Silent Cerebral White Matter Lesions and Cognitive Function in Middle-Aged Essential Hypertensive Patients

Cristina Sierra, Alejandro de la Sierra, Manel Salamero, Javier Sobrino, Elisenda Gómez-Angelats, and Antonio Coca

Background: An association between midlife blood pressure levels and late-life cognitive impairment has been reported. Hypertension is one of the most important factors related to the presence of cerebral white matter lesions, which is a prognostic factor for the development of cognitive impairment. Studies have shown a relationship between white matter lesions and cognitive decline in elderly hypertensive patients. The aim of the present study was to evaluate cognitive function in asymptomatic middle-aged hypertensive patients according to the presence or absence of white matter lesions.

Methods: Sixty never-treated essential hypertensive patients (38 men, 22 women), aged 50 to 60 years (mean age, 54.4 ± 3.8 years), without clinical evidence of target organ damage, were studied. All patients underwent brain magnetic resonance imaging to establish the presence or absence of white matter lesions, using the Rotterdam criteria. Cognitive function was evaluated by a neuropsychologic test battery measuring attention, memory, intelligence, anxiety, and depression.

Results: Twenty-three hypertensive patients (38%) were found to have white matter lesions on brain resonance. These patients exhibited a significantly worse performance on digit span forward, a standardized measure of attention than hypertensives without white matter lesions (4.86 ± 1.14 v 5.51 ± 0.97; P = .027). Hypertensive patients with white matter lesions showed no differences on both visual and logical memory tests when compared with patients without lesions.

Conclusions: We conclude that the presence of silent cerebral white matter lesions in middle-aged hypertensive patients is associated with a mild decline in basic attention.

Key Words: Cognitive function, hypertension, white matter lesions, magnetic resonance imaging.

Hypertension is known to be the most important factor for developing macrovascular cerebral complications such as stroke, and consequently, vascular dementia. Hypertension may also predispose to the development of more subtle cerebral processes based on microvascular pathologic changes. It has been suggested that cerebral microvascular disease contributes to the development of vascular cognitive impairment. Results from cross-sectional and longitudinal studies have shown a correlation between blood pressure (BP) and cognitive function in elderly people, and there is also some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment or vascular dementia through BP control.

Various studies have shown an association between the presence of cerebral white matter lesions (WML) and cognitive function in both normotensive and hypertensive elderly populations. The association between hypertension and WML has been established in cross-sectional and longitudinal studies. The presence of WML has been associated with the severity of high BP values, the lack of BP control in treated hypertensives, the presence of concentric left ventricular hypertrophy, and the presence of the DD genotype of the angiotensin-converting enzyme gene.


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It is unclear whether the impact of elevated BP on cognitive decline in late-life is mediated through its chronic and negative effect on the structural characteristics of the brain. It has been suggested that previously increased BP may increase the risk of cognitive impairment by inducing small vessel disease and WML. However, most studies have been performed in elderly people or have included a mixed population of both normotensive and hypertensive individuals, or patients with a history of cardiovascular disease and diabetes. There are studies that have reported a link between cognitive impairment and heart disease and diabetes. In addition, studies carried out in hypertensive patients included both untreated and treated hypertensives, adding the confounding influence of antihypertensive treatment and BP control in evaluating both the incidence of WML and cognitive function.

Cognitive function in middle-aged hypertensive patients and its possible relationship with the presence or absence of WML has not been fully explored. This study analyzes cognitive function in an homogeneous sample of asymptomatic, middle-aged, never-treated essential hypertensive patients according to the presence or absence of WML on brain magnetic resonance imaging (MRI).

Methods
Patient Selection

Sixty never-treated essential hypertensive patients of both genders, aged 50 to 60 years, were consecutively selected from the Hypertension Unit of the Hospital Clinic, Barcelona, Spain. Patients were referred to the Hypertension Unit for diagnosis and management of hypertension and they were consecutively recruited in their first visit if they complied with inclusion criteria. The diagnosis of essential hypertension was considered on the basis that no known cause of high BP could be detected after complete clinical, biochemical, and radiologic examination. All patients had a systolic BP ≥140 mm Hg or a diastolic BP ≥90 mm Hg in at least three different measurements at 1-week intervals. A trained nurse using a mercury sphygmomanometer, according to standard procedures, measured office BP three times after a 10-min rest period. Blood pressure was considered as the average of the last two readings. Exclusion criteria included type 2 diabetes mellitus (fasting plasma glucose, >6.6 mmol/L), carotid stenosis >50% measured by ultrasonography, alcohol intake >30 g of pure ethanol per day, clinical evidence of cerebrovascular or coronary heart diseases (positive clinical history, electrocardiographic abnormalities, or positive exercise test), cardiac failure, atrial fibrillation, papilloedema, and renal impairment (serum creatinine, >115 μmol/L). Patients were not undergoing pharmacologic treatment for any reason. All patients gave informed consent and the study was approved by the Ethics Committee of the Hospital Clinic and by the Spanish Health Authority.

Cerebral MRI and White Matter Lesion Classification

Magnetic resonance imaging of the brain was performed using a 1.5 Tesla Siemens MAGNETON SP equipment (Siemens AG, Erlangen, Germany). In each patient, axial plane T1- (spin-echo technique: repetition time [TR] 608 msec, echo time [TE] 14 msec), T2- (TR 2500 msec, TE 90 msec) and proton density- (TR 2500 msec, TE 15 msec) weighted images were applied. In addition, images were made in the sagittal plane with short pulse frequencies (spin-echo, TR/TE 608/14 msec) and coronal plane (fast spin-echo T2-, TR/TE 4600/90 msec). Slice thickness was 5 mm. Two investigators who were blinded to all clinical information analyzed the recordings. The final diagnosis of WML was made by consensus. Details of the image interpretation protocols used for this study were the same as the Rotterdam Study. Briefly, we distinguished between white matter hyperintensities directly adjacent to the ventricles (periventricular lesions) and punctate or confluent white matter hyperintensities at some distance from the ventricles (focal lesions). Small caps on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal as other investigators have previously reported. Lesions appearing as lacunar infarctions were not included in this study. In the same way, the presence of brain atrophy was marginal in this cohort of asymptomatic middle-aged people. On the basis of these criteria and in accordance with the Rotterdam Study, the severity of WML was graded as follows. Grade 0 scans showed no or slight periventricular hyperintensity (small caps or pencil-thin lining), fewer than five focal lesions, and no confluent lesions. Grade 1 scans showed moderate periventricular hyperintensity (caps on both anterior and posterior horns of the lateral ventricles, corpus only partly involved, not irregularly extending into the deep white matter) or five or more focal lesions, or both, but no confluent lesions. Grade 2 scans showed severe periventricular hyperintensity (irregularly extending into the deep white matter or marked areas of hyperintensity completely surrounding the lateral ventricles) or confluent lesions.

Cognitive Function Tests

The neuropsychologic test battery included an Intelligence Quotient estimation by means of Vocabulary and Kohs’ Cubes subtests of the Spanish adaptation of the Wechsler Adult Intelligence Scale (WAIS). Tests of attention and working memory included the Digit Forward and Backward Span test, respectively, from the WAIS-Revised, which requires subjects to repeat in normal and in reverse order a series of digits. Digits Forward is a test of immediate auditory memory and is highly sensitive to the capacity to focus and sustain attention. In contrast, Digits Backward requires that the subject focus and sustain attention and perform a mental operation on the digits being held in working memory. Tests for evaluating memory
included the Russell Revision of the Logical Memory subscale and the Visual Reproduction subscale of the Wechsler Memory Scale. These subtests require subjects to recall the details of a short story (logical) and to reproduce several geometric shapes (visual), both immediately after reading or seeing and after a 30-min delay. We calculated the percentage of recall after delay according to the formula:

\[
\text{percentage of recall after delay} = \frac{\text{delayed memory/immediate memory}}{100}
\]

The tests were administered by a trained neuropsychologist in a standardized order during one session in a quiet room, and the Hospital Anxiety and Depression Scale test was also administered.

**Statistical Analyses**

Differences between hypertensive patients with and without WML were analyzed by the two-tailed unpaired Student t test or the nonparametric Mann-Whitney test, for numerical variables. The \( \chi^2 \) or Fisher’s exact tests, as appropriate, were applied for categorical variables. The ANCOVA was used to assess the association of neuropsychologic tests performance and WML, adjusting for age. Values are expressed as mean (standard deviation) for normally distributed variables and as median (range) for variables that deviated from normal distribution. A value of \( P < .05 \) was considered statistically significant.

**Results**

Essential hypertensive patients were classified into three groups on the basis of the severity of WML, using the aforementioned criteria. Thirty-seven patients (61.7%) showed grade 0 (absence), 16 hypertensives (26.7%) had grade 1 (moderate), and 7 patients (11.7%) exhibited grade 2 (severe) WML. Due to small number of patients exhibiting abnormalities grade 2, and to better identify real differences depending on the presence or absence of WML, hypertensive patients with abnormalities grades 1 and 2 were considered together for the analysis (23 patients; 38.3%). Main baseline characteristics including age, gender distribution, body mass index, plasma glucose and cholesterol levels, and renal function did not differ between groups (Table 1). In contrast, essential hypertensive patients with WML showed significantly higher values of systolic BP (170.5 ± 10.9 mm Hg vs 161.8 ± 13.6 mm Hg; \( P = .014 \)) and diastolic BP (101.6 ± 5.6 mm Hg vs 97.6 ± 6.4 mm Hg; \( P = .021 \)) compared to hypertensives without WML.

No differences in intelligence, education, anxiety, or depression scales were observed between groups (Table 2). As it is known that intelligence, education levels, and anxiety can influence cognitive tests measuring attention and memory, the lack of differences between groups allows the comparison in terms of cognitive performance. Essential hypertensive patients with WML performed significantly worse on digit span forward, a standardized measure of attention, than hypertensives without WML (digit span forward: \( 4.86 ± 1.14 \) vs \( 5.51 ± 0.97 \); \( P = .027 \)). This association remained significant (\( P = .030 \)) after adjusting for age. The standardized measure of working memory did not differ between groups (digit span backward: \( 4.00 ± 0.43 \) vs \( 4.12 ± 0.99 \); \( P = .444 \)). In addition to this poorer attention capacity, hypertensive patients with WML showed slightly lower scores on the visual memory test when compared with patients without (visual reproduction, percentage recall after delay: 83% ± 18% vs 89% ± 16%; \( P = .218 \)), whereas no differences were found in the logical memory test (Table 3). All neuropsychologic tests were normally distributed.

**Discussion**

This study shows an association between the presence of WML in brain MRI and the existence of poorer performance on neuropsychologic tests in asymptomatic, middle-aged, never-treated essential hypertensive patients. Hypertensive patients with WML had a significantly poorer digit span forward performance, a standardized measure of attention, and slightly lower scores on visual memory test than hypertensives without WML. Logical and working memory tests showed no differences when hypertensives with and without cerebral WML were compared.

With relation to studies performed in hypertensive population, Schmidt et al. studying 32 asymptomatic hyper-

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**Table 1.** Baseline characteristics of essential hypertensive patients with and without cerebral white matter lesions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without WML (n = 37)</th>
<th>With WML (n = 23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53.9 (3.5)</td>
<td>55.2 (4.2)</td>
<td>.216</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/13</td>
<td>14/9</td>
<td>.788</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.1 (2.7)</td>
<td>29.4 (3.5)</td>
<td>.406</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>35.1</td>
<td>21.7</td>
<td>.387</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>161.8 (13.6)</td>
<td>170.5 (10.9)</td>
<td>.014</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>97.6 (6.4)</td>
<td>101.6 (5.6)</td>
<td>.021</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>81.4 (13.7)</td>
<td>83.0 (15.4)</td>
<td>.702</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>5.3 (0.9)</td>
<td>5.2 (0.8)</td>
<td>.829</td>
</tr>
<tr>
<td>Serum glucose (mmol/L)</td>
<td>5.4 (0.7)</td>
<td>5.3 (0.7)</td>
<td>.242</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation). WML = cerebral white matter lesions; BP = blood pressure.
tensive patients aged 22 to 49 years (24 undergoing antihypertensive treatment), found no differences in neuropsychologic tests performance between hypertensives with \((n/H11005_{12})\) and without \((n/H11005_{20})\) WML. Hypertensive patients had more WML (38%) than controls (20%) and performed tests significantly worse, suggesting that neuropsychologic deficits in hypertensive patients were not related to WML. In a larger study \(^{30}\) of 89 hypertensive patients aged 50 to 80 years (45 of them undergoing antihypertensive therapy, 52% with cardiac disease), the same group found that hypertensives performed tests significantly worse and had more WML than controls. Moreover, they reported that neuropsychologic test results were similar between hypertensives and control subjects without WML, and a significant cognitive decline was observed in hypertensives and controls with WML. The researchers suggested that the high rate of silent WML, but not arterial hypertension per se, had been the cause of the hypertension-related cognitive alterations. Van Swieten et al.\(^ {11}\) studying hypertensives aged 57 to 77 years, found that those with WML \((n/H11005_{10})\) performed significantly worse in neuropsychologic tests than hypertensives without WML \((n/H11005_{24})\).

Because aging and associated factors may influence both cognitive performance and the presence of WML, the present study includes an homogeneous sample of middle-aged essential hypertensive patients, with established risk factors for the development of cerebrovascular damage such as diabetes or significant alcohol intake being excluded. All hypertensive patients included had never received antihypertensive treatment that could have influenced the presence of WML\(^ {16–18}\) and cognitive impairment\(^ {8,9}\) through BP control. Patients with a history of cardiovascular disease were also excluded, as an association between these diseases and the presence of WML\(^ {15}\) and cognitive impairment\(^ {23}\) has been reported.

This study only found significant differences on the digits forward span test, suggesting a decline in basic attention in hypertensive patients with WML compared with those without. Tests measuring memory (working and logical memory and visual reproduction) showed no significant differences between groups. Attention is a brain neurocognitive state that is a result of cortical and subcortical networks. The measure of attention is one of the cognitive domains included in the Mini Mental State Examination, and also in most neuropsychologic tests. There are dementias with more severe deficits on attentional function, as dementia with Lewy bodies that shows significantly greater impairment on a range of attentional tasks. On the other hand, attentional control declines during the early stages of Alzheimer’s disease and there are some selective attention skills in differentiating between Alzheimer’s disease and normal aging.\(^ {31}\)

The fact that we found differences on digit forward

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**Table 2.** Demographic characteristics of essential hypertensive patients with and without cerebral white matter lesions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range of Scores in General Population (normative scores)</th>
<th>Without WML ((n = 37))</th>
<th>With WML ((n = 23))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intelligence quotient</td>
<td>35–164 (normal &gt;75)</td>
<td>96 (21)</td>
<td>103 (26)</td>
<td>.431</td>
</tr>
<tr>
<td>Education (y)</td>
<td>10.8 (3.0)</td>
<td>11.2 (3.7)</td>
<td>.727</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0–21 (normal &lt;10)</td>
<td>10 (1–20)</td>
<td>8 (4–19)</td>
<td>.811</td>
</tr>
<tr>
<td>Depression</td>
<td>0–21 (normal &lt;10)</td>
<td>3 (0–16)</td>
<td>4 (0–16)</td>
<td>.517</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) except anxiety and depression expressed as median (range). Abbreviation as in Table 1.

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**Table 3.** Neuropsychological results of hypertensive patients with and without cerebral WML

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range of Scores in General Population (normative scores)</th>
<th>Without WML ((n = 37))</th>
<th>With WML ((n = 23))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span WAIS-R forward</td>
<td>0–9 (4–6)</td>
<td>5.51 (0.97)</td>
<td>4.86 (1.14)</td>
<td>.027</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span WAIS-R backward</td>
<td>0–8 (3–5)</td>
<td>4.12 (0.99)</td>
<td>4.00 (0.43)</td>
<td>.444</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical memory: % recall after delay</td>
<td>0–100% (80–100%)</td>
<td>82 (16)</td>
<td>82 (15)</td>
<td>.994</td>
</tr>
<tr>
<td>Visual reproduction: % recall after delay</td>
<td>0–100% (70–100%)</td>
<td>89 (15)</td>
<td>83 (18)</td>
<td>.218</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation).

WAIS-R: Wechsler Adult Intelligence Scale revised; other abbreviation as in Table 1.
span but not on digit backward span tests could be because the digit forward test measures attention, whereas the digit backward measures the working memory, which integrates several different and complex capacities.\textsuperscript{32} It seems logical that a mild cognitive impairment can affect only the attention capacity, whereas a subtle alteration in one of the tasks of the working memory can be compensated for by the remaining areas. Other studies have shown this dissociation in neurologic conditions such as schizophrenia\textsuperscript{33} and dementia with Lewy bodies compared with Alzheimer’s disease.\textsuperscript{34}

Schmidt et al\textsuperscript{30} found no differences on the digit forward and backward span tests between hypertensives with ($n = 58$) and without WML ($n = 32$). They found significant differences in tests measuring concentration and speed of mental processing (Trail making test, Complex reaction time test), but, as in the present study, found no differences with respect to the memory test. Differences between the present study and the results of Schmidt et al could be because their patients were older than those included in our study, and 50\% of them were undergoing antihypertensive treatment. In addition, Schmidt et al considered systolic BP/diastolic BP $>160/95$ mm Hg as high BP. Van Swieten et al\textsuperscript{11} showed that elderly hypertensives with WML ($n = 10$) performed worse in concentration and speed tests (Trail making test, Stroop test) and memory tests (visual reproduction-WMS) than elderly hypertensives without WML ($n = 24$), but found no differences in the digit forward and backward span tests. In this study, high BP was defined as systolic BP/diastolic BP $>160/95$ mm Hg and some patients had a history of cardiovascular disease.

As in the present study, Boone et al\textsuperscript{35} found a significant association between lower scores on digit forward span and the presence of WML in a group of 100 elderly people (21\% hypertensives). They found no differences on digit backward span, concentration, and speed tests (Stroop test, Digit Symbol), and logical and visual memory tests between individuals with or without WML. They also found an association between poor performance on frontal lobe function tests and WML. They suggested that a mild decline in basic and “divided” attention could be consistent with the early stages of subcortical dementia, a hypothesis supported by the results of the present study. However, whether declines in basic attention are a replicable characteristic of WML awaits confirmation. Moreover, it is unclear whether the mild disturbance in attention may represent the skills most susceptible to disruption and those that decline first as a result of WML. In the same way, whether this slight difference in one measure of attention has any prognostic significance in terms of clinical outcomes later in life remains to be determined.

This study has some limitations related to methodologic aspects. The study has a cross-sectional design and a small sample size. Only 23 patients had WML and thus, the study could appear underpowered to detect differences that would be expected to be small in an asymptomatic middle-aged sample. On the other hand, the limited number of cognitive domains assessed could lead to an altered estimation of true relationships.

Strengths of this study include the relative young study population, for attempting to address the relationship between WML and cognitive function at early stages. In addition, we included an homogeneous sample of never-treated hypertensive patients to control for a number of potentially confounding factors for the development of cerebrovascular damage, such as diabetes, significant alcohol intake, or previous history of cardiovascular disease. All patients were asymptomatic hypertensives with neither a history of neurologic deficit nor symptoms such as headache, dizziness, or cognitive complaints, which may influence the incidence of such alterations.

In summary, this study found an association between the presence of silent cerebral WML and a mild decline in basic attention in middle-aged and never-treated essential hypertensive patients. It is established that the prevalence and incidence of vascular dementia increase exponentially after 70 years of age, but little is known about the cognitive status of middle-aged individuals. Cognitive decline is, perhaps, not an inevitable consequence of aging. In fact, hypertension appears to predispose patients to the development of cognitive impairment and dementia, after a period varying from a few years to several decades, in which subtle cognitive impairment could already be detected, and related to the presence of early cerebrovascular damage, such as WML. Nevertheless, exactly how early high BP may begin to exert their influence is not well understood.

References


