Cognitive Correlates of Ventricular Enlargement and Cerebral White Matter Lesions on Magnetic Resonance Imaging

The Rotterdam Study

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Background and Purpose Ventricular enlargement and white matter lesions are frequent findings on cerebral magnetic resonance imaging scans of elderly subjects. In demented subjects they seem related to the severity of the dementia, but in nondemented subjects their clinical significance is less clear. We investigated the relation of size of the lateral ventricles and white matter lesions with cognitive function in a population-based random sample of nondemented elderly persons.

Methods The study population consisted of 90 subjects, aged 65 to 84 years, who were randomly selected from the cohort of the Rotterdam Study, and who were not demented. The presence of white matter lesions and the ventricle-to-brain ratio were assessed on magnetic resonance scans. Participants were tested with a neuropsychological battery that covered a broad range of cognitive functions.

Results Ventricular enlargement and white matter lesions were both and independently associated with poorer performance on all tests. After adjustment for age and sex, ventricular enlargement was significantly associated with worse scores on tests assessing global cognitive function (Mini-Mental State Examination, \( P = .02 \); Groninger Intelligence Test, \( P = .01 \)), memory (Word List Learning delayed recall, \( P = .03 \)), and executive control functions (Stroop part II, \( P = .02 \); Trail Making Test B, \( P < .01 \)); for white matter lesions the differences were significant for tests measuring executive control functions and mental speed (Trail Making Test A and B, \( P = .01 \) and \( P < .01 \), respectively; verbal fluency, \( P = .01 \)), and memory (Word List Learning delayed recall, \( P = .04 \)).

Conclusions This study suggests that white matter lesions are primarily related to impairment of subcorticalfrontal functions, whereas enlargement of the lateral ventricles is associated with disturbances of cortical functions as well. (Stroke. 1994;25:1109-1115.)

Key Words • cognition • dementia • epidemiology • magnetic resonance imaging

Cerebral white matter lesions are frequently observed on magnetic resonance imaging (MRI) scans in elderly subjects and have been related to vascular dementia. Clinical, epidemiological, and pathological studies consistently indicate a vascular cause for the majority of these lesions. However, their clinical significance in nondemented subjects remains controversial. Most previous studies that investigated whether these lesions are related to cognitive impairment suffered from methodological drawbacks that limited the interpretation of their results; e.g., they mainly included demented patients, or had very small sample sizes. It is of major importance to know whether these lesions truly reflect the early stages of vascular dementia because potential measures of intervention are available.

Another frequent finding in elderly persons that also has been related to cognitive decline is an increase in ventricular volume. It is generally assumed that this ventricular enlargement occurs, ex vacuo, by shrinkage of periventricular structures. This view has also often been taken to explain the positive relation between ventricular size and occurrence of dementia in subjects with multiple infarcts, although some studies suggested that the effects of ventricular enlargement and the size of the infarcted area on cognitive performance are partly independent. Until now, few studies have investigated the relevance of ventricular volume per se for cognitive performance.

In this article we present the results of a study conducted in a random sample from the general population to investigate the associations between cerebral white matter lesions and size of the lateral ventricles on the one hand and cognitive performance on the other.

Subjects and Methods

Subjects The Rotterdam Study is a single-center prospective follow-up study of the total population aged 55 years or older of the suburb of Ommoord in Rotterdam, the Netherlands. The number of eligible subjects was 11 854; institutionalized persons were included. The study has been approved by the Medical Ethics Committee of Erasmus University. Written
informed consent was obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere. To study the prevalence and determinants of cerebral white matter lesions on MRI, subjects aged 65 to 84 years were randomly selected, stratified by sex and 5-year age groups, from the cohort of the Rotterdam Study. At the time of the MRI study the participation rate in the Rotterdam Study was 82% for those aged 65 to 84 years; 111 (87%) of the 128 subjects who were invited to the additional MRI study consented to participate. To investigate the relations of cerebral white matter lesions as well as of ventricular enlargement with cognitive function, all participants in the MRI study were subsequently invited for additional neuropsychological testing, with the exception of 2 patients with Parkinson's disease and 6 patients with a diagnosis of probable Alzheimer's disease, according to the criteria of the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association. We also excluded 7 subjects who had either a history of stroke confirmed by a neurologist or evidence of stroke on the MRI scan. Of the 96 eligible subjects 6 declined further examinations, leaving 90 persons in the present study.

Magnetic Resonance Imaging
T2-weighted axial MR images of the brain were obtained by means of a 1.5-T Philips Gyroscan. Presence and severity of white matter lesions were graded as follows. Grade 0 scans showed no or slight periventricular hyperintensity, less than 5 punctate lesions, and no confluent lesions. Grade 1 scans showed moderate periventricular hyperintensity or more than 5 punctate lesions, or both, but no confluent lesions. Scans with severe periventricular hyperintensity or confluent lesions were graded as 2, regardless of the presence of punctate lesions. To measure lateral ventricular volume we traced the MRI films on each axial slice on which the lateral ventricles were present, with the use of a light table and transparent paper to identify the perimeter of the entire brain and of the ventricles. Subsequently, these areas were measured in pixel percentages by means of an IBAS 2000 (Zeiss-Kontron) and summed over all slices to arrive at total volume of the lateral ventricles and corresponding total brain volumes. To control for differences in individual head size and height, the volume of the lateral ventricles was expressed as the percentage of the total brain volume (ventricle-to-brain ratio).

Assessment of Cognitive Function
The following neuropsychological tests were administered: Stroop test (parts I, II, and III), verbal fluency tests, Trail Making Test A and B, Digit Span forward and backward (WAIS), Word List Learning (CERAD [Consortium to Establish a Registry for Alzheimer's Disease]), Mini-Mental State Examination (MMSE), CAMCOG (the cognitive test that is part of the CAMDEX, the Cambridge examination for mental disorders of the elderly), and a shortened version of the Groninger Intellgence Test (GIT), a Dutch intelligence test. Verbal fluency was assessed as phonological word fluency, in which test the subject was asked to produce as many words as possible within 1 minute that begin with a specified letter (letter B), and as semantic word fluency, which demands generating words that belong to a specific category (animals). The Stroop test, Trail Making Test, and verbal fluency tests are timed tasks that measure executive control functions (mental flexibility, vulnerability to interference, conceptual tracking), sustained attention, and mental speed; these functions are assumed to be localized principally in subcortical and frontal areas. Digit Span assesses auditory attention span. The CAMCOG and the MMSE are global cognitive tests developed for use in dementia screening and appeal mainly to cortical functions. Word List Learning and the several subtests of the GIT also address primarily cortical functions, that is, visual verbal memory and verbal abstraction, calculation, and mental visuospatial construction. The neuropsychological test battery was always administered after the MRI scans had been made, with a mean interval of 19 days. Information regarding the level of formal education was elicited in the home interview of the Rotterdam Study.

Analysis
Mean test scores were calculated for subjects with (grade 1 or 2) and without (grade 0) white matter lesions. Since age and sex were associated with test scores as well as with presence of white matter lesions, we used multiple linear regression to compute adjusted differences (with 95% confidence intervals [CI]) between the groups with and without lesions. The relation between ventricle-to-brain ratio (as a continuous variable) and test scores was examined through multiple linear regression analysis, with adjustment for age and sex. The potential confounding effect of education was investigated by inclusion of the level of education as an additional covariate in the model. Persons who were unable to complete the more difficult parts of the Stroop test or the Trail Making Test were assigned the worst score obtained by those who did complete the tests. To assess whether the relation between MRI abnormalities and cognitive functioning was dependent on age, additional stratified analyses were performed in two 10-year age strata (65 to 74 years and 75 to 84 years). To investigate whether the associations of white matter lesions and of ventricular enlargement with cognitive performance were statistically independent, we assessed the relation between white matter lesions and neuropsychological test scores while adjusting for ventricle-to-brain ratio, and vice versa.

Results
In Table 1 the most important characteristics of the eligible study population are presented. Age was significantly associated with presence and severity of white matter lesions; female sex showed a similar but nonsignificant tendency that was independent of age. The proportion of subjects who refused further neuropsychological testing increased with the severity of white matter lesions. The severity of white matter lesions was positively associated with ventricle-to-brain ratio (P<.01; adjusted for age and sex).

Table 2 shows the results of the neuropsychological tests according to presence or absence of white matter lesions. Subjects with white matter lesions performed worse on all tests, except for the subtest of the GIT that assessed verbal abstraction (matrices). When age and sex were taken into account the direction of the differences did not change, but they remained significant only for the Trail Making Test (A and B), phonological word fluency (letter B), and delayed verbal recall (Word List Learning) (Table 2).

For the relation between lateral ventricular size and cognitive function we found that the larger the lateral ventricles (expressed as increasing ventricle-to-brain ratio), the poorer the performance on all neuropsychological tests. When adjusted for age and sex the associations were significant for the Stroop test (part II), the Trail Making Test (B), the MMSE, delayed verbal recall (Word List Learning), two of the three subtests of the GIT (matrices and calculation), and the summary scores on the GIT (total score and IQ) (Table 3).

Age-stratified analyses showed the associations of white matter lesions and ventricle-to-brain ratio with cognitive performance for younger subjects (aged 65 to 74 years) to be similar to those for older subjects (aged 75 to 84 years).
The level of education itself was highly correlated with test scores, even after adjustment for age and sex, but education was associated with neither ventricular enlargement nor the presence of white matter lesions (Table 1). Therefore, it appeared not to be a confounder for the relations that we investigated, and the adjusted differences did not change when level of education was included in the model as a covariate.

Finally, we found that the associations of white matter lesions and lateral ventricular volume with cognitive performance were largely independent: when we entered ventricle-to-brain ratio and presence of white matter lesions simultaneously in the regression model, together with age and sex, the magnitude and significance of all associations remained virtually unchanged (Tables 2 and 3).

Discussion

We investigated the relation with cognitive function of cerebral white matter lesions and enlargement of the lateral ventricles in nondemented stroke-free subjects who were randomly sampled from the general population. We found that the presence of either of these anatomical abnormalities was associated with worse performance on all tests of cognitive function. After adjustment for age and sex, individuals with white matter lesions performed significantly worse on tests addressing primarily subcortical and frontal functions (executive control functions, attentional abilities, and mental speed). Enlargement of the lateral ventricles was also significantly associated with poor performance on tests that assess executive control functions, but in addition it was significantly associated with poor performance on tests that aim to assess cortical functions (Table 4). Although presence of white matter lesions and increasing ventricle-to-brain ratio were correlated, their effects on cognitive performance were independent.

There are three important methodological issues that distinguish our study from most previous investigations. First, we randomly sampled subjects from the general population and excluded only subjects with neurological diseases known to potentially impair cognitive function. Consequently, the only possible bias in our data is the one introduced by selective refusal. The participation rate in the initial MRI study was high, particularly in view of the age of the study population and the kind of investigation. However, subjects with MRI abnormalities more often refused further neuropsychological testing, which probably resulted in an underestimation of the deleterious effects of white matter lesions and ventricular enlargement. It is likely that in studies that were based on volunteers selective participation has led to an even larger depreciation of the importance of these MRI characteristics in the general population. Assuming that vascular lesions of the white matter can accumulate over time to result eventually in overt dementia, one would expect to find a continuous distribution of cognitive impairment related to such vascular lesions in the population. Most previous studies that investigated nondemented subjects did not show a clear relation between white matter lesions on MRI and cognitive function. However, small sample sizes or restricted sampling of the population (including only subjects with cerebrovascular events or, conversely, excluding subjects with vascular risk factors or selecting volunteers on the basis of good performance) may have resulted in too little power to detect existing differences.

A second important methodological issue is age. Age is the strongest determinant of cognitive function in the elderly and needs to be taken into account in the assessment of other putative determinants. By limiting the overall age span of subjects to be included in the study to 20 years and by age-stratified sampling within this range, we ensured adequate numbers in all age groups to correct for the effect of age when studying the consequences of white matter lesions and ventricular enlargement.

A third methodological point is the selection of the neuropsychological tests. The studies that have reported more or less convincing evidence for a relation between white matter lesions on MRI and cognitive impairment showed, as we did, primarily worse performance on tests of subcortical and frontal functions. These findings are in accordance with the theory that multifocal white

Table 1. General Characteristics of the Study Population, for All Subjects and by Level of Severity of Cerebral White Matter Lesions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>No/Slight*</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>96</td>
<td>73</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.6 (6.2)</td>
<td>72.3 (5.8)</td>
<td>76.9 (6.1)</td>
<td>79.0 (5.2)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>44/52</td>
<td>37/36</td>
<td>6/9</td>
<td>1/7</td>
</tr>
<tr>
<td>Refusals (%)</td>
<td>6 (6%)</td>
<td>3 (4%)</td>
<td>1 (7%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Ventricle-to-brain ratio, %</td>
<td>7.6 (1.9)</td>
<td>7.2 (1.6)</td>
<td>8.6 (2.6)</td>
<td>9.3 (2.2)</td>
</tr>
<tr>
<td>Level of education†</td>
<td>2.8 (1.5)</td>
<td>2.8 (1.5)</td>
<td>2.2 (1.6)</td>
<td>2.6 (1.1)</td>
</tr>
</tbody>
</table>

Age, ventricle-to-brain ratio, and level of education values are mean (SD).

*<5 Focal lesions, no/slight periventricular hyperintensities, and no confluent lesions.
†<5 Focal lesions, moderate periventricular hyperintensities, and no confluent lesions; or ≥5 focal lesions, no/slight/moderate periventricular hyperintensities, and no confluent lesions.
‡Confluent lesions and/or severe periventricular hyperintensities.
§Attained level of education, classified in accordance with the International Standard Classification of Education (United Nations Educational, Scientific, and Cultural Organization, Paris, France, 1976) on a scale that ranges from 1 (primary school or less) to 7 (university).
matter lesions collectively cause a disconnection syndrome.

 Neuropsychological tests that focus mainly on cortical functions such as language and visuoperceptual abilities and that are less sensitive to slowing of mental speed and impairment of attentional abilities may not detect subcortical functional decline in its early stages. By selecting a test battery that covered a broad range of functions we were able to evaluate subcortical and frontal as well as cortical functions.

 We found ventricular enlargement to be related to cognitive performance, independent of age or presence of white matter hyperintensities. Few other studies investigated the relation between ventricle size and cognitive function in nondemented subjects. Kaye et al found that after adjustment for age, cerebral atrophy as measured by ventricular enlargement was not related to cognitive performance in nondemented persons. However, they based their conclusions on a relatively small number of subjects who were extensively tested (n=39).

 Since that sample comprised a broad age range, their study may have had little power to detect a relation between ventricular volume and cognitive function once the confounding effect of age had been taken into account. Our population-based results fit well with the results from Pujol et al in a selected group of vascular patients with leukoaraiosis. They found that ventricular enlargement was significantly associated with global deterioration of complex cognitive functions, and that this was complementary to the degree of leukoaraiosis. They suggested that ventricular enlargement had the greatest clinical significance. Our results lend support to this latter proposition. The magnitude of the associations of size of the lateral ventricles with various tests of cognitive function, as well as the fact that these associations are not confined to tests that are presumed to measure subcorticalfrontal functions but exist also with tests addressing cortical functions, seems to indicate that lateral ventricular enlargement is at least as important an MRI indicator of cognitive impairment as are white matter hyperintensities.

 How should we interpret the relation between white matter lesions and cognition? It is tempting to conclude...
that white matter lesions on MRI are a morphological substrate of dementia related to vascular disease. However, all evidence until now has been based on cross-sectional studies. A single study suggested that on follow-up subjects with white matter lesions had declined most, but the findings were based on very small groups and the subjects with lesions were older than those without. Furthermore, not all lesions on MRI reflect ischemic changes, and a smooth periventricular halo may have causes other than irregular periventricular or deep white matter hyperintensities. Population-based follow-up studies including large series of subjects are needed to fully ascertain the relevance of cerebral white matter lesions among nondemented subjects.

With regard to ventricular size a question that remains to be answered is what factors contribute to the process of cerebral atrophy underlying enlargement of the lateral ventricles. Vascular factors seem to be implicated in a substantial proportion of patients with dilatation of the ventricle system. Hypertension, the predominant risk factor for stroke and vascular dementia, is associated with brain atrophy even when subjects with severe periventricular hyperintensities are excluded. In patients with multiple infarcts or with subcortical arteriosclerotic encephalopathy the accompanying dilatation of the ventricular system is thought to be secondary to the white matter changes resulting from ischemia. However, this does not explain why several studies found, as we did, that the relation between ventricular enlargement and cognitive function, or subsequent development of dementia, was independent of the effect of white matter lesions and infarcts. Our results suggest that the two measures to some extent reflect different underlying processes. Degeneration of cortical neurons and the subsequent axonal degeneration and loss of cerebral white matter, from preclinical stages of Alzheimer’s disease or from other causes, can also contribute to expansion of the ventricle volume and would explain our finding that cortical functions are

<table>
<thead>
<tr>
<th>Test</th>
<th>Adjusted for Age and Sex</th>
<th>Adjusted for Age, Sex, and White Matter Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Difference*</td>
<td>95% CI</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (word reading)</td>
<td>49.0</td>
<td>0.7</td>
</tr>
<tr>
<td>II (color naming)</td>
<td>66.8</td>
<td>1.9</td>
</tr>
<tr>
<td>III (color interference)</td>
<td>135.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>19.5</td>
<td>-0.3</td>
</tr>
<tr>
<td>Letter B</td>
<td>12.4</td>
<td>-0.3</td>
</tr>
<tr>
<td>Trail Making</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test A</td>
<td>56.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Test B</td>
<td>132.9</td>
<td>14.9</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.1</td>
<td>-0.2</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>92.2</td>
<td>-0.7</td>
</tr>
<tr>
<td>Digit Span</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>4.7</td>
<td>-0.1</td>
</tr>
<tr>
<td>Backward</td>
<td>3.6</td>
<td>-0.1</td>
</tr>
<tr>
<td>Word List Learning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct recall</td>
<td>18.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>6.4</td>
<td>-0.3</td>
</tr>
<tr>
<td>Recognition</td>
<td>19.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>GIT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matrices</td>
<td>8.7</td>
<td>-0.6</td>
</tr>
<tr>
<td>Calculation</td>
<td>11.7</td>
<td>-0.6</td>
</tr>
<tr>
<td>Perceptual puzzle</td>
<td>9.3</td>
<td>-0.2</td>
</tr>
<tr>
<td>Total</td>
<td>29.9</td>
<td>-1.4</td>
</tr>
<tr>
<td>IQ</td>
<td>116.4</td>
<td>-2.7</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; MMSE, Mini-Mental State Examination; CAMCOG, cognitive part of CAMDEX (Cambridge examination for mental disorders of the elderly); and GIT, Groninger Intelligence Test.

* Differences reflect the adjusted average change in test score when the ventricle-to-brain ratio increases with one unit of measurement (ie, with 1%: mean ratio, 7.8%; range, 3.9%-18.1%).

† Subjects who were unable to complete the test were included by assigning them the worst score.
TABLE 4. Summary of Different Patterns in Associations Between Test Results* and Scan Characteristics

<table>
<thead>
<tr>
<th>Test</th>
<th>White Matter Lesions</th>
<th>Ventricular Enlargement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests assessing primarily subcortical and frontal functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop II (color naming)</td>
<td>NS</td>
<td>↓</td>
</tr>
<tr>
<td>Word fluency, letter B</td>
<td>↓</td>
<td>NS</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>↓</td>
<td>NS</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Tests assessing primarily cortical functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>NS</td>
<td>↓</td>
</tr>
<tr>
<td>Word List Learning, delayed recall</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>GIT matrices</td>
<td>NS</td>
<td>↓</td>
</tr>
<tr>
<td>GIT calculation</td>
<td>NS</td>
<td>↓</td>
</tr>
<tr>
<td>GIT total</td>
<td>NS</td>
<td>↑</td>
</tr>
<tr>
<td>GIT IQ</td>
<td>NS</td>
<td>↑</td>
</tr>
</tbody>
</table>

*Only tests on which statistically significant differences were observed are listed.

Acknowledgments
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