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

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Abstract

Objective—White matter lesions are often seen on MR scans of elderly nondemented 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 is 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 and 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,11 whereas subcortical white matter lesions may be related to late onset depression.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,1–3 5–17 but some based their analysis on a summary score of subcortical and periventricular white matter lesions,13 as in other studies.1–3 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 then men.14 15 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 Zoetermeer Study and the Rotterdam Study. Both studies have been described in detail elsewhere.16 17 In short, the Zoetermeer 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 neurologic-  
cal, cardiovascular, locomotor, and ophthalmologi-  
ical 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 Ne-  
therlands.

CONFounding 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 $\geqslant 160$ mm Hg and/or a diastolic blood pres-  
sure of $\geqslant 95$ 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 scanned with a  
1.5T MR Gyroscan (Philip’s, Best, The Nether-  
lands) and participants from the Rotterdam  
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  
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  
semiquantitatively 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-  
egories (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  
severity of white matter 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 lesions 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  
control for the presence of other risk factors  
and the presence of severe white matter lesions  
was associated with a reduced cognitive function.  
We therefore separately analyzed severe subcortical  
and periventricular white matter lesions for  
each sex by means of an age adjusted logistic  
model study were scanned with a 1.5T MR  

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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 v 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 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 2 Sex specific mean grade of periventricular white matter lesions/region/10 year 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=1077)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=226)</td>
<td>Women (n=238)</td>
<td>Men (n=204)</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>0.02 (0.02)</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 grades of periventricular white matter lesions/region/10 year age stratum†

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<td>Men (n=204)</td>
<td>Women (n=212)</td>
</tr>
<tr>
<td>Frontal</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</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>
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</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 was non-significantly higher among women than men (2.5 (SE 0.1) v 2.3 (SE 0.1); 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 1.2; 95% CI 0.9–1.7) 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

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<td>50.0</td>
<td>29.9</td>
<td>14.9</td>
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<td>1</td>
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<td>8.9</td>
<td>25.5</td>
<td>40.4</td>
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<td>0.5</td>
<td>1.5</td>
<td>5.3</td>
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<td>43.8</td>
<td>51.0</td>
<td>43.6</td>
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<td>5</td>
<td>9.7</td>
<td>18.6</td>
<td>30.9</td>
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<td></td>
<td></td>
<td>6</td>
<td>0.9</td>
<td>3.4</td>
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<td>7</td>
<td>17.1</td>
<td>48.2</td>
<td>25.6</td>
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<td>20.8</td>
<td>27.9</td>
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<tr>
<td></td>
<td></td>
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<td>18.1</td>
<td>34.4</td>
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<td></td>
<td></td>
<td>10</td>
<td>1.3</td>
<td>5.8</td>
<td>17.4</td>
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</table>

Numbers are percentages. *p=0.005 (Overall χ² test).
we have relatively overestimated the frontal or parietal lobes, but again the magnitude of the difference in the volume of white matter lesions is much higher. This is not a result 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.22–24 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.25 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 estradiol 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.26,27 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.28 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.29

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.

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HISTORICAL NOTE

Saint Vitus and his dance

In the current nomenclature Saint Vitus' dance or chorea (from the Greek 


covita for dance) has been largely displaced by the eponym Sydenham's chorea. The exchange occurred recently, although the association of the saint and his dance 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 his illustrious 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 Diocletian of his demons, by laying his hands over him. The patient cannot keep it a side. The patient cannot keep it a side. Then it is seen in the hand of the same


d it is seen in the hand of the same side. The patient cannot keep it a moment 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 the early 19th century to make the association. Bright could not be faulted for a misguided notion of the disease in the 19th century that the infectious process in rheumatic fever was accomplished by the work of A F Coburn, among others. The cerebral lesion of chorea and its relation to the damage in other organs remains unresolved issue. Nevertheless, we have advanced far in our understanding of Saint Vitus' dance, or in modern usage, Sydenham's chorea.

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