)</td>
<td>1.8 (0.8)</td>
<td>10.1 (5.7)</td>
<td>18.7 (9.7)</td>
</tr>
<tr>
<td>No</td>
<td>448</td>
<td>21.1 (22.6)</td>
<td>1.8 (0.8)</td>
<td>9.6 (5.6)</td>
<td>18.0 (8.9)</td>
<td>43.0 (22.8)</td>
</tr>
<tr>
<td><strong>Complaints of</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urine incontinence</td>
<td>Yes</td>
<td>124</td>
<td>23.1 (23.0)</td>
<td>1.8 (0.8)</td>
<td>10.4 (5.7)</td>
<td>19.0 (9.2)</td>
</tr>
<tr>
<td>No</td>
<td>494</td>
<td>20.7 (22.6)</td>
<td>1.8 (0.8)</td>
<td>9.6 (5.7)</td>
<td>18.0 (9.1)</td>
<td>43.4 (23.6)</td>
</tr>
<tr>
<td><strong>Complaints of</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gait disturbances</td>
<td>Yes</td>
<td>255</td>
<td>24.7 (25.2)</td>
<td>1.9 (0.8)</td>
<td>10.6 (5.9)</td>
<td>19.7 (9.5)</td>
</tr>
<tr>
<td>No</td>
<td>355</td>
<td>18.6 (20.4)**</td>
<td>1.7 (0.8)</td>
<td>9.1 (5.5)**</td>
<td>17.0 (8.7)**</td>
<td>41.9 (21.8)</td>
</tr>
<tr>
<td>not applicable</td>
<td>8</td>
<td>21.7 (17.5)</td>
<td>1.8 (0.8)</td>
<td>9.8 (4.5)</td>
<td>18.1 (8.4)</td>
<td>42.3 (26.3)</td>
</tr>
<tr>
<td><strong>Memory complaints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>393</td>
<td>22.1 (23.0)</td>
<td>1.8 (0.8)</td>
<td>9.9 (5.7)</td>
<td>18.4 (9.1)</td>
<td>45.4 (24.7)</td>
</tr>
<tr>
<td>No</td>
<td>225</td>
<td>19.5 (21.9)*</td>
<td>1.8 (0.8)</td>
<td>9.6 (5.7)</td>
<td>17.8 (9.1)</td>
<td>41.1 (23.9)</td>
</tr>
</tbody>
</table>

†: Mann-Whitney test ‡: χ² for trend
*: p < 0.05 **: P < 0.01
assessments only, we were able to establish a significant difference in lesion load between subjects with and without memory symptoms.

**Mean Lesion Volume and Lesion Count**

Fazekas score 1 corresponded to a mean lesion volume of 0.20 mL, score 2 to 0.45 mL per lesion and score 3 to 1.26 mL per lesion (Table 2). The differences were statistically significant between all groups. Table 2 also shows mean total WMH for each Fazekas category, which was also statistically significant between the groups. Subjects in the Fazekas score 2 category tended to have most lesions. Number of lesions did not discriminate significantly between groups with and without symptoms (Table 1).

<table>
<thead>
<tr>
<th>Fazekas 1</th>
<th>Fazekas 2</th>
<th>Fazekas 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean volume per lesion, ml (SD)†</td>
<td>0.20 (0.1)</td>
<td>0.45 (0.4)</td>
</tr>
<tr>
<td>Mean WMH volume, ml (SD)†</td>
<td>6.49 (4.7)</td>
<td>18.83 (7.7)</td>
</tr>
<tr>
<td>Mean number of lesions (SD)†</td>
<td>33.2 (18)</td>
<td>53.6 (25)</td>
</tr>
</tbody>
</table>

| Table 3. Differences in a group of subjects with WMH volume 15 - 30 ml |
|------------------------|-----------------|-----------------|-----------------|
|                        | Fazekas 1 | Fazekas 3 | p-value |
| Total subjects       | 17  | 29  | |
| Mean Age (years)     | 74.4 | 73.2 | 0.47* |
| % Male               | 58.8 | 37.9 | 0.2† |
| % History of depression | 29.4 | 27.6 | 0.9 † |
| % Urinary incontinence complaints | 29.4 | 20.7 | 0.5 † |
| % Gait disturbance complaints | 41.2 | 62.1 | 0.1 † |
| % Memory complaints  | 82.4 | 58.6 | 0.1 † |

*: Student’s t-test
†: Chi-square
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Lesion Pattern

We found no significant differences in clinical features between the groups with punctate (Fazekas 1) and confluent (Fazekas 3) lesions (Table 3).

Correlation Between Visual Rating Scales and Volumetric Measurement

Scatter plots for the Fazekas and ARWMC scales with WMH volume are shown in figures 1 and 2. The scatter and shape of the plot for the Scheltens score was similar to the scatter plot of the ARWMC score (data not shown). Increasing volume correlated with higher visual scores (Spearman $\rho$ 0.86), and scatter increased with higher WMH visual scores. The relationship with WMH volume was better described by a quadratic than a linear model, indicated by higher $R^2$ (Table 4). When corrected for difference in variance, the difference between the linear and quadratic model was statistically significant ($P<0.01$).
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Intraobserver Reliability

Intrarater agreement for the scales was good with a $\kappa$ for Fazekas score of 0.84. Intraclass correlation coefficients were 0.93 (ARWMC scale), 0.92 (Scheltens scale), and 0.99 (volume measurement). The mean difference between the 2 measurements was not statistically significant when tested against 0 using a 1-sample $t$ test.

Table 4. Mathematical models of the relationship between visual rating scales and WMH volume

<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fazekas scale</strong></td>
<td></td>
</tr>
<tr>
<td>linear</td>
<td>0.58</td>
</tr>
<tr>
<td>quadratic</td>
<td>0.62*</td>
</tr>
<tr>
<td><strong>ARWMC scale</strong></td>
<td></td>
</tr>
<tr>
<td>linear</td>
<td>0.67</td>
</tr>
<tr>
<td>quadratic</td>
<td>0.71*</td>
</tr>
<tr>
<td><strong>Scheltens scale</strong></td>
<td></td>
</tr>
<tr>
<td>linear</td>
<td>0.60</td>
</tr>
<tr>
<td>quadratic</td>
<td>0.63*</td>
</tr>
</tbody>
</table>

*: difference significant at the 0.01 level
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Discussion

The results indicate that volumetry may be more sensitive to detect small group differences. This is in line with previous research, correlating WMH measurement methods with cognitive performance. Subjective and objective memory symptoms are not interchangeable for the assessment of cognition, but both seem to be related with WMH. The best method for the measurement of WMH with respect to objective cognitive measures is still to be established. The ARWMC and Scheltens rating scales have a greater range than the Fazekas scale and were found to differentiate better between groups. This finding corresponds with a review on the relationship between WMH and cognition. The Fazekas scale seems most appropriate for defining different WMH groups. No group differences were detected for symptoms of urinary incontinence and depression. One of the reasons could be that only WMH in certain areas correlate with these symptoms. Frontal WMH has been associated with mood disorders, cognitive functions, and gait problems. On the other hand, it was shown that WMH in different regions are highly correlated and that their influence on clinical signs may therefore not be limited to certain areas of the brain. To our knowledge, this is the first report on lesion count as a measure of WMH severity. We found that it was not sensitive to detect associations with clinical signs, possibly because lesion count does not take into account lesion size. In progressing disease, lesions can merge, leading to a smaller total number of lesions. Few lesions could therefore indicate either mild or severe disease. This lack of correlation between number of lesions and clinical findings was also found in individuals with multiple sclerosis (MS). This caused studies in MS to focus on total T2 lesion volume and T1 gadolinium enhancing lesions instead of number of lesions. We compared subjects with punctiforme and confluent lesion patterns who had comparable WMH volumes. We found no differences in symptoms between the groups. Although these subanalyses limited the number of subjects studied, it illustrates the arbitrary nature of the qualitative scoring system. We confirmed the good correlations between all three visual rating scales and the WMH volume, but the current study shows that the variability in WMH volume is large in the patient groups with high visual scores. Subject group with higher visual scores contains subjects with different degrees of WMH burden, leading to decreased correlation with clinical data. When progression of WMH is measured, this ceiling effect can be even greater. A previous study on the detection of WMH progression with conventional visual rating scales showed lack of sensitivity compared with WMH volume measurement. This effect is especially of interest because WMH progression seems to occur fastest in patients with a high lesion load. The WMH volume in this study was significantly higher than reported in previous studies.
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designed to enroll a large population of subjects with WMH, and participants were stratified into three categories of WMH severity. This approach is different from population-based studies and resulted in a relatively large group of subjects with a high WMH lesion load. Results are therefore not directly applicable to the healthy elderly population. The advantage of this design is the possibility of studying a broad spectrum of lesion loads. WMH burden can be presented as volume or as a proportion of the total white matter or intracranial volume, depending on the focus of the study. This makes comparison between studies complicated. We did not correct for intracranial volume or white matter volume because we wanted to compare the raw volumes with visual scales that are also uncorrected. Wen and Sachdev investigated uncorrected WMH volume and found no differences in WMH volumes between men and women, whereas in our study, men had a larger mean WMH volume than women. The subjects in their study were younger than our study participants (60 to 64 years versus 65 to 85 years), which could partly explain this difference. We did not control for risk factors for WMH such as hypertension. In addition, objective measures for cognition, gait, depression, and urinary incontinence were also not included here. This was done because the focus of this study was not to establish a causal relationship of WMH with clinical data but a comparison between scoring methods in their association with symptoms, which is clearly of clinical relevance for clinicians dealing with these patients.
Appendix
Participating Centers and Personnel

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Acknowledgments

The authors thank Ronald van Schijndel for his support with the volumetric measurements and Dirk Knol for his help with the curve fitting.
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References

Chapter 3.2

Measuring Progression of Cerebral White Matter Lesions on MRI
Visual rating and volumetrics

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H.A. Vrooman
P.J. Koudstaal
P. Scheltens
M.M.B. Breteler
F. Barkhof

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Chapter 3

Abstract

To evaluate the concordance of a volumetric method for measuring white matter lesion (WML) change with visual rating scales the authors selected a stratified sample of 20 elderly people (mean age 72 years, range 61 to 88 years) with an MRI examination at baseline and at 3-year follow-up from the community-based Rotterdam Scan Study (RSS). Four raters assessed WML change with four different visual rating scales: the Fazekas scale, the Scheltens scale, the RSS scale, and a new visual rating scale that was designed to measure change in WML. The authors assessed concordance with a volumetric method with scatter plots and correlations, and interobserver agreement with intraclass correlation coefficients.

For assessment of change in WML, the Fazekas, Scheltens, and periventricular part of the RSS scale showed little correlation with volumetrics, and low interobserver agreement. The authors’ new WML change scale and the subcortical part of the RSS scale showed good correlation with volumetrics. After additional training, the new WML change scale showed good interobserver agreement for measuring WML change.

Commonly used visual rating scales are not well suited for measuring change in white matter lesion severity. The authors’ new white matter lesion change scale is more accurate and precise, and may be of use in studies focusing on progression of white matter lesions.
Characteristics of WMH on imaging

Introduction

Cerebral white matter lesions (WML) are thought to result from small vessel disease, and their presence and severity increase with age and the presence of arterial hypertension. Although the clinical significance of these lesions remains to be fully understood, WML have been associated with dementia, depression, and stroke. In healthy elderly people, WML are associated with adverse cognitive function and the presence of depressive symptoms. Patients with Alzheimer disease (AD), vascular dementia, and depression have more severe WML than controls. It has been suggested that WML progress gradually over time, and may ultimately lead to subcortical vascular dementia and vascular depression or contribute to the clinical expression of AD. Studies that have determined progression of WML over time are limited, and comparison of their findings is difficult due to the use of different visual rating scales for the assessment of WML progression. Evaluation of WML progression is of clinical importance, since it is needed to determine the natural course of these lesions, and to study the effect of intervention studies. Visual rating scales have proven their value in cross-sectional studies, but very little is known about the sensitivity and reliability of these scales for measuring change in WML over time. Volumetric methods may provide the most objective assessment method, but are often time consuming, and therefore not always feasible in large studies. The objective of the present study was to evaluate three commonly used visual rating scales—the Fazekas scale, the Rotterdam Scan Study (RSS) scale, and the Scheltens scale—in terms of accuracy and precision in measuring change of WML in a defined population. We compared the degree of concordance with a volumetric method, and the reproducibility of these scales. In addition, we introduce a simple visual rating scale that was designed to measure change in WML over time. We compared the performance of this WML change scale with the other three visual rating scales, and with the volumetric method.

Methods

Subjects

The scan material used in the present study originates from subjects participating in the RSS, a population-based study that was designed to study causes and consequences of age-related brain changes in elderly people. In 1995 through 1996, 1,077 nondemented elderly people aged 60 to 90 years underwent a baseline examination that included a cranial MRI scan. In 1999 through 2000, 787 of the 973 participants who were alive and eligible (not
institutionalized, not moved abroad) were re-examined (response rate 81%). Of these participants, 668 underwent a second MRI (response rate 69%). We selected scan pairs from 10 participants, in a nonrandom manner, to serve as a training set. Additionally, we randomly selected 20 participants who had a baseline and follow-up scan, in three strata of baseline subcortical WML severity, as assessed with the RSS scale. We selected seven participants from the first tertile of subcortical WML severity, seven from the second tertile, and six from the third tertile to cover the whole range of the WML distribution. The mean age of participants was 72 years (range 61 to 88 years), 10 (50%) were women, and 8 (40%) had hypertension. The mean time between the first and second MRI was 3.3 years (range 2.9 to 4.0 years).

**MRI scanning and white matter lesions**

Axial T1, T2, and proton density weighted cerebral MR scans were made on a 1.5-Tesla scanner (Siemens, Erlangen, Germany). The following pulse sequences were applied: T1 (700 msec/14 msec/2 [repetition time/echo time/excitations]), T2 (2,200 msec/80 msec), and proton density (2200 msec/20 msec). Slice thickness was 5 mm, with an interslice gap of 1 mm, and a matrix size of 192 x 256 pixels. MRI protocols were identical at baseline and at follow-up. We defined WML as hyperintense lesions, located in the cerebral white matter, that are visible on both T2- and proton density-weighted images, and do not have a hypointense center on proton density weighted images (as in lacunes). Lesions were considered periventricular in location when directly adjacent to the ventricles; otherwise we considered them as subcortical. If periventricular lesions extended 10 mm perpendicularly from the ventricular border, the extending part was per definition scored as a subcortical lesion.

**Rating scales**

We assessed WML severity at baseline and WML progression with four different visual rating scales. The Fazekas scale rates WML both in the periventricular and subcortical region on a 0 to 3 scale. The Scheltens scale rates WML in the periventricular region on a 0 to 6 scale, and in the subcortical region on a 0 to 24 scale, on the basis of the size and number of the lesions. It also includes ratings for basal ganglia and infratentorial areas, which were not used in this report. The RSS scale rates WML in the periventricular region on a 0 to 9 scale, and for subcortical WML a lesion volume is approximated based on number and size of the lesions. In addition, we designed and used a new simple scale to measure WML change: the WML change scale. In this scale change in WML (-1 decrease, 0 no change, +1 increase) is scored in three periventricular locations (frontal caps, lateral bands, occipital caps) resulting in a periventricular score of -3 to +3, and in four subcortical locations (frontal, parietal, temporal, and occipital),
resulting in a subcortical score of -4 to +4. Increase is defined as the occurrence of a new focal lesion or the enlargement of a previously visible lesion; decrease is defined as the reverse (i.e., disappearance or shrinkage).

Visual rating system

All ratings were performed at the VU medical center. The MRI studies were in digital format. Four raters (N.D.P., E.C.W.v.S., E.J.v.D., M.S.) analyzed WML on baseline and follow-up images, using the four different visual rating scales. Raters were blinded to clinical information, but not to name, age, and scan year. WML were rated on proton density and T2-weighted images, by direct scan comparison on a personal computer, using the viewing program Radworks (version 5.1, Applicare, Zeist, the Netherlands). To optimize the comparability of the baseline and follow-up scans, images had been registered and resliced using the software package Mirit, which uses mutual information as optimization criteria. After a training session in which the four raters in couples assessed 10 scan pairs of the training set, a consensus meeting was held among the authors to identify and resolve any possible differences in application of the various scales. Following this training stage, each rater then individually scored the 20 series of baseline and follow-up MRI studies. The rating scales were always applied in the same order: first the Fazekas scale, second the RSS scale, third the Scheltens scale, and finally our WML change scale. Raters were aware which was the baseline and follow-up scan, and this may lead to bias toward finding a positive change in WML severity. In order to estimate this potential systematic measurement error, two raters reassessed the 20 series with the WML change scale in the native domain, first blinded to scan date, and 2 weeks later not blinded to scan date.

Volumetric assessments

We used proton density images for the volumetric quantification of WML volume on a workstation (Sparc 5; SUN, Palo Alto, CA). One reader identified lesions on the registered images, and then determined the areas of the lesions using home-developed software (Show_Images, version 3.6.1) in the native domain to avoid artificial enlargement of lesion areas due to reslicing. We used a seed growing method to determine WML areas on each slice for periventricular WML (frontal caps, lateral bands, occipital caps), and subcortical WML (frontal, parietal, temporal, and occipital). WML areas were not recorded separately for the right and left hemisphere. By summing the areas of each slice multiplied by the interslice distance, we calculated total WML volumes for the different regions. The volumetric assessments were performed twice, with an interval of 6 months, and the mean value of the two assessments was
used in the analyses. The intraclass correlation coefficients reflecting the intrarater agreement for the baseline assessment were 0.84 for periventricular and 0.97 for subcortical WML volume, with a SD of the difference between the two ratings of 1.4 mL for periventricular and 0.86 mL for subcortical WML.18

Data analysis
For the volumetric assessment, change in WML volume was calculated by subtracting the baseline WML volume from the follow-up volume.19 Pearson’s correlation coefficient was used to assess the relation between baseline WML severity and WML change in the periventricular and subcortical region. For the visual rating scales (Fazekas scale, Scheltens scale, RSS scale), change in WML score was calculated by subtracting the baseline from the follow-up rating for each rater separately. Progression on the visual rating scales was defined as an increase of 1 point or more on the scale. We made scatter plots to visualize the relation between the change in WML assessed with the volumetric method (in mL), and the visual rating scales. Furthermore, we assessed concordance between visual scales and volumetrics by the nonparametric Spearman’s rho. Spearman’s rho values of 0 were considered no relationship between the variables; values equal to 1 were considered to reflect perfect correlation. We quantified the interobserver agreement on the visual rating scales with intraclass correlation coefficients. The intraclass correlation coefficient is the biologic variation between participants divided by the sum of the variation between participants and the rater variation. We estimated the possible bias in the visual ratings that may have been introduced by being aware which were the baseline and follow-up images. Bias was expressed as the mean difference in scores on the WML change scale between not-blinded ratings and blinded ratings.18 Furthermore, we assessed the 95% limits of agreement between the not-blinded and blinded method.

Results

WML severity at baseline and change
The median WML volumes as assessed with the volumetric method were 3.3 mL (range 1.6 to 10.4) at baseline and 0.7 mL (range-2.1 to 6.7) increase for the periventricular region, and 0.2 mL at baseline (range 0 to 15.2) and 0.1 mL (range -0.4 to 3.5) increase for the subcortical region. Mean increase in the periventricular region was 1.4 (SD 2.2) and in the subcortical region 0.5 (SD 0.9). This corresponds to a mean WML increase at a rate of 0.42 mL per year in the periventricular region and 0.15 mL per year in the subcortical region. Figure 1
Figure 1. White matter lesions (WML) progression in an 88-year-old woman who participated in our study. 
A. a slice from the baseline study. B. a corresponding slice from the follow-up study. After 3 1/2 years, WML progression has occurred (arrows) in the left and right occipital cap (periventricular region), extending into the parietal subcortical regions.
Table 1. WML severity at baseline, change, and number of participants with progression for the four visual rating scales and for the four raters

<table>
<thead>
<tr>
<th>Rating scale</th>
<th>Rater 1</th>
<th>Rater 2</th>
<th>Rater 3</th>
<th>Rater 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas scale, 0 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2 (2-3)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>2 (2-3)</td>
</tr>
<tr>
<td>Change</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Progression</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>RSS scale, 0 to 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6 (4-9)</td>
<td>5 (3-9)</td>
<td>5 (3-9)</td>
<td>5.5 (3.3-9)</td>
</tr>
<tr>
<td>Change</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>0 (0)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Progression</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
<td>0 (0%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Scheltens scale, 0 to 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4 (3-6)</td>
<td>3 (3-6)</td>
<td>3 (2-6)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>Change</td>
<td>0 (0-2)</td>
<td>0 (0-3)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Progression</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>WML change scale, -3 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>1 (0-3)</td>
<td>1 (-1-3)</td>
<td>0 (0-3)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>Progression</td>
<td>11 (55%)</td>
<td>11 (55%)</td>
<td>5 (25%)</td>
<td>8 (40%)</td>
</tr>
</tbody>
</table>
### Subcortical

<table>
<thead>
<tr>
<th></th>
<th>Fazekas scale, 0 to 3</th>
<th>RSS scale, mL</th>
<th>Scheltens scale, 0 to 24</th>
<th>WML change scale, -4 to 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>1 (0-3)</td>
<td>0.2 (0-9.8)</td>
<td>5.5 (0-23)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td><strong>Change</strong></td>
<td>0 (0-1)</td>
<td>0.2 (0-1.4)</td>
<td>1 (0-3)</td>
<td>2 (-1-4)</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>3 (15%)</td>
<td>0.2 (0-1.4)</td>
<td>11 (55%)</td>
<td>16 (80%)</td>
</tr>
</tbody>
</table>

**Progression on the visual rating scales, including the WML change scale, was defined as a positive change of 1 point or more on the scale. WML = white matter lesion; RSS = Rotterdam Scan Study.**
Figure 2. Scatter plots showing the relation between change in white matter lesions (WML) measured with the volumetric method (x-axis) and the different visual rating scales (y-axis) in the periventricular region: (A) Fazekas scale, (B) Rotterdam Scan Study (RSS) scale, (C) Scheltens scale, (D) WML change scale; and in the subcortical region: (E) Fazekas scale, (F) RSS scale, (G) Scheltens scale, (H) WML change scale.
shows an example of WML progression in the periventricular and subcortical region. WML volumes at baseline were positively correlated with WML change (Pearson correlation coefficient 0.70, \( p = 0.001 \) for periventricular WML; 0.90, \( p < 0.001 \) for subcortical WML).

Table 1 gives the WML severity at baseline and WML change as well as the number of participants with WML progression, as assessed with the different visual rating scales for the four raters. Several methods showed on average an increase in WML in both the periventricular and subcortical region, but the number of participants showing progression varied largely between the different methods applied.

### Correlation between volumetric assessment and visual rating scales

We evaluated the concordance between the volumetric WML change and the change assessed with the visual rating scales. This was done separately for the four raters, and after averaging the visual rating of the four raters in order to reduce noise due to interobserver disagreement. Figure 2 shows the scatter plots of the relationship between WML change measured with the volumetric assessment and the visual rating scales (average of four raters) in the periventricular and subcortical region. Visual inspection of the scatter plots shows comparatively good agreement between the WML change scale and the volumetric method,
Characteristics of WMH on imaging

although the WML change scale tends to overestimate lesion change in the subcortical region (figure 2D), and may systematically underestimate lesion change in the periventricular region as volume change gets larger (figure 2H). Table 2 gives the nonparametric Spearman’s rho between the volumetric method and the four visual rating scales on WML change. Only the subcortical part of the RSS scale and the WML change scale showed significant correlation with the volumetric method for rater 1, 2, and 3, and for the average of the four raters (see table 2).

Interobserver agreement

The intraclass correlation coefficients for the interobserver agreement on baseline WML severity and change for the visual rating scales including our new WML change scale are presented in table 3. Values <0.20 were considered to reflect poor agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement, and 0.81 to 1.00 very good agreement.18 The interobserver agreement for the baseline ratings on the Fazekas, Scheltens, and RSS scales was fair to good for the periventricular region and good to very good for the subcortical region (see table 3). However, agreement on change was poor for the Fazekas and Scheltens scale, fair for the WML change scale and the periventricular part of the RSS scale, and moderate for the subcortical part of the RSS scale. The raters had been using the existing rating scales by Fazekas, Scheltens, and the RSS previously and thus were better acquainted with them. In a post hoc study that was performed using the new WML change scale after additional training, two of the raters rated 200 additional pairs of scans. In this second sample, the interobserver agreement was 0.73 for the periventricular region, and 0.72 for the subcortical region, indicating good agreement.

Effect of blinding to the scan date

Mean difference in score on the WML change scale between the not-blinded and blinded method were +0.075 (SD 0.40) points in the periventricular region, and -0.025 (SD 0.44) in the subcortical region. This indicates there is no substantial bias toward higher progression when images are scored with knowledge of which are the baseline and which are the follow-up images. The 95% limits of agreement between the not-blinded and the blinded method were (-0.71 to +0.86) for the periventricular region, and (-0.84 to +0.89) for the subcortical region, which suggests that for an individual the not-blinded and blinded method are unlikely to disagree more than one point on the WML change scale.
Table 3. Interobserver agreement for the visual rating scales for baseline and change measurements

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Periventricular WML</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas scale</td>
<td>0.37</td>
<td>0.08</td>
</tr>
<tr>
<td>Rotterdam Scan Study scale</td>
<td>0.64</td>
<td>0.23</td>
</tr>
<tr>
<td>Scheltens scale</td>
<td>0.56</td>
<td>0.18</td>
</tr>
<tr>
<td>WML change scale</td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Subcortical WML</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas scale</td>
<td>0.84</td>
<td>0.18</td>
</tr>
<tr>
<td>Rotterdam Scan Study scale</td>
<td>0.90</td>
<td>0.47</td>
</tr>
<tr>
<td>Scheltens scale</td>
<td>0.84</td>
<td>0.003</td>
</tr>
<tr>
<td>WML change scale</td>
<td></td>
<td>0.24</td>
</tr>
</tbody>
</table>

Numbers are intraclass correlation coefficients.
WML = white matter lesions.

Discussion

We evaluated three commonly used visual rating scales, and one new simple visual rating scale in terms of their ability to measure change in WML severity on MRI. We assessed the concordance of the visual assessments with volumetric change, and quantified the reproducibility of the scales for measuring WML change. In a stratified sample from a defined population, during a 3-year time period, both the volumetric method and the visual rating scales showed, on average, an increase in WML. We found significant correlations with volumetric change for the subcortical part of the RSS scale and for the new WML change scale. The interobserver agreement was moderate for change on the subcortical part of the RSS scale, and fair for the WML change scale. In a post hoc study, the interobserver agreement for the WML change scale improved to good agreement after observers had become familiarized with the scale. The Fazekas, Scheltens, and periventricular part of the RSS scale showed poor correlation with volumetric change, and poor to fair interobserver agreement on the change measurements. Several methodologic issues need to be addressed. First, there is currently no gold standard for the assessment of WML change, and our volumetric method cannot be interpreted as such.
Second, the comparison between volumetric WML change and WML change measured with different visual scales is complicated by differences in type of data (continuous versus categorical) obtained with the different methods. We used rank correlation to evaluate the relationship between the visual scales and volumetrics. Unlike agreement, correlation is not affected by the scale of measurement, but does depend on the range of the quantity of the sample. Therefore, the presented correlations cannot be interpreted as agreement between the visual scales and volumetrics, although they do allow for comparison between the visual scales. Third, visual rating was performed side by side, and with knowledge of the time sequence of scans, which may have led to some bias toward a higher progression rating. However, we evaluated this possible bias in a post hoc analysis, and found that this effect was very small. Fourth, registration of the follow-up scans on the baseline scans may have caused blurring effect, and although this effect was judged to be small, it may have contributed to higher progression rating with the visual rating scales. The Fazekas, Scheltens, and RSS scales were designed for cross-sectional assessments of WML. When applied in a cross-sectional fashion these scales show both good intra- and interobserver agreement, which largely corresponds to our findings of fair to very good interobserver agreement for the baseline assessments. A previous study reported that visual rating with the Fazekas and Scheltens scales shows significant correlation with quantitative volumetric assessments. However, visual assessment of WML change with these scales is problematic. There are several explanations for the disappointing performance of these scales in measuring WML change. As shown in our and other data sets, baseline WML severity is positively correlated with WML change. WML that were already rated in the highest category at baseline (and which are most likely to progress) cannot contribute to progression on these scales due to a ceiling effect. Furthermore, new lesions may develop or lesions may grow without crossing the limits of the categories of the scales, and thereby remain below detection on the visual scales. The subcortical part of the RSS scale performed better in capturing change, most likely because it incorporates the number and size of lesions in more detail, thus avoiding a ceiling effect. However, the subcortical part of this scale is elaborate and time consuming. Our new WML change scale that was designed to measure WML change not only seemed to be valid, but also takes less time to apply. Although agreement on progression initially was fair, it approved to good agreement after additional training. We found that during a 3-year period WML volume increased at a mean rate of 0.42 mL per year in the periventricular region and 0.15 mL per year in the subcortical region. These figures on rate of change do not directly reflect the rate of change in the population at large because of the way we constructed our sample for this validation study. The NHLBI Twin Study reported a mean WML volume increase of 0.38 mL per year in 168 individual male twins with a mean age of 72 years, which is comparable to the
range of our findings on rate of change. When we compare the interobserver agreement on the visual scales for the baseline assessments in the present study to those reported in the literature, interobserver agreement was comparable for periventricular WML on the Fazekas scale (0.37 versus 0.35 to 0.74) and for subcortical WML on the RSS scale (0.90 versus 0.88), higher for subcortical WML on the Fazekas scale (0.84 versus 0.34 to 0.78) and Scheltens scale (0.84 versus 0.69), but lower for periventricular WML on the Scheltens scale (0.56 versus 0.71) and RSS scale (0.64 versus 0.79 to 0.90).\textsuperscript{1,15,20}

Acknowledgment

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Characteristics of WMH on imaging

References

Chapter 4

Clinical impact of cerebral vascular lesions
Chapter 4
Chapter 4.1

Vascular Lesions increase likelihood of progressing from Mild Cognitive Impairment to Dementia

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F. Barkhof
R.C. Petersen
L.J. Thal
C.R. Jack Jr.
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for members of the Alzheimer’s Disease Cooperative Study Group*

*Members of the Alzheimer’s Disease Cooperative Study who participated in this MRI study are presented in the appendix at the end of the chapter

Submitted

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Abstract

White matter hyperintensities (WMH) have an effect on cognition and are increased in severity among individuals with amnestic mild cognitive impairment (aMCI). The influence of WMH on progression of aMCI to Alzheimer’s disease (AD) is less clear. Data were drawn from a three-year prospective, double blind, placebo controlled clinical trial that examined the effect of donepezil or vitamin E on progression from aMCI to AD. WMH from multiple white matter regions were scored on MR images obtained at entry into the trial from a subset of 152 study participants using a standardized visual rating scale. Cox proportional hazards models adjusting for age, education and treatment arm were used to investigate the role of WMH on time to progression from aMCI to AD. 55 of the 152 (36.2%) aMCI subjects converted to AD. Only periventricular hyperintensities (PVH) were related to an increased risk of AD within three years (HR=1.59, 95% CI = 1.24 – 2.05, p-value<0.001). Correcting for medial temporal lobe atrophy or the presence of lacunes did not change this relation. PVH are associated with an increased risk of progression from aMCI to AD. This suggests that PVH, an MRI finding thought to represent cerebrovascular damage, contributes to AD onset in vulnerable individuals independent of Alzheimer pathology.
Clinical impact of cerebral vascular lesions

Introduction

Recent data suggest that older individuals who have considerable, but circumscribed cognitive impairment may be in a transition phase between normal aging and dementia that is often denoted as mild cognitive impairment (MCI).\textsuperscript{1-3} MCI may be divided into multiple subtypes.\textsuperscript{4} Individuals with the amnestic subtype of MCI (aMCI) have memory impairment as the primary cognitive deficit and a subsequently high likelihood of progressing to clinically probable Alzheimer’s disease (AD).\textsuperscript{5,8} While it has been suggested that most individuals with aMCI are in the earliest stages of AD, cerebrovascular disease (CVD) is also associated with this clinical syndrome.\textsuperscript{9,11} Amongst subjects with extensive white matter hyperintensities (WMH), clinically relevant episodic memory impairment may result from dysfunction of working memory and of executive control processes.\textsuperscript{12} Additional studies support this notion by showing that WMH are associated with reduced frontal glucose metabolism.\textsuperscript{13,14} Although substantial work has been done to study the role of the AD process on progression from aMCI to dementia, studies examining the impact of CVD markers on progression to dementia are more limited and have resulted in opposing results.\textsuperscript{15,17} We therefore examined the impact of WMH on a random subgroup of 152 individuals with aMCI. We hypothesized that increased WMH would be associated with an increased risk of progressing to AD.

Methods

Subjects

Subjects were drawn from the prospective, double-blind placebo controlled study to test the efficacy of donepezil and vitamin E on the progression of aMCI to dementia.\textsuperscript{18} The details of study rationale, design and subject characteristics for the parent study and the MRI sub-study have been previously described, including description of previous qualitative estimates of medial temporal atrophy measures that were used as part of this study.\textsuperscript{18-20} In brief, 769 participants were recruited from 69 Alzheimer’s Disease Cooperative Study (ADCS) centers in the United States and Canada. Inclusion was based on criteria for amnestic MCI and modified to utilize the Logical Memory II subtest of the Wechsler Memory Scale-Revised adjusted for education.\textsuperscript{2,21} Additional requirements included a Clinical Dementia Rating (CDR) scale score of 0.5 and insufficient impairment to meet National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association criteria for AD (NINCDS-ADRDA).\textsuperscript{22,23} The study was conducted according to Good Clinical Practice
guidelines, the Declaration of Helsinki, and the U.S. Code of Federal Regulations title 21 Part 50 (Protection of Human Subjects) and title 21 Part 56 (Institutional Review Boards). Written informed consent was obtained from all participants and study partners who had knowledge of the participants’ functional activities. A data and safety monitoring board reviewed the blinded safety data every three months during the trial. Subjects were followed-up for three years and time to progression to dementia was recorded. AD was the clinically determined etiology for dementia in 99% of the subjects. There was no significant treatment effect in the parent study. A subset of 195 individuals received a research brain MRI examination at entry to the study as part of an ancillary study.24,25 These individuals were selected based solely on their willingness to undergo a research MRI and the availability of suitable MRI machinery at clinical sites that participated in the parent trial. No other criteria were used to select these subjects and subjects from 24 separate sites of the parent study were enrolled into this sub-study. Participants of the MRI sub-study closely represented those of the parent study.24

MRI studies

The imaging protocol included a 3D T1-weighted gradient echo sequence, with 124 contiguous, 1.6 mm thick coronal slices and 2D proton density (PD) and T2-weighted spin-echo sequences with 24 transverse slices, slice thickness 5 mm. MRI data were sent from the participating centers to a central location at the Mayo Clinic in Rochester, Minnesota for quality check, storage and analysis. For this study, images were stripped from identity data and transferred to the Imaging of Dementia and Aging (IDeA) laboratory at the University of California at Davis. Of the original 195 scans, WMH from 43 MRIs could not be read due to image artefact or incomplete image acquisition of the T2-weighted series, leaving 152 subjects with MRI for analysis.

MRI visual rating

One independent rater (EvS), who was blinded to all demographic and treatment related data, applied a semi-quantitative visual rating scale for the analysis of WMH.26 Using this scale, deep subcortical WMH were assessed on a 0 – 6 scale in different brain regions, where score 0 reflects no WMH, and score 6 confluent lesions. The regions assessed were the frontal, parietal, occipital and temporal lobes, basal ganglia and infratentorial regions. A total deep WMH score (D-WMH) was composed by summing up the scores of the frontal, parietal, occipital and temporal regions (range 0 – 36). In addition, periventricular hyperintensities (PVH) were assessed on a scale ranging from 0 – 2 scale in three regions (frontal and occipital caps and bands). A total periventricular score was composed of the scores of these three regions (range 0 –
Clinical impact of cerebral vascular lesions

6). A total WMH score (T-WMH) was created by summing up the scores for D-WMH and PVH. Intra-observer variability was good with an intraclass correlation coefficient (ICC) of 0.92. The number of lacunes was assessed, where a lacune was defined as a T1-hypointense and T2-hyperintense CSF-like lesion surrounded by white matter or subcortical gray matter with a minimum diameter of 2 mm and was not located in areas with a high prevalence of widened perivascular spaces (vertex, anterior commissure). Medial temporal lobe atrophy (MTA) was assessed on this data set in an earlier study by one independent rater (PS) on coronal T1 images, using a qualitative visual rating scale. This scale ranges from 0 – 4 for both left and right medial temporal lobe region with higher scores indicative of increased atrophy. The scores for the left and right medial temporal lobe region were averaged and used as a general measure of medial temporal atrophy.

Statistical analyses

The primary outcome of interest was time of progression to AD, according to the NINCDS-ARDA criteria. Those that had not converted were considered censored at their last assessment. Cox proportional hazards models were used to assess the association of qualitative white matter ratings with progression to AD. Models were adjusted for age and education. In a second step, we added MTA score, treatment arm and number of lacunes to the model to correct for the presumed influence of the AD process, treatment effect of donepezil or vitamin E, and vascular subcortical changes other than WMH. Kaplan-Meier curves were generated to illustrate the findings, by comparing those in the highest 25th percentile of white matter ratings to the remainder of the subjects. Mean differences in T-WMH, D-WMH, and PVH scores between individuals who converted to AD and those who did not were assessed using Mann-Whitney tests. All assumptions of the models were checked both graphically and numerically and were met by the data.

Results

Demographics and WMH scores of the total group of 152 subjects, converters (subjects who progressed to dementia, n = 55) and non-converters (subjects who did not progress to dementia, n = 97) are presented in Table 1. The demographics of this MRI subgroup were similar to parent study. The mean age was 72.4 ± 6.6 years, the mean educational achievement was 15.0 ± 3.0 years and women made up 55.3% of the sample. Mean baseline MMSE scores (SD) were nearly identical between the parent study (27.3 ± 1.8) and the current study (27.5 ± 1.8). Randomization by treatment arm was also well balanced in this study with 30% randomized to donepezil, 32% to
vitamin E and 38% to placebo. A total of 55 subjects (36%) converted to dementia over the 3-year study period. Subjects progressing to dementia were slightly older and included a higher percentage of women, but the differences were not significant. Converters, however, performed worse on baseline MMSE testing (26.8 ± 1.9) than did non-converters (27.9 ± 1.6), p < 0.001. Mean WMH scores amongst those who converted to dementia also tended to be higher. These differences were small and non-significant, although a trend was found for the PVH ratings.

Table 1. Demographic characteristics of the study group

<table>
<thead>
<tr>
<th></th>
<th>Total group (n = 152)</th>
<th>Converters (n = 55)</th>
<th>Non-converters (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years, (SD)</td>
<td>72.5 (6.6)</td>
<td>73.4 (6.6)</td>
<td>72.0 (6.7)</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>15 (3)</td>
<td>15 (3)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>% male</td>
<td>54.2</td>
<td>48.1</td>
<td>57.6</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>27.9 (1.8)</td>
<td>26.9 (1.9)</td>
<td>27.9 (1.7) **</td>
</tr>
<tr>
<td>Mean T-WMH score (SD)</td>
<td>13.4 (8.4)</td>
<td>13.7 (9.7)</td>
<td>13.1 (7.7)</td>
</tr>
<tr>
<td>Mean PVH score (SD)</td>
<td>3.6 (1.2)</td>
<td>3.9 (1.4)</td>
<td>3.5 (1.1)</td>
</tr>
<tr>
<td>Mean D-WMH score (SD)</td>
<td>7.3 (5.4)</td>
<td>7.4 (6.2)</td>
<td>7.2 (5.0)</td>
</tr>
<tr>
<td>Mean basal ganglia score (SD)</td>
<td>1.5 (2.2)</td>
<td>1.5 (2.2)</td>
<td>1.6 (2.3)</td>
</tr>
<tr>
<td>Mean infratentorial score (SD)</td>
<td>0.9 (1.7)</td>
<td>0.9 (1.8)</td>
<td>0.9 (1.7)</td>
</tr>
<tr>
<td>Number of subjects with lacunes</td>
<td>13</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>MTA score (SD)</td>
<td>1.2 (0.8)</td>
<td>1.3 (0.9)</td>
<td>1.1 (0.7)*</td>
</tr>
</tbody>
</table>

D-WMH: Deep White Matter Hyperintensities, PVH: Periventricular Hyperintensities, T-WMH: Total White Matter Hyperintensities. *: p < 0.05, **: p < 0.001

(p= 0.057). Lacunes were seen in 13 subjects, of which seven converted. Mean T-WMH, D-WMH and PVH scores were higher in subjects with lacunes (19.4 ml (SD 12.2), 10.6 ml (SD 7.6), and 4.5 (SD 1.4) respectively against 12.8 ml (SD 7.8), 7.0 (SD 5.1), and 3.5 (SD 1.2) in subjects without lacunes). Mean MTA ratings were significantly higher in converters than non-converters.

Table 2 shows the additional risk of progression to dementia with each one-point increase on the WMH rating scale. Only PVH was significantly associated with an increased risk of progression after correcting for age and education. A one-point increase in the rating was
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associated with a 59% increased hazard of progression. This is also illustrated by figure 1, which shows the relationship between the highest quartile of PVH (scores > 4) as compared to lower scores (scores ≤ 4) and progression to AD over time. Correcting for MTA and number of lacunes did not change the significance of this association, even though total PVH and MTA ratings were significantly correlated (r = 0.31).

Table 2. Hazard ratios (95% confidence intervals) of increase of 1 point WMH

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 3</td>
</tr>
<tr>
<td>PVH</td>
<td>1.59 (1.24 – 2.05)**</td>
<td>1.49 (1.15 – 1.93)*</td>
<td>1.42 (1.08-1.87)*</td>
</tr>
<tr>
<td>D-WMH</td>
<td>1.02 (0.97 – 1.08)</td>
<td>0.99 (0.94 – 1.05)</td>
<td>0.97 (0.92-1.03)</td>
</tr>
<tr>
<td>Basal ganglia hyperintensities</td>
<td>1.06 (0.94-1.20)</td>
<td>1.05 (0.92-1.20)</td>
<td>1.01 (0.88-1.16)</td>
</tr>
<tr>
<td>Infratentorial hyperintensities</td>
<td>1.08 (0.90-1.28)</td>
<td>1.06 (0.89-1.27)</td>
<td>1.01 (0.84-1.21)</td>
</tr>
<tr>
<td>T-WMH</td>
<td>1.03 (0.99-1.06)</td>
<td>1.01 (0.97-1.05)</td>
<td>1.00 (0.96-1.04)</td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.001

Model 1: Age and education included in the model
Model 2: Age, education, MTA, and treatment arm included in the model
Model 3: Age, education, MTA, treatment arm, and presence of lacunes included in the model

In order to compare the relative risk for progression to dementia related to PVH and MTA, which were rated on different scales, we also fitted the Model 2 after z-score transformation. One standard deviation increase in the total PVH rating was associated with a 64% increased hazard (β=0.49, SE=0.17, p-value=0.003, HR=1.64, 95% CI=1.18-2.27), while one standard deviation increase in MTA rating was associated with a 42% increased hazard (β=0.35, SE=0.15, p=0.04, HR=1.42, 95% CI=1.01-1.99).

Since ApoE genotype was a powerful predictor of progression from MCI to dementia in the parent study, we also assessed the relationship between WMH, MTA, and ApoE genotype. Mean PVH, D-WMH, T-WMH and MTA scores were significantly higher in ApoE4 allele carriers as compared to the non-carriers (p<0.01 for the WMH scores and p = 0.046 for MTA).
Figure 1. Relationship between high total Periventricular Hyperintensities score (scores > 4; upper 25th percentile of scores) and low total Periventricular Hyperintensities score (scores <=4) and progression to dementia.

Discussion

Our results indicate that PVH, and not deep subcortical WMH, increase the likelihood of progressing from amnestic MCI to AD. This is in line with previous cross-sectional studies. Earlier studies showed influence of PVH on decline in cognition in non-demented elderly and risk of dementia. Moreover, the effect of PVH on progression to dementia was unchanged after correction for atrophy of the medial temporal lobe suggesting that WMH lesions may have effects independent of a presumed AD process and may increase the likelihood of clinically evident AD through an additive mechanism. This adds to the growing body of evidence that vascular factors increase lifetime risk of AD.

Quantitative measures of WMH and medial temporal lobe atrophy differ notably between AD and healthy controls. If we assume that most individuals with amnestic MCI have...
Clinical impact of cerebral vascular lesions

at least some AD pathology, WMH would be expected to increase the likelihood of progression to dementia as a second mechanism for brain injury similar to studies of stroke and AD.35,37 Hypertension is a known risk factor for WMH and can contribute also to cortical atrophy, including in the medial temporal lobe. Moreover, since WMH can lead to deficits in cognitive areas other than memory, such as executive function or attention, WMH related brain injury may result in additional cognitive deficits that would contribute to dementia diagnostic criteria.38 The above mentioned studies, however, did not differentiate between deep WMH and PVH, a notion that creates confusion and needs clarification for future studies.39

In our study, subcortical WMH did not substantially add to the risk of progression to dementia. There are at least two possible explanations for this finding. First, it may be that qualitative estimates of PVH closely estimate total WMH volume.40 Second, it is possible that the periventricular region includes functionally important (cholinergic) neural pathways.41,42 Of course, the combined effect of total volume and location may be important. Finally, the significance of the PVH finding may be a limitation to the qualitative scoring method as neuropathological research suggests that the substrate of larger deep and periventricular lesions (a likely co-occurrence when PVH scores are high) is similar.43 Irrespective of potential etiology, qualitative estimates of PVH seem to reflect the cognitive effect of subcortical subtotal vascular disease better than the deep WMH and can therefore serve as a better surrogate marker for disease in this population of amnestic MCI subjects.

ApoE4 genotype has been found to increase the risk of developing AD, presumably by increasing amyloid beta protein (Aβ) deposition and enhancing the vulnerability of neurons for Aβ.44 We found an association between ApoE4 and increased MTA and WMH scores. ApoE is also important to cholesterol metabolism and the ApoE4 genotype is associated with increased risk for cardiovascular and possibly cerebrovascular disease.45 The association of ApoE4 with both MTA and WMH may, therefore, reflect a role in the development of vascular lesions as well as AD pathology and contribute to the apparent association between AD pathology, vascular factors and dementia.

One limitation of this study could be the use of the visual scale for the assessment of WMH. Visual scales are not always linear and the effect measured could be limited due to ceiling effects.46 Our findings, however, showed a significant relationship of PVH with clinical data, indicating that the PVH assessment was sensitive enough in this population. An effect of WMH in general on progression from MCI to dementia, however, has not consistently been found. Small subject groups and limited number of individuals, who convert to dementia during the period of observation, may account for these discrepancies. In addition, we used the MTA scale, a qualitative rating scale. Visual MTA scores may not reflect hippocampal atrophy as
precise as volumetric measurement of this structure on MRI, although differences between visual and volumetric scoring methods seem small with respect to clinical and cognitive characteristics.\textsuperscript{47}

Results of double-blind, placebo-controlled, clinical trials to test efficacy and safety of drugs proven to be efficacious in AD, such as cholinesterase inhibitors and vitamin E, are being carried out in MCI populations and the first results are becoming available.\textsuperscript{18,48,49} In animal models, permanent oxidative stress is a major contributor to neurodegeneration, leading to the investigation of protective effect of vitamin E as anti-oxidative agent.\textsuperscript{50} However, intervention studies have not been able to demonstrate an effect in humans.\textsuperscript{51} Cholinesterase-inhibitors reduce cognitive deficits in AD and VaD, but no effect has been demonstrated in prevention of AD.\textsuperscript{52}

Whatever the exact mechanism by which PVH exert their influence on progression from MCI to AD, these findings could have implications for therapeutic strategies. Effect of medication in subjects with neurodegenerative dementia could vary depending on coexisting vascular burden. Given the results of this study and others, prevention of vascular lesions such as PVH through control of vascular risk factors may prove helpful in reducing the likelihood of dementia for at risk populations.\textsuperscript{17,53,54}
Clinical impact of cerebral vascular lesions

Appendix

Members of the Alzheimer’s Disease Cooperative Study who participated in this MRI study include:

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Geoffrey Ahern, University of Arizona, Tucson
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Sandra Black, Sunnybrook Health Sciences, Toronto
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Neill Graff-Radford, Mayo Clinic, Jacksonville, FL
Danilo Guzman, E. Bruyere Memory Disorder Research, Ottawa
Jeffrey Kaye, Oregon Health and Science University, Portland
Alan Lerner, University Hospitals Health System, Cleveland
Richard Margolin, Vanderbilt University, Nashville
Marsel Mesulam, Northwestern University, Chicago
Richard Mohs, Mt. Sinai School of Medicine, Bronx, NY
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Myron Weiner, University of Texas Southwestern Medical Center, Dallas
Kristine Yaffe, University of California, San Francisco
References

Clinical impact of cerebral vascular lesions

Chapter 4.2

Risk factor profiles for different radiological expressions of cerebrovascular disease;
Findings from the LADIS study

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on behalf of the LADIS study group

Submitted
Chapter 4

Abstract

Ischemic cerebrovascular disease (CVD) is expressed on MRI as white matter hyperintensities (WMH), lacunes and large vessel infarcts. This study was conducted to investigate specific profiles of vascular risk factors associated with each of these CVD types in independently living elderly subjects.

Baseline data of 618 subjects from the multicenter prospective Leukoaraiosis And DISability (LADIS) study were used. Mean WMH volume was 21.2 ml (SD 22.6), 48 % of study subjects had one or more lacunes, 9 % had one or more clinically silent or minor large vessel infarct. We assessed associations between vascular risk factors and CVD with uni- and multivariate linear regression (WMH) and logistic regression (lacunes, large vessel infarcts) using the following risk factors: age, gender, smoking, history of high cholesterol level, diabetes, peripheral vascular disease, hypertension, and heart disease (defined as heart failure, atrial fibrillation, cardiac valve disease, and/or myocardial infarction).

The CVD types were only slightly correlated with each other (0.08 < r <0.23, p < 0.01). Male gender was associated with all CVD types, older age and hypertension with WMH volume. Diabetes was associated with large vessel infarcts.

Specific vascular risk profiles can be identified for large and small vessel CVD. These data may be used to focus research in future preventive strategies.
Clinical impact of cerebral vascular lesions

Introduction

Ischemic cerebrovascular disease (CVD) is expressed on magnetic resonance imaging (MRI) as white matter hyperintensities (WMH), lacunes and large vessel infarcts. WMH and lacunes are thought to reflect small vessel disease, while large vessel infarcts are due to obstruction of large cerebral or carotid arteries, thromboembolic or by local arteriopathy. WMH seem indicative of incomplete infarction or ischemia, whereas lacunes and large vessel infarcts are caused by complete infarction.

CVD may give rise to a variety of clinical symptoms and signs, including cognitive decline and dementia. The cognitive profile of patients with WMH and lacunes is typically subcortical with impaired executive function and reduced mental speed, whereas large vessel infarcts can lead to cortical deficits, including aphasia, alexia, agnosia and memory loss. Symptoms of lacunes and large vessel infarcts most often present acutely, whereas deficits due to WMH are of more gradual onset.

Risk factors for individual types of CVD have been studied before. Risk factors of WMH that have been repeatedly reported are age and hypertension. Results with respect to other risk factors, including smoking, hypercholesterolemia, diabetes mellitus, and cardiac disease have been inconsistent. Hypertension and diabetes mellitus are among the most consistently found risk factors for lacunes. Older age, smoking, and carotid and cardiac disease have also been reported. Finally, large vessel infarcts have been found to be associated with hypertension, heart disease, atrial fibrillation, diabetes mellitus, smoking and hyperlipidemia.

It is conceivable that each of these expressions of CVD is associated with a specific profile of vascular risk factors. Some vascular risk factors may be associated with several expressions of CVD, whereas others are more specific. However, former studies remain inconclusive, as no study investigated the associations between vascular risk factors and the three CVD types at the same time in one sample. In the current study we assessed the associations between vascular risk factors and WMH, lacunes and clinically minor or silent large vessel infarcts, respectively, in a large sample of independently living elderly.

Materials and Methods

Subjects

Baseline clinical and radiological data of the Leukoaraiosis And DIStability study (LADIS) were used. This prospective multicenter multinational project aims to assess the role of

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WMH on the transition to disability in every day life of elderly subjects who were functioning independently at time of enrollment and who had different degrees of WMH. Details on purpose and methods of this study were reported previously. Since subjects were independent in instrumental activities of daily living, the cerebral vascular lesions studied here were not largely disabling. At baseline, 639 participants were included and underwent extensive assessment including standardized questionnaires on vascular risk factors, neuropsychological tests and cerebral MR imaging.

**Vascular risk factors**

In the present study we examined the following risk factors: age (dichotomized in 65 – 74 and 75 – 85 years), gender, smoking (defined as positive in case of current or past smoking), history or presence of high blood cholesterol (total cholesterol >200, LDL >130, HDL <35 mg/dL, and/or hypertriglyceridermia based on serum triglyceride >200 mg/dL, on at least two occasions), diabetes mellitus (treatment with antidiabetic medications, or at least 8-hour fasting plasma glucose ≥ 7.0 mmol/L or 126 mg/dL), peripheral vascular disease (symptomatic disease presenting as intermittent claudication and/or critical leg ischemia), hypertension (subjects receiving antihypertensive treatment or with values ≥140/90 mmHg, based on measurements taken on several separate occasions), heart disease, defined as presence of at least one of the following: symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed toward heart failure, atrial fibrillation (based on history and/or available clinical records as ECG characterized by the presence of rapid, irregular, fibrillatory waves that vary in size, shape and timing, usually associated with an irregular ventricular response), cardiac valve disease (presence of one or more of the following: aortic stenosis, chronic aortic regurgitation, mitral stenosis, mitral regurgitation, multiple valve disease, prosthetic heart valves), or myocardial infarction (documented by history, ECG or cardiac enzymes). Data on high cholesterol were missing in 20 subjects, on smoking in 1, on diabetes in 4, on peripheral vascular disease in 6, on hypertension in 2, and on heart disease in 6.

**MRI**

MRI studies consisted of a sagittal or coronal T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with 1-1.5 mm slices and axial T2 and Fluid Attenuated Inversion Recovery (FLAIR) images of 5 mm thickness. WMH were measured semi-automatically by a single rater (ECWvS) on the FLAIR images using a home-developed seed-growing program (Show_Images, version 3.6.1) on a Sparc 5 workstation (SUN, Palo Alto,
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Briefly, lesions were marked manually and automatically outlined based on the locally set threshold for upper and lower intensity values, rendering a WMH volume. WMH volume measurements were not available for 21 subjects due to insufficient scan quality. Total number of lacunes was assessed on the MPRAGE, a lacune being defined as a hypointense focus of at least 3 mm in the largest diameter, surrounded by white matter or subcortical gray matter, and not located in areas with a high prevalence of widened perivascular spaces (vertex, anterior commissure). Large vessel infarct was defined as a parenchymal defect in an arterial territory involving the cortical gray matter.

Statistical analyses

Associations among different types of CVD were assessed using Spearman’s rank correlation analysis. Univariate and multivariate linear (WMH) and logistic (lacunes, large vessel infarcts) regression analyses were performed with dichotomized vascular risk factors as independent variables and WMH, lacunes and large vessel infarcts as the dependent variables. WMH volumes (ml) were used and the number of lacunes and large vessel infarcts was dichotomized in zero, or at least one. First, we performed univariate models for each risk factor separately (Model 1). Second, all risk factors were entered simultaneously (Model 2), Finally, the two other CVD types were entered as additional covariates in the multivariate model (Model 3).

Results

In the present study, 618 subjects were analysed, of which 278 (45%) males and 270 (44%) in the older age group. Mean WMH volume was 21.2 ml (SD 22.6, range 0.7 – 156.1). 48% of study subjects had one or more lacunes, 9% had one or more large vessel infarct. Location of the infarcts was frontal in 12 subjects, parietal in 21, occipital in 16, temporal in 11, infratentorial in 13, and in the basal ganglia in 4. The three CVD types were only slightly correlated (0.08 < r <0.23, p < 0.01). The prevalence of risk factors in the study sample is shown in figure 1. Hypertension was very common with a frequency of 70%. In addition, there was a relatively large group of subjects with a positive history of smoking and hypercholesterolemia.
Figure 1. Number of subjects in each risk factor category.

PVD: peripheral vascular disease

Univariate linear regression analyses showed that WMH volume was associated with older age, male gender, and smoking (table 1, model 1). In the multivariate analysis, older age, male gender and hypertension were significant predictors (model 2). When lacunes and large vessel infarcts were additionally corrected for, age and gender remained statistically significant (model 3). Univariate logistic regression analyses showed positive associations for older age and male gender with the presence of lacunes (table 2, model 1). Male gender was a significant predictor in the multivariate analyses (model 2 and 3) and together with older age when corrected for other CVD types (model 3).

The presence of large vessel infarct was related to several risk factors in univariate logistic regression analyses (table 3, model 1). In the multivariate analyses, the associations with male gender and diabetes remained significant (model 2 and 3).
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<table>
<thead>
<tr>
<th>Table 1. Associations between vascular risk factors and WMH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>risk factor</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>65 – 74</td>
</tr>
<tr>
<td>75 – 85</td>
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<tr>
<td>Gender</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Smoking</td>
</tr>
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<td>Hypercholesterolemia</td>
</tr>
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</tr>
<tr>
<td>yes</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>no</td>
</tr>
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<td>Hypertension</td>
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</tr>
<tr>
<td>Heart disease</td>
</tr>
<tr>
<td>no</td>
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<tr>
<td>yes</td>
</tr>
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</table>

Data are presented as $\beta$ (se). Model 1 represents univariate linear regression analyses. Model 2 represents multivariate analysis with mentioned risk factors only. Model 3 represents multivariate linear regression analysis including mentioned risk factors, lacunes and infarcts included in the model. *: $p \leq 0.05$, **: $p \leq 0.001$
Table 2. Associations between vascular risk factors and lacunes

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>% Lacunes</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 – 74</td>
<td>51</td>
<td>0.7</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>75 – 85</td>
<td>43</td>
<td>(0.5 – 1.0)*</td>
<td>(0.5 – 1.1)</td>
<td>(0.5 – 0.9)*</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
<td>2.0</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Male</td>
<td>57</td>
<td>(1.4 – 2.7)**</td>
<td>(1.3 – 2.6)**</td>
<td>(1.1 – 2.4)**</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>1.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>(0.9 – 1.8)</td>
<td>(0.7 – 1.5)</td>
<td>(0.7 – 1.4)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>(0.9 – 1.7)</td>
<td>(0.9 – 1.7)</td>
<td>(0.8 – 1.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>47</td>
<td>1.3</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>53</td>
<td>(0.8 – 2.0)</td>
<td>(0.7 – 1.8)</td>
<td>(0.6 – 1.7)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>47</td>
<td>1.7</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Yes</td>
<td>61</td>
<td>(0.9 – 3.3)</td>
<td>(0.7 – 2.8)</td>
<td>(0.7 – 2.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42</td>
<td>1.4</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>(1.0 – 1.9)</td>
<td>(0.9 – 2.0)</td>
<td>(0.9 – 1.9)</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>1.3</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>63</td>
<td>(0.9 – 1.9)</td>
<td>(0.7 – 1.6)</td>
<td>(0.7 – 1.6)</td>
</tr>
</tbody>
</table>

Data for models 1 – 3 are presented as OR (95% CI). Model 1 represents univariate logistic regression. Model 2 represents multivariate logistic regression with mentioned risk factors only. Model 3 represents multivariate logistic regression with mentioned risk factors, WMH, and infarcts.

*: p ≤ 0.05 , **: p ≤ 0.001
### Table 3. Associations between vascular risk factors and large vessel infarcts

<table>
<thead>
<tr>
<th>风险因素</th>
<th>% infarcts</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 – 75</td>
<td>8</td>
<td>1.3</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>75 – 85</td>
<td>11</td>
<td>(0.8 – 2.3)</td>
<td>(0.9 – 3.1)</td>
<td>(0.8 – 2.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>5</td>
<td>3.3</td>
<td>3.5</td>
<td>2.9</td>
</tr>
<tr>
<td>male</td>
<td>15</td>
<td>(1.8 – 6.0)**</td>
<td>(1.8 – 6.7)**</td>
<td>(1.5 – 5.7)**</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>9</td>
<td>1.1</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>yes</td>
<td>10</td>
<td>(0.6 – 1.8)</td>
<td>(0.4 – 1.4)</td>
<td>(0.4 – 1.3)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>8</td>
<td>1.5</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>yes</td>
<td>11</td>
<td>(0.8 – 2.5)</td>
<td>(0.9 – 1.9)</td>
<td>(0.9 – 3.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>7</td>
<td>3.5</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>yes</td>
<td>21</td>
<td>(1.6 – 6.4)**</td>
<td>(2.5 – 5.5)**</td>
<td>(1.4 – 5.4)**</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>9</td>
<td>1.7</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>yes</td>
<td>14</td>
<td>(0.7 – 4.2)</td>
<td>(0.5 – 3.8)</td>
<td>(0.5 – 4.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>5</td>
<td>2.2</td>
<td>1.7</td>
<td>1.6</td>
</tr>
<tr>
<td>yes</td>
<td>11</td>
<td>(1.1 – 4.4)*</td>
<td>(0.8 – 3.7)</td>
<td>(0.7 – 3.4)</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>8</td>
<td>2.2</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>yes</td>
<td>16</td>
<td>(1.2 – 3.9)**</td>
<td>(0.9 – 3.2)</td>
<td>(1.0 – 3.5)</td>
</tr>
</tbody>
</table>

- 以上各列数据均以OR (95% CI) 表示。
- Model 1 代表单变量逻辑回归分析。Model 2 代表包含上述风险因素的多变量逻辑回归分析。Model 3 代表包含上述风险因素、WMH 和脑软化症的多变量逻辑回归分析。

#### Discussion

在当前研究中，探讨了不同类型的 CVD 风险因素。同时考虑了共病性脑血管病，结果与之前针对 WMH、脑软化症和大血管梗死的研究结果相当相似，说明年龄和高血压与 WMH 体积相关，而糖尿病与大血管梗死相关。

我们发现年龄、性别和高血压是独立的风险因素。
Chapter 4

factors for WMH, male gender for lacunes, and male gender and diabetes mellitus for clinically minor or silent large vessel infarcts. In addition, our data suggest that male gender is a general risk factor for CVD, which is in congruence with former studies on risk factors for cardiovascular disease as well as cerebrovascular disease. Gender differences could be partly due to differences in prevalence of risk factors. However, in the multivariate analyses we corrected for the prevalence of other risk factors. Alternatively, men may be more susceptible to the effect of vascular risk factors. Finally, a cardioprotective role of estrogens until menopause and a later onset of vascular disease in women could also partly explain the differences between males and female.

The design of this study has the advantage that a large number of subjects were included, examined and scanned in an identical fashion, information on risk factors was collected uniformly and contributions of the risk factors could be compared directly. One of the limitations of the study may be the subject selection. The stratification by WMH may prevent generalizability of the results to a general population of elderly. However, the LADIS sample likely suits with the patient population with WMH encountered in clinical practice because of the broad range of reasons for referral. In addition, subjects who were not independently living could not be included. Cerebrovascular disease leading to major deficits was therefore not present in the LADIS study population. The large vessel infarcts analysed here were clinically silent or minor.

This study shows different vascular risk profiles for the large and small vessel CVD categories. Except the administration of thrombolytic medication in the first hours after ischemic stroke, therapeutic strategies for ischemic disease are focused on prevention of recurrence of ischemic events. This includes strict control of blood pressure and correction of hyperlipidemia. Preventive treatment can be potentially more focused when risk factor profiles are known.
Clinical impact of cerebral vascular lesions

References


General discussion, conclusions and future directions
Chapter 5
General discussion

Vascular lesions on MRI

The effect of compromised vascularisation of the brain can be visualized on MRI and has several appearances. The different T1- and T2-weighted sequences have their own qualities and when combined give complementary information on the characteristics and probable cause of the ischaemic pathology. This may be important to fulfill diagnostic criteria, as mentioned below, and changes the role of neuroimaging from excluding possibly treatable causes of cognitive decline to a more diagnostic approach. T1-weighted images reveal lacunes and cortical infarcts, FLAIR is best suited for the assessment of WMH and we found that conventional T2-weighted images are preferred in the assessment of WMH in the thalamus and infratentorial regions. In addition, T2* sequences (e.g. gradient-echo) can be used for the detection of microbleeds. An imaging protocol using T1, T2, T2* and FLAIR images may therefore optimizes diagnostic capabilities of MRI for VaD (table 1).

Diagnosing VaD

For diagnosing VaD the NINDS-AIREN criteria are the most recent and widely used criteria. To fulfill a diagnosis of VaD according to those criteria, a subject is required to be a) demented, b) have clinical and radiological signs of vascular disease and c) have an onset of symptoms within a couple of months after the vascular ictus. The criteria were originally designed for research purposes in 1993, but are now also widely used in patient care. Already in 1993, the authors recognized the added value of neuroimaging and some form (CT or MRI) was required for the diagnosis. The criteria include a radiological part, which includes a list of vascular lesions thought to be leading to cognitive deficits. This list is complex; only lesions in specific areas of the cerebrum and of certain severity are regarded sufficient to lead to VaD. We demonstrated that the radiological part of the NINDS-AIREN criteria has poor agreement between raters and we hypothesized that this may at least be partly due to lack of description of the areas and severity of the lesions. Operationalization (using a manual on how to apply the criteria and used to create uniformity between raters) only improved agreement in raters that were already experienced in the assessment of vascular lesions on MRI. Operationalization does not change criteria and therefore can not address all problems related to diagnosing VaD. Further work is certainly needed to elaborate on the radiological evidence needed to demonstrate VaD.
Table 1. Example of imaging protocol for the detection of cerebral vascular lesions

<table>
<thead>
<tr>
<th>Coronal 3D T1 gradient echo</th>
<th>TR</th>
<th>15 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TE</td>
<td>7 ms</td>
</tr>
<tr>
<td></td>
<td>TI</td>
<td>500 ms</td>
</tr>
<tr>
<td></td>
<td>Slice thickness</td>
<td>1 mm</td>
</tr>
<tr>
<td></td>
<td>Flip-angle</td>
<td>15-30 degrees</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Axial T2 Turbo Spin Echo</th>
<th>TR</th>
<th>4600 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TE</td>
<td>119 ms</td>
</tr>
<tr>
<td></td>
<td>Slice thickness</td>
<td>3-5 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Axial FLAIR</th>
<th>TR</th>
<th>9000 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TE</td>
<td>105 ms</td>
</tr>
<tr>
<td></td>
<td>TI</td>
<td>2200 ms</td>
</tr>
<tr>
<td></td>
<td>Slice thickness</td>
<td>3-5 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Axial T2* gradient-echo</th>
<th>TR</th>
<th>650 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TE</td>
<td>15 ms</td>
</tr>
<tr>
<td></td>
<td>Slice thickness</td>
<td>3-5 mm</td>
</tr>
<tr>
<td></td>
<td>Flip-angle</td>
<td>&gt;20 degrees</td>
</tr>
</tbody>
</table>

TR = repetition time, TE = echo time, TI = inversion time

Based on observations of patients with multiple infarctions and dementia, the stepwise progression of cognitive decline and the presence of other focal neurological deficits were adopted in the criteria. Extensive WMH as a cause of VaD only gained general recognition since the 1980’s with the availability of cerebral CT and MR imaging. In the years after 1993, when imaging became available on a wider scale and could be used for patient care as well as research, it was more obvious that VaD due to WMH is in fact the most common form of VaD\(^2,3\), and that the requirements of a stepwise progression and other focal neurological deficits are typically not applicable to this group of VaD subjects.
General discussion

Radiological considerations of WMH

Pathology / etiology

WMH are considered to be an expression of small vessel disease. Arteriolopathy of the small vessels penetrating the white matter may compromise the supply of oxygen, leading to subtotal ischemia and partial demyelination. The ensuing alterations in the biochemical properties of the tissue lead to altered relaxation behavior facilitating the visibility of WMH on MRI. Neuropathological studies showed that WMH, as seen on MRI, correspond with rarefaction of myelin, gliosis, and axonal loss to a varying degree. Further work is needed to improve the possibilities to differentiate WMH into more benign and more severe types of tissue damage, and thereby hopefully improving the clinico-radiological associations.

Assessment of lesion distribution and severity

Several methods exist to measure severity of WMH. Visual rating scales are quick, easily applicable and interobserver reliability is good for most used scales. On the other hand, the scales do usually not provide details on size and location of the lesions and most are not linear. To obtain lesion volume, a computerized method can be used. Most of these techniques are semi-automated, meaning that some operator interference is necessary, leading to time-consuming measurements. In addition, these volumetric methods require a designated computerized environment, which has limited availability. We demonstrated in chapter 3.1 that correlations with clinical data are dependent of the method used, and the volumetric methods seem more sensitive. Especially in small study samples this seems therefore the preferred technique. In addition, computerized volume measurements can be used in several applications: by combining computerized lesion outlines with an anatomic map (which can be registered to the subject space), it is possible to generate regional lesion loads. When intracranial volumes are assessed, these can be included in the analyses. Further work is needed to automate lesion detection using computer algorithms, which provides plausible results in some labs, but typically are difficult to apply to images generated by other MR scanners.

Clinical considerations of WMH

Research has shown that WMH can lead to memory problems, mood disorders, gait disturbances and bladder control dysfunction. It was hypothesized that this could be due to the disruption of axons, running through the white matter regions, and hereby change connections between cortical regions and other parts of the CNS. On the other hand, ischemia of basal forebrain cholinergic nuclei, basal ganglia or white matter that have extensive cholinergic cortical projections may result in cholinergic deficits and clinical symptoms. The severity of
Chapter 5

the WMH correlates with clinical symptoms, but there are individuals with extensive and confluent lesions without significant clinical correlates, although they are at greater risk for becoming impaired in daily life. The recruitment of other cortical areas than originally designed for the task can possibly mask the deficits. WMH can lead to cognitive deficits to such extend that a vascular dementia syndrome becomes present. There are, however, also indications that these lesions contribute to the development of AD. The exact mechanisms are not completely understood and a number of possible causes have been postulated. WMH might lead to deficits in cognitive areas other than memory, such as executive function or attention, and can therefore contribute to AD in an earlier stage than by AD pathology alone. Another explanation could be that vascular lesions can lead to enhanced neuronal degeneration. Recently, it was shown that oxidative stress was one of the earliest pathological changes in AD, possibly leading to cell dysfunction and degenerative changes.

Future Directions

Diagnosing VaD

We were able to demonstrate that operationalization of the criteria for VaD improves interobserver reliability in experienced observers to a clinically acceptable level. Further work however, is needed to refine the radiological criteria, and make them more widely applicable in a reliable fashion. Since good interobserver reliability is needed for criteria to clinically diagnose a disease, we suggest the current criteria to be revised with the incorporation of exact imaging criteria. Second, the knowledge that the subcortical subtype is more prevalent than previously believed and the clinical course and signs that are applicable to the cortical subtype do not apply to the subcortical form should in our opinion be incorporated in the definition of VaD.

Imaging and assessment of WMH

We showed that the method used for the assessment of WMH can increase statistical power in studies describing the relationship of WMH with clinical parameters. It can be hypothesized that this is also true for the evaluation of risk factors for WMH. If automated quantitative measurements will be further developed, precision might be improved, and operator assistance and time of assessment can be reduced. This offers the possibility of monitoring disease
General discussion

progression and effects of therapeutic interventions. Other imaging techniques, such as diffusion fiber tracking techniques, may show the anatomical connections of different cortical regions through white matter tracts and provide more information on the (degree of) disruption of specific fiber tracts affected by WMH and the loss of function that follows.

Treatment of VaD

Symptomatic treatment has been focused on the cholinergic deficits that have been found in VaD. Acetylcholine can induce vasodilation and studies on the effect of cholinesterase inhibitors, approved for the treatment of AD, have shown beneficial effects on cognition and daily functioning in subjects with VaD as well, although the effects were not as large as in individuals with AD. Memantine, a N-methyl-d-aspartate receptor antagonist possibly preventing neurodegeneration by reducing the cells’ pathologically increased sensitivity to glutamate, leads to modest improvement of cognition and behavior in individuals with mild to moderate VaD.

A more causal therapy for VaD would be the prevention of (further) vascular damage to the brain. Several risk factors have been identified, some of which are amenable to treatment. A reduction in the incidence of dementia by treating hypertension has been reported. Potential secondary preventive agents such as NSAID's are also subject of study. In two retrospective studies, subjects with VaD using antiplatelet or anticoagulant medication had a longer life expectancy that those without. Caution should be taken not to generalize the results to the entire VaD population, since subjects with microbleeds possibly are at greater risk of developing hemorrhagic strokes and have not been studied separately. The first study only included individuals with ischemic VaD and the second study included 79 VaD patients with the number of subjects with microbleeds not mentioned. In longitudinal designs, the effect of prevention of progressing dementia by changing vascular risk factors still needs to be studied.
References

General discussion

Chapter 5
Chapter 6
Summary

The incidence of dementia is increasing to the stunning number of 30,000 new cases each year in the Netherlands. Despite progress in knowledge of the several forms of dementia, causal therapies are yet not available at this moment. However, several therapeutic agents are being investigated in different groups of dementia and it is therefore important to be able to differentiate between different causes of dementia. This especially holds for the distinction between Alzheimer’s disease versus vascular dementia.

In the past, brain imaging was regarded as optional, mainly to exclude possibly surgically treatable causes of dementia, such as mass lesions. Today imaging can contribute to specifically diagnose the illness underlying a dementia syndrome, for example by demonstrating medial temporal lobe atrophy in Alzheimer’s disease. MRI is very sensitive to vascular lesions. With $T_1$-weighted series, cortical infarcts and lacunes can be visualized. $T_2$-weighted sequences, like Fluid-Attenuated Inversion Recovery (FLAIR) and dual-echo Turbo Spin Echo (TSE) are used to show subcortical lesions; FLAIR is able to distinguish between WMH on one hand and lacunes and perivascular spaces on the other, while TSE is preferred for the basal ganglia (and thalamus) and infratentorial regions.

VaD is thought to be the second most common type of dementia. The NINDS-AIREN criteria for VaD are the most recent and widely used. These criteria contain a radiological part, necessitating evidence of vascular disease on brain imaging. In chapter 2.2 we showed that overall interobserver agreement of these radiological criteria is poor (Cohen’s $\kappa$ 0.29), and that operationalization only improves agreement between already experienced raters of vascular lesions on MRI ($\kappa = 0.62$), but that it does not affect agreement between raters who are not trained in scoring vascular lesions (from $\kappa = 0.17$ to $\kappa = 0.18$ after operationalization).

According to the NINDS-AIREN radiological criteria for VaD, bilateral vascular lesions in the thalamus can account for a VaD syndrome. In Chapter 2.3, axial TSE imaging is compared to axial FLAIR with respect to these thalamic lesions. In a blinded review of MRIs of 73 subjects, meeting the NINDS-AIREN radiological criteria of VaD, TSE was found to be more sensitive. Using FLAIR, only 55% of the probable vascular lesions are detected. For TSE, this is 97%. Those results signify that, when applying the NINDS-AIREN criteria, FLAIR should not be the only $T_2$-weighted sequence.

WMH can be assessed qualitatively, using a visual scale, or quantitatively, with volumetric methods. Chapter 3.1 shows the characteristics of several visual scales for WMH in comparison with a semiautomated volumetric assessment. The visual scales appear to have ceiling effects.
and their relationship with increase in WMH volume is not linear, possibly compromising their 
ability to detect differences between groups. Several visual scales for the assessment of WMH 
were investigated with respect to their power of detecting WMH changes over time in chapter 
3.2. It is reported that on 3-year interval MRIs of subjects with varying degree of WMH, the 
rating scales that are developed for the assessment of WMH on cross-sectionally, are largely 
unable to pick up changes in WMH burden over time within subjects. Volumetric assessment or 
the use of a visual rating scale, specifically designed to detect change over time, are more 
sensitive to progression of WMH, and are therefore preferred in longitudinal studies.

Vascular lesions can lead to VaD, but there is a growing body of evidence that they also 
might play a role in the etiology of AD. Vascular lesions are more common in subjects with AD 
compared to healthy controls of the same age. We investigated the presence of WMH in a 
sample of subjects with amnestic MCI, which is regarded by some as a transition phase between 
normal aging and AD, and who were followed up over a period of three years. Using a visual 
rating scale, WMH was assessed in several brain regions: subcortical, periventricular, in the 
basal ganglia, and infratentorial. We found that WMH located in the periventricular regions was 
significantly more prevalent in the individuals who later progressed to AD. This may indicate 
that vascular factors influence the development of degenerative dementia such as AD.

Ischemic vascular brain lesions can be divided into cortical (large vessel) infarcts, lacunar 
(subcortical) infarcts and WMH (subtotal ischemia). In chapter 4.2 we investigated risk factor 
profiles of these three types of CVD and found that male gender is a risk factor for all of these 
CVD types.
Summary
Chapter 7

Nederlandse samenvatting
Samenvatting

De incidentie van dementie neemt toe tot 30.000 nieuwe gevallen per jaar in Nederland. Ondanks toename van kennis over de verschillende vormen van dementie is een causale behandeling nog niet beschikbaar op dit moment. Omdat diverse medicijnen worden onderzocht op werkzaamheid, is het belangrijk om onderscheid te kunnen maken tussen de verschillende vormen van dementie, met name tussen de ziekte van Alzheimer (AD) en vasculaire dementie (VaD).

Voor het stellen van de diagnose dementie was het verrichten van beeldvorming van de hersenen in het verleden optioneel en met name gericht op het uitsluiten van mogelijk chirurgisch behandelbare oorzaken, zoals ruimte-innemende processen. Tegenwoordig kan beeldvorming bijdragen om de onderliggende ziekte bij dementie te diagnosticeren, zoals het aantonen van atrofie van de mediale temporaal kwab bij AD. Met MRI kunnen vasculaire lesies zeer goed worden aangetoond. Met T1-gewogen opnamen kunnen corticale en lacunaire infarcten zichtbaar worden gemaakt. T2-gewogen series, zoals Fluid-Attenuated Inversion Recovery (FLAIR) en dual-echo Turbo Spin Echo (TSE) kunnen worden gebruikt om subcorticale lesies in beeld te brengen; met FLAIR kan onderscheid worden gemaakt tussen witte stof hyperintensiteiten (WMH) enerzijds en lacunaire infarcten en perivascularaire ruimten anderzijds, terwijl TSE het meest geschikt is voor de beoordeling van de basale kernen (en thalamus) en infratentoriële gebieden.

Er wordt aangenomen dat VaD de op één na meest voorkomende oorzaak is van dementie. De International Workshop of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria zijn de meeste recente en meest gebruikte criteria voor VaD. Ze bevatten een radiologisch deel, waardoor beeldvorming nodig is om aan deze criteria te kunnen voldoen. In dit proefschrift wordt beschreven dat de overeenstemming tussen personen die deze radiologische criteria toepassen laag is (Cohen’s κ 0.29), en dat het operationaliseren van de criteria de overeenstemming alleen vergroot tussen personen die al ervaring hebben met het beoordelen van vasculaire lesies op MRI (κ = 0.62). Overeenstemming tussen beoordelaars zonder deze ervaring neemt hierdoor niet toe (van κ = 0.17 tot κ = 0.18) (hoofdstuk 2.2).

Vasculaire lesies in de thalamus kunnen, volgens het radiologische deel van de NINDS-AIREN criteria, leiden tot VaD. In hoofdstuk 2.3 bleek TSE sensitiever dan FLAIR voor de detectie van deze lesions bij de beoordeling van MRI scans van 73 personen, die voldeden aan de
NINDS-AIREN radiologische criteria. Met FLAIR werd 55% van de lesies gevonden, met TSE 97%. Dit suggereert dat voor de beoordeling van vasculaire lesies FLAIR niet de enige T2-gewogen serie zou moeten zijn.

WMH kunnen kwalitatief beoordeeld worden, door middel van een visuele schaal, of kwantitatief, met volumetrische methoden. In hoofdstuk 3.1 worden de kenmerken van diverse visuele schalen en een semi-automatische volumetrische methode beschreven. De visuele schalen blijken plafond-effecten te vertonen en hoogte van WMH score met behulp van deze schalen houdt niet lineair verband met het WMH volume. Hierdoor zou het onderscheidend vermogen van de schalen om verschillen tussen groepen te detecteren verminderd kunnen zijn. Diverse visuele schalen voor de beoordeling van WMH waren ook beoordeeld met betrekking tot hun vermogen om verschillen in tijd te detecteren. In hoofdstuk 3.2 wordt beschreven dat de visuele WMH schalen, die ontwikkeld zijn voor de cross-sectionele beoordeling van WMH, grotendeels niet in staat zijn om veranderingen in volume van WMH, beoordeeld op MRI's met een drie-jaar interval van personen met verschillende ernst van WMH, in score tot uitdrukking te brengen. Volumetrische methoden en een visuele schaal die specifiek voor de beoordeling van verandering van WMH is ontworpen zijn sensitiever voor progressie van lesies en daarom te verkies in longitudinale studies.

Cerebrale vasculaire lesies kunnen leiden tot VaD, maar er zijn steeds meer aanwijzingen dat ze ook een rol spelen bij de ontwikkeling van AD. Ze komen vaker voor bij personen met AD in vergelijking met leeftijdgenoten zonder de ziekte. De aanwezigheid en uitgebreidheid van WMH werd beoordeeld in een groep personen met amnestische MCI, hetgeen mogelijk een transitiefase is tussen normale veroudering en AD. Met een visuele schaal werden WMH gescoord in verschillende hersengebieden (subcorticale, periventriculair, in de basale kernen en infratentoriel) op baseline MRI (hoofdstuk 4.1). Personen die na 3 jaar follow-up AD hadden ontwikkeld, bleken significant vaker WMH in de periventriculaire gebieden te hebben dan de personen die na 3 jaar geen AD hadden.

Ischemische cerebrale vasculaire lesies kunnen worden onderverdeeld in corticale infarcten, lacunaire (subcorticale) infarcten en WMH (subtotale ischemie). In hoofdstuk 4.2 worden de vasculaire risicoprofielen beschreven van deze drie typen CVD. Mannelijk geslacht was een risicofactor voor alle typen CVD.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ADDTC</td>
<td>Alzheimer’s Disease Diagnostic and Treatment Centers</td>
</tr>
<tr>
<td>ARWMC</td>
<td>Age-related White Matter Hyperintensities</td>
</tr>
<tr>
<td>CAA</td>
<td>Cerebral Amyloid Angiopathy</td>
</tr>
<tr>
<td>CADASIL</td>
<td>Cerebral Autosomal Dominant Angiopathy with Subcortical Infarcts and Leukencephalopathy</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid Attenuated Inversion Recovery</td>
</tr>
<tr>
<td>HIS</td>
<td>Hachinski Ischemic Scale</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Disease - 10th edition</td>
</tr>
<tr>
<td>LADIS</td>
<td>Leukoaraiosis and Disability in the Elderly</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic Resonance Angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTL</td>
<td>Medial temporal lobe</td>
</tr>
<tr>
<td>NINDS-AIREN</td>
<td>National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences</td>
</tr>
<tr>
<td>RSS</td>
<td>Rotterdam Scan Study</td>
</tr>
<tr>
<td>T2-WI</td>
<td>T2-weighted image</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
</tr>
<tr>
<td>TSE</td>
<td>Turbo Spin Echo</td>
</tr>
<tr>
<td>VaD</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td>VCI</td>
<td>Vasualr cognitive impairment</td>
</tr>
<tr>
<td>WMH</td>
<td>White Matter Hyperintensities</td>
</tr>
<tr>
<td>WML</td>
<td>White Matter Lesions</td>
</tr>
</tbody>
</table>
Dankwoord

Ik wil de vele mensen bedanken die betrokken zijn geweest bij het tot stand komen van dit proefschrift en een antal mensen in het bijzonder. Allereerst ben ik alle vrijwillige deelnemers aan het dementie-onderzoek en hun partners dank verschuldigd, en met name de deelnemers aan het LADIS onderzoek. Naast het feit dat het hard werken was om alle benodigde gegevens te verzamelen was het ook vaak gezellig en kijk ik terug op een prettige samenwerking.

Mijn promotoren prof.dr. Ph. Scheltens en prof.dr. F. Barkhof.

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promotiecommissie plaats te nemen en voor de samenwerking op verschillend gebied in de loop van de jaren.

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