Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study

F-E de Leeuw, J C de Groot, E Achten, M Oudkerk, L M P Ramos, R Heijboer, A Hofman, J Jolles, J van Gijn, M M B Breteler

Abstract

Objective—White matter lesions are often seen on MR scans of elderly non-demented and demented people. They are attributed to degenerative changes of small vessels and are implicated in the pathogenesis of cognitive decline and dementia. There is evidence that especially periventricular white matter lesions are related to cognitive decline, whereas subcortical white matter lesions may be related to late onset depression. The frequency distribution of subcortical and periventricular white matter lesions according to age and sex was reported.

Methods—A total of 1077 subjects aged between 60–90 years were randomly sampled from the general population. All subjects underwent 1.5T MR scanning; white matter lesions were rated separately for the subcortical region and the periventricular region.

Results—Of all subjects 8% were completely free of subcortical white matter lesions, 20% had no periventricular white matter lesions, and 5% had no white matter lesions in either of these locations. The proportion with white matter lesions increased with age, similarly for men and women. Women tended to have more subcortical white matter lesions than men (total volume 1.45 ml v 1.29 ml; p=0.33), mainly caused by marked differences in the frontal white matter lesion volume (0.89 ml v 0.70 ml; p=0.08). Periventricular white matter lesions were also more frequent among women than men (mean grade 2.5 v 2.3; p=0.07). Also severe degrees of subcortical white matter lesions were more common in women than in men (OR 1.1; 95% confidence interval [95% CI] 0.8–1.5) and periventricular white matter lesions (OR 1.2; 95% CI 0.9–1.7), albeit that none of these findings were statistically significant.

Conclusions—The prevalence and the degree of cerebral white matter lesions increased with age. Women tended to have a higher degree of white matter lesions than men. This may underlie the finding of a higher incidence of dementia in women than in men, particularly at later age.

Keywords: white matter lesions; prevalence; magnetic resonance imaging; population based

White matter lesions are often found on MR scans of elderly people, they are attributed to degenerative changes of long penetrating arteries.1,4 Reported prevalence ranges from 5% to 90%, depending on study design, study population, and rating scales.1–3,5–10 There is evidence that periventricular white matter lesions are especially related to cognitive decline,1,11 whereas subcortical white matter lesions may be related to late onset depression.1,12 White matter lesions can be divided into those in the subcortical and those in the periventricular region. Only a few studies considered lesions in these regions separately,1,12 but some based their analysis on a summary score of subcortical and periventricular white matter lesions,13 as in other studies.1,12 Although it is well established that the prevalence of white matter lesions increases with age, little is known about site specific frequency, including possible differences between the subcortical and periventricular region and the lobar location of the lesions. This distinction may be of potential interest as the subcortical and periventricular white matter lesions might have a different pathogenesis and may result in different cognitive or motor consequences. Some studies reported a higher prevalence of white matter lesions among women than men.1,12 The differences were, however, not statistically significant, and were only reported for total white matter lesions.

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

Methods

STUDY POPULATION

The Rotterdam Scan Study was designed to study determinants and cognitive consequences of age related brain abnormalities in elderly people. In 1995–6, 1904 normal healthy subjects aged between 60–90 years were randomly selected in strata of age (5 years) and sex from two large ongoing prospective follow up cohort studies, the Zötermeer Study and the Rotterdam Study. Both studies have been described in detail elsewhere.16–17 In short, the Zötermeer Study is a prospective population based study among 10 361 subjects, aged between 5–91 years at baseline, which studies determinants of chronic diseases. The Rotterdam Study is a population based prospective cohort study,
among 7983 elderly subjects aged 55 years and over, which studies determinants of neurologi-
cal, cardiovascular, locomotor, and ophthalmol-
mological diseases in elderly people.

For the Rotterdam Scan Study subjects were
invited by a letter, and subsequently contacted
by telephone. On agreement to participate a list
of contraindications was reviewed to assess eli-
gibility (dementia; blindness; or presence of
standard MRI contraindications). From 1904
invited subjects 1717 were eligible. Complete
information was obtained, including a cerebral
MR scan, from 1077 persons (response rate
63%); 563 from the Rotterdam Study and 514
from the Zoetermeer Study). Each participant
signed an informed consent form. The study
was approved by the medical ethics committee
of Erasmus University Rotterdam, The Neth-
erlands.

CONFUNDING VARIABLES
Blood pressure was measured twice on the
right arm in a sitting position, by means of a
random zero sphygmomanometer. The average
of these two measurements was used. Hyper-
tension was defined as a systolic blood pressure
of ≥160 mm Hg and/or a diastolic blood pres-
sure of ≥95 mm Hg or the self reported use of
blood pressure lowering drugs. The ankle to
brachial index was used as an indicator of
atherosclerosis and was assessed by taking the
ratio of the systolic blood pressure measured
at the tibial artery to the systolic blood pressure
measured at the right arm with a random zero
sphygmomanometer, in a sitting position.
Information on diabetes mellitus was obtained
with the use of a standardised questionnaire,
which was checked by a physician during the
interview. Diabetes mellitus was considered
present if the participant was taking oral
antidiabetics or insulin.

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

WHITE MATTER LESIONS RATING SCALE
White matter lesions were considered present if
these were hyperintense on both PD and T2
weighted images and not hypointense on T1
weighted images. White matter lesions were
classified into those in the subcortical and
periventricular region.11 The number and size
of subcortical white matter lesions was rated on
hard copy according to the largest diameter of
one lesion within all slices in which the lesion
could be seen in categories of small (<3 mm),
medium (3–10 mm), or large lesions (>10
mm). To calculate the volume of subcortical
white matter lesions on hard copy, they were
considered to be spherical with a fixed
diameter per size category (range 0–29.5 ml).
Periventricular white matter lesions were rated
semi-quantitatively per region: adjacent to fron-
tal horn (frontal capping), adjacent to lateral
wall of lateral ventricles (bands), and adjacent
to occipital horn (occipital capping) on a scale
of 0 (no white matter lesions), 1 (pencil thin
periventricular lining), 2 (smooth halo or thick
lining), or 3 (large confluent white matter
lesions). This was done for both hemispheres
simultaneously. The overall degree of periven-
tricular white matter lesions was calculated by
adding up the scores for the three separate cat-
ergories (range 0–9). White matter lesions could
be rated for all subjects except in two in whom
the quality of the MR scan did not allow
reliable rating of the subcortical white matter
lesions. All MR scans were examined by two
raters who were blinded to age, sex, and other
risk factors for white lesions. In case of a disa-
greement of more than one point, a consensus
reading was held in all other cases. The readings
of both readers were averaged. The interrater
and intrarater studies showed a good to excel-
lent agreement. For grading the periventricular
white matter κ values were calculated by taking
into account the difference between the scores
of the two raters. These so called weighted κ
values were between 0.79–0.90. For total sub-
cortical white matter volume the interrater and
intrarater intraclass correlation coefficient was
0.88 and 0.95, respectively.

STATISTICAL ANALYSIS
The prevalence of white matter lesions was
defined as the presence of any white matter
lesion (regardless of size or location) in the
brain. The relation between the prevalence of
white matter lesions and age was assessed by
means of age and sex adjusted linear regression
analyses. The frequency distribution of either
type of white matter lesions was calculated by
10 years age strata (60–70, 70–80, and 80–90
years). The relation between sex and white
matter lesions was assessed by means of age
adjusted linear regression with white matter
lesions as the dependent variable. Analysis of
covariance (ANCOVA) was performed to
obtain sex specific mean volume of subcortical
white matter lesions per 10 year age stratum or
the mean grade of the periventricular white
matter lesions. Sex differences for each cat-
ergory (0, 1, 2, and 3) of periventricular white
matter lesions per region, were analyzed with
the χ² test. There is increasing evidence that
there exists a dose dependent relation between
severity of white matter lesions and cognitive
consequences.12 and that especially the pres-
ence of severe white matter lesions is associated
with a reduced cognitive function.13–15 We
therefore separately analyzed severe subcortical
and periventricular white matter lesions for
each sex by means of an age adjusted logistic
Results

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

In our study 8% of all subjects were completely free of subcortical white matter lesions, 20% had no periventricular white matter lesions and 5% had no white matter lesions in either of these locations. Frequency distribution of white matter lesions at both locations strongly depended on age (figs 1 and 2). Of subjects aged between 60–70 years, about 13% were completely free of subcortical white matter lesions and 32% were free of periventricular matter lesions, whereas for subjects aged between 80–90 years these percentages were 0 and 5, respectively. The relation between age and the prevalence of white matter lesions was similar for men and women. The prevalence of subcortical and periventricular white matter lesions significantly increased, by 0.2% and 0.4% per year, respectively. Possible confounding variables including hypertension, diabetes, and indicators of atherosclerosis were equally distributed between men and women. Adjustment for these factors did not alter the magnitude of the associations presented below.

Table 1 shows the volume of subcortical white matter lesions/10 year age stratum by sex. The mean volume of subcortical white matter lesions was highest in the frontal lobe, followed by the parietal, occipital, and temporal lobes. This applied to both sexes and all age groups. The mean volume of subcortical white matter lesions increased from 0.6 ml (SE 0.1) for subjects between 60–70 years of age to 3.2 ml (SE 0.4) for subjects aged between 80–90 years (p<0.01). Women had greater volumes of subcortical white matter lesions than men (total volume 1.45 ml v 1.29), mainly caused by differences in the volume of frontal white matter lesions (0.89 ml v 0.70), but these differences were not significant (p=0.33 and p=0.08, respectively).

Table 2 shows sex specific mean grades of periventricular white matter lesions/10 year age category. The mean grade of periventricular

---

**Table 1** Mean volume (ml) of subcortical white matter lesions/lobar location/10 y age stratum†

<table>
<thead>
<tr>
<th>Lobar location</th>
<th>60–70 y (n=464)</th>
<th>70–80 y (n=415)</th>
<th>80–90 y (n=196)</th>
<th>Overall (n=1075)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=226)</td>
<td>Women (n=238)</td>
<td>Men (n=203)</td>
<td>Women (n=212)</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.23 (0.06)</td>
<td>0.43 (0.06)*</td>
<td>0.75 (0.12)</td>
<td>0.90 (0.12)</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.25 (0.05)</td>
<td>0.26 (0.05)</td>
<td>0.50 (0.07)</td>
<td>0.45 (0.06)</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.01 (0.01)</td>
<td>0.02 (0.01)</td>
<td>0.05 (0.02)</td>
<td>0.02 (0.02)</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.01 (0.02)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Whole brain</td>
<td>0.49 (0.10)</td>
<td>0.72 (0.10)</td>
<td>1.31 (0.18)</td>
<td>1.38 (0.18)</td>
</tr>
</tbody>
</table>

*p<0.05.
†Expressed as mean ml white matter lesion volume on hard copy (SE).

**Table 2** Sex specific mean grade of periventricular white matter lesions/region/10 y age stratum†

<table>
<thead>
<tr>
<th>Lobar location</th>
<th>60–70 y (n=465)</th>
<th>70–80 y (n=416)</th>
<th>80–90 y (n=196)</th>
<th>Overall (n=1077)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=226)</td>
<td>Women (n=239)</td>
<td>Men (n=204)</td>
<td>Women (n=212)</td>
</tr>
<tr>
<td>Frontal capping</td>
<td>0.5 (0.0)</td>
<td>0.6 (0.0)*</td>
<td>0.8 (0.1)</td>
<td>1.0 (0.1)**</td>
</tr>
<tr>
<td>Bands</td>
<td>0.6 (0.0)</td>
<td>0.5 (0.0)</td>
<td>0.9 (0.1)</td>
<td>1.0 (0.1)</td>
</tr>
<tr>
<td>Occipital capping</td>
<td>0.3 (0.1)</td>
<td>0.3 (0.1)</td>
<td>0.7 (0.1)</td>
<td>0.8 (0.1)</td>
</tr>
<tr>
<td>Total periventricular</td>
<td>1.4 (0.1)</td>
<td>1.5 (0.1)</td>
<td>2.4 (0.1)</td>
<td>2.8 (0.1)</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01.
†Expressed as mean grade (SE).
white matter lesions increased from 1.5 (SE 0.1) for subjects between 60–70 years of age to 2.4 (SE 0.1) for subjects aged between 80–90 years (p<0.01). The mean grade of the total periventricular white matter lesions increased from 1.5 (SE 0.1) for subjects aged between 60–70 years to 2.3 (SE 0.1) for subjects aged between 80–90 years (p=0.07), mainly caused by the significant difference in severity of frontal capping between men and women in all age categories.

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

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

**Discussion**

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

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

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

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

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

Our study showed that subcortical white matter lesion volume was highest in the frontal and parietal lobes, 20 and 100 times higher than in the occipital and temporal lobes, respectively. Although the frontal and parietal lobes are larger than the occipital and the temporal lobes, this difference cannot explain the vast difference in white matter lesion volume. Scheltens et al found in a study of 24 “normal” elderly subjects (mean age 68.0 years) that the severity of white matter lesions was highest in the frontal lobe. This finding was even more marked in subjects with Alzheimer’s disease.
we have relatively overestimated the frontal or parietal lobes, but again the magnitude of the difference in the volume of white matter lesions seems out of proportion to this. We are not aware of any difference in vascularisation between the lobes that might explain the large interlobe difference in the prevalence of white matter lesions.

Our study confirms previous findings of a relatively high prevalence and severity of white matter lesions among women. This was also found in the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study. This could be mainly attributed to the significant differences for the subcortical and periventricular white matter lesions in the frontal region. The higher prevalence of white matter lesions among women was in accordance with magnetic resonance spectroscopy studies that were done in the Rotterdam Study part of our study population. We found an increased variance in the ratio between choline, creatinine, and N-acetyl aspartate concentrations in the frontal periventricular region, and concentrations of those metabolites in the whole brain in women compared with men, which may be compatible with the finding of an increased prevalence of white matter lesions in women. It is unclear how these sex differences must be explained. One possibility is an increased susceptibility for ischaemia of the brain secondary to the reduction in estrogen concentrations after menopause plays a part. The occurrence of hypoxia or ischaemia in the cerebral white matter is commonly considered as an intermediate factor in the pathogenesis of white matter lesions. Estrogens have important functions in the brain, including an increase in cerebral blood flow, protection against oxidative stress, stimulation of synaptogenesis, and prevention of neuronal atrophy. The postmenopausal estrogen reduction might make the female brain more vulnerable by reduction of cerebral blood flow (ischaemia) and impairment of neuronal repair mechanisms. This hypothesis is supported by in vitro studies, which showed protective effects of estrogens on menopause related cerebral damage by excitotoxicity and the action of free radicals, as occurs during cerebral ischaemia. As there is a morphological and epidemiological overlap between vascular dementia and Alzheimer’s disease, the increased prevalence of cerebral white matter lesions in women could underlie the higher incidence of Alzheimer’s disease among women, even after adjustment for prolonged life expectancy, especially at high ages. This hypothesis, which we did not attempt to test in this study, about the possible role of estrogens is supported by the finding of a significantly increased incidence of Alzheimer’s disease among women who did not use estrogen replacement therapy.

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

This study was supported by a grant from the Netherlands Organization for Scientific Research (NWO) and the Netherlands Health Research and Development Council (ZON). MAMBB is a fellow of the Royal Netherlands Academy of Arts and Sciences. We thank Bart Schraa and Deni Kraus from the Daniel den Hoed Cancer Clinic, Erasmus Medical Center Rotterdam, The Netherlands and technicians from the Department of Radiology, University Hospital Utrecht, The Netherlands for their skilled experience in making the MR scans.

HISTORICAL NOTE

Saint Vitus and his dance

In the current nomenclature Saint Vitus' dance or chorea (from the Greek χορεία for dance) has been largely displaced by the eponym Sydenham’s chorea. The exchange occurred recently, although the association of the saint and his disease had a long evolution. It attested to the durability of the cult of Saint Vitus in which the early notions of the dance underwent differentiation by physicians centuries later.

The legend and tradition

According to hagiographic texts, Saint Vitus or Guy was born during the third century in Sicily, southern Italy. He came from an illustrious family and against the wishes of family and teachers he became a Christian. During a brief career Vitus was said to have performed numerous miracles. On one occasion he cured the paralysis of the hands of his tormentors. On another, his father lost his sight on seeing angels in front of his son. Vitus prayed for him, whereupon his father regained his vision. In another episode the saint relieved the son of the emperor Diocletianus of his demons, by laying his hands over the head. These miraculous feats contributed to the making of Vitus’ later reputation as the patron saint of neurological disorders. It was the same Diocletianus who had Vitus, still a boy, put to death in 303. Vitus’ iconography included many depictions of him, inside or outside a church, holding a boiling cauldron, the symbol of his martyrdom. Afterwards his relics were transported to Paris and Prague. His cult grew with the establishment of many chapels of Saint Vitus throughout Europe. Veneration of the saint appeared particularly strong among the Germans, Czechs, and Slavs who sought his cure of hydrophobia and other illnesses.

The association with chorea

The saint's relics was thought to be especially efficacious for the sick with “unsteady step, trembling limbs, limping toes, bent fingers and hands, paralysed hands, lameness, crookedness, and withering body”. The signs and symptoms in this grouping mimicked the movements of a dance, and thus the linkage of Vitus and his dance acquired a popular coinage. As the clinical features were heterogeneous, Saint Vitus’ dance (also known as triste mal) became an umbrella term for an assortment of conditions with movement disorder. The association was further enhanced during the middle ages when breakthroughs in medicine and other delirious behaviour struck Europe. Pieter Brueghel the Elder in 1564 depicted the mania of Saint Vitus’ dance in a well known print entitled “Procession of the Possessed”, reproduced in Schedcher. The explanation of these historical events remains unclear. Whether they represented mass hysteria, epidemic infection, or food poisoning has not been resolved. The identification of these epidemics with the present day Sydenham’s chorea is also problematic. However, the dance did undergo a process of differentiation. In the 16th century Paracelsus designated Saint Vitus’ dance as “chorea naturalis”. He recognised that the loss of emotional stability and motor control was central in the disease acquired a popular coinage. As the disease acquired a popular coinage. As the disease Sandemian, in 1686, clarified the kinetic disturbances: “...Saint Vitus’ dance is a sort of convulsion which attacks boys and girls from the tenth year till they have done growing. At first it shows itself by a halting, or rather an unsteady movement of one of the legs, which the patient drags. Then it is seen in the hand of the same side. The patient cannot keep it in its place, whether he lay it upon his breast or any other part of his body. Do what he may, it will be jerked elsewhere convulsively ...”.

Sydenham also described rheumatic fever with its articular manifestations, but he failed to connect it with the chorea. The failure was due in part to the fact that Sydenham and his colleagues did not have a clear idea of the visceral involvement in rheumatic fever. The lack of an auscultation method undoubtedly hampered Sydenham in making the diagnosis of rheumatic carditis. It remained for Richard Bright in 1825 to accurately describe rheumatic carditis. The instances of the combination and alteration of rheumatism and chorea are very numerous; and though I doubt not, in some cases the coverings of the cerebrospinal mass may be and are implicated, yet I believe that the much more frequent cause of chorea, in conjunction with rheumatism, is the inflammation of the pericardium. The irritation probably was communicated thence to the spine ...”.

We have here the chorea, the peripheral, and systemic manifestations of rheumatic fever grouped together for the first time. Others, notably See in 1850, also articulated the uryitary view that the chorea, carditis, and the articular features were all components of the rheumatic fever. Bright could not be faulted for a misguided notion of the disease pathogenesis, for it was not until the 1930s that the infectious process in rheumatic fever was elucidated by the work of A F Coburn, among others. The cerebral lesion of chorea and its relation to the damage in other organs remain unresolved issues. Nevertheless, we have advanced far in our understanding of Saint Vitus’ dance, or in modern usage, Sydenham’s chorea.

A C EFTYCHIADIS
T S N CHEN
15 Georgaki Olympiou Street,
Athens 11741, Greece

Correspondence to: Dr A C Eftychiades