The Contribution of Medial Temporal Lobe Atrophy and Vascular Pathology to Cognitive Impairment in Vascular Dementia

António J. Bastos-Leite, MD; Wiesje M. van der Flier, PhD; Elisabeth C.W. van Straaten, MD; Salka S. Staekenborg, MD; Philip Scheltens, MD, PhD; Frederik Barkhof, MD, PhD

Background and Purpose—Besides cerebrovascular disease, medial temporal lobe atrophy (MTA), a neuroimaging finding suggestive of degenerative pathology, has been shown in vascular dementia (VaD). However, it is unknown to what extent MTA contributes to the pattern of cognitive impairment observed in VaD. Therefore, our purpose was to investigate the relative contribution of cerebrovascular disease and MTA to cognitive impairment in patients fulfilling diagnostic criteria for VaD.

Methods—We examined 590 patients (374 men; mean age, 73 years; standard deviation, 8) with probable VaD according to the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria at inclusion into a multicenter clinical trial. Cerebrovascular disease and the degree of MTA were evaluated by using MRI. Cognitive testing included the Mini-Mental State Examination, and the vascular dementia assessment scale.

Results—On the basis of the operational definitions for the neuroimaging part of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria, 485 (82.2%) patients had small vessel VaD and 153 (25.9%) had large vessel VaD. More than half (59.8%) of the patients had considerable MTA. Multiple linear regression analyses revealed that after correction for sex, age, education, and duration of dementia, neuropsychological tests showed that patients with higher grades of MTA or large vessel VaD had significantly worse general cognitive and executive functioning, whereas associations with small vessel disease were restricted to worse executive functioning.

Conclusions—Both MTA and large vessel disease contribute to global cognitive impairment in VaD. Small vessel disease contributes to executive dysfunction. (Stroke. 2007;38:000-000.)

Key Words: Alzheimer’s ■ cerebrovascular disease ■ MRI ■ neuroradiology ■ vascular dementia
their interactions to cognitive impairment in a large sample of patients fulfilling diagnostic criteria for VaD.

Materials and Methods

Patients

We examined the baseline data of 590 patients (374 men, 216 women) enrolled into the VantagE study (Novartis International AG, Basel, Switzerland), a multicenter, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with VaD. Trial inclusion criteria included fulfillment of the clinical and radiological parts of the NINDS-AIREN criteria for probable VaD with central assessment of the neuroimaging criteria at the Image Analysis Center (VU University Medical Center, Amsterdam, The Netherlands). For the current study, all patients were required to have complete cognitive and MRI data. Patients with lobar hemorrhages or space-occupying lesions were excluded.

To evaluate cognitive function, patients were submitted to a set of tests, which included the Mini-Mental State Examination (possible range of scores, 0 to 30) and the Alzheimer disease assessment scale (possible range of scores, 0 to 12). We used 5 additional subtests covering neuropsychological domains (executive function, attention, working memory, and verbal fluency) frequently involved in VaD: symbol digit modalities test (number of correct answers; possible range, 0 to 110), digits backward test (number correct; possible range, 0 to 12), maze task (maximum time to completion, 240 seconds), digit cancellation task (number of targets hit), and verbal fluency tests (number of correct words).

MRI Protocol

All patients underwent an MRI examination before randomization. MRI scanners operating between 0.5 and 1.5 T were used. Axial fluid-attenuated inversion recovery images (echo time: 110 to 150 ms; repetition time: 2000 to 2200 ms); and axial, sagittal, and coronal spin-echo T2-weighted images (T2-WI; echo time: 80 to 120 ms; repetition time: 3000 to 4000 ms; slice thickness, 5 mm); and axial, sagittal, and coronal spin-echo T1-weighted images (T1-WI; echo time: 11 to 20 ms; repetition time: 500 to 700 ms; slice thickness, 5 mm) were acquired.

Image Assessment

Vascular abnormalities and MTA were evaluated by a single reader blinded to clinical information using the original digital image files. The assessment of vascular abnormalities included the items of the radiological NINDS-AIREN criteria for VaD according to published operational definitions and patients fulfilled criteria for large vessel VaD, small vessel VaD, or both. For the assessment of WMH, we used the age-related white matter changes scale (possible range of scores for each side, 0 to 4). MTA was evaluated by using a visual rating scale based on the choroidal fissure width, the temporal horn width, and the hippocampal height (possible range of scores for each side, 0 to 4).

Statistical Analysis

Statistical analysis was done by means of SPSS 11.0 (SPSS for Windows). Variables representing cerebrovascular disease were dichotomized as follows: large vessel VaD absent or present, multiple subcortical lacunar infarcts and bilateral thalamic lesions absent or present, and extensive WMH absent (total age-related white matter changes score ≤12) or present (total age-related white matter changes score >12). Left/right average MTA scores ≥1.5 were regarded as representing considerable MTA. We used the Pearson’s χ² test to compare categorical variables and the Mann-Whitney U test to compare scores. For comparisons of continuous variables, the independent sample Student’s t test or the Mann-Whitney U test were used, according to the distribution of data. Correlations were tested by using the Spearman rank correlation coefficient (rs). To determine whether the occurrence of large vessel VaD, small vessel disease, or MTA independently influenced cognitive function, we used multiple linear regression analyses with sex, age, education, and duration of dementia as covariates. We also tested interactions between the occurrence of large vessel VaD, small vessel disease, and MTA by entering bivariate product terms in the model. Statistical significance was considered when probability values were <0.05.

Results

Table 1 summarizes baseline characteristics of the patients. On the basis of the operational definitions for the radiological part of the NINDS-AIREN criteria, 437 (74.1%) patients had small vessel VaD, 105 (17.8%) had large vessel VaD, and 48 (8.1%) had both small and large vessel VaD. Three hundred-ninety (66.1%) patients had extensive WMH (total age-related white matter changes score >12) and 103 (17.5%) had multiple subcortical lacunar infarcts in association with bilateral thalamic lesions. More than half (59.8%) of the patients had considerable MTA (left/right average MTA score ≥1.5).

A significant association was found between the occurrence of extensive WMH and the occurrence of multiple lacunar infarcts and thalamic lesions (P<0.001). In addition, a significant association was found between the occurrence of extensive WMH and MTA (P<0.05). MTA scores in patients with large vessel VaD were significantly lower than in patients with small vessel VaD (P<0.01), although the proportion of patients with considerable MTA did not significantly differ between those groups.

With the exception of the Mini-Mental State Examination score, which was significantly lower (P<0.05) in patients with large vessel VaD, the results of the remaining neuropsychological tests almost did not differ between groups of patients with and without large vessel VaD.

Multiple linear regression analyses revealed that after correction for sex, age, education, and duration of dementia, most of the neuropsychological tests showed that patients...
with higher grades of MTA or large vessel VaD had worse general cognitive and executive functioning (Table 2). The occurrence of multiple lacunar infarcts and thalamic lesions was found to be associated with worse verbal fluency. Extensive WMH were associated with worse performance in the following tests of executive functioning: symbol digit modalities and digit cancellation. In addition, significant interactions between MTA and WMH were found to influence the results of the symbol digit modalities ($P<0.01$) and digit cancellation ($P<0.05$) tests (Figure), suggesting that the effect of WMH was specific for patients without considerable MTA.

### Discussion

Our study shows that both MTA and the occurrence of large vessel VaD are independently associated with general cognitive and executive dysfunction in patients with VaD. In addition, it shows that small vessel disease seems to be related to worse executive functioning, especially in patients without considerable MTA.

A large proportion of patients with dementia have a combination of degenerative and vascular pathology in the brain.\textsuperscript{15} From a radiological point of view, MTA is usually considered to be a surrogate marker of degenerative pathology, because neuropathological changes underlying Alzheimer disease first occur in the medial temporal lobe.\textsuperscript{16} Therefore, it is plausible that the occurrence of MTA in our patients, as well as its association with cognitive impairment, is attributable to concomitance of Alzheimer pathology. Alternatively, MTA may be secondary to vascular pathology, more precisely to small vessel disease and ischemia. Nevertheless, when there is neuroimaging evidence of mixed pathology (degenerative and vascular), atrophy seems to predict or correlate better with dementia than small vessel disease.\textsuperscript{17–20} Our results are in agreement with those findings, because we showed that, in a large sample of patients fulfilling diagnostic criteria for VaD, WMH have a more restricted effect on cognitive function than MTA.

With respect to the causal relation between vascular lesions alone and dementia, it is currently considered that such a relation is only clear when patients are young and it is unlikely they have associated Alzheimer pathology; when cognitive functions are normal before stroke, impaired immediately after, and do not worsen over time; when vascular lesions are located in strategic regions; and when well-defined vasculopathies known to cause dementia are proven such as cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or some types of cerebral amyloid angiopathies. In other circumstances, it is possible that both degenerative and vascular pathology may contribute to cognitive impairment.\textsuperscript{21,22} In our sample, we found a clear association between large vessel disease and cognitive impairment. However, the majority of our patients had small vessel VaD and the contribution of MTA to cognitive dysfunction was more pronounced than the contribution of small vessel disease.

Executive dysfunction is usually considered to be a major characteristic of VaD.\textsuperscript{23} Given that we found associations between small vessel disease and worse performance in tests of executive functioning, it is conceivable that the degree of such dysfunction may be justified, in part, by the severity of small vessel disease. Nevertheless, results from a recent neuropathological study indicate that the cognitive effects of small vessel cerebrovascular disease are variable and not especially distinct.\textsuperscript{24} Strong elements of the current study include the large sample of patients that were rigorously screened for their fulfillment of radiological criteria for probable VaD by

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>Large Vessel VaD</th>
<th>Multiple Lacunae and Bilateral Thalamic Lesions</th>
<th>WMH</th>
<th>MTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>1 -1.28 (0.35)‡</td>
<td>0.44 (0.41)</td>
<td>0.26 (0.32)</td>
<td>-0.89 (0.31)†</td>
</tr>
<tr>
<td></td>
<td>2 -1.56 (0.41)‡</td>
<td>0.12 (0.42)</td>
<td>0.48 (0.38)</td>
<td>-0.90 (0.31)†</td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>1 2.33 (0.85)†</td>
<td>-0.33 (1.00)</td>
<td>0.22 (0.79)</td>
<td>3.91 (0.75)‡</td>
</tr>
<tr>
<td></td>
<td>2 3.44 (0.99)†</td>
<td>0.20 (1.01)</td>
<td>1.67 (0.91)</td>
<td>3.89 (0.75)‡</td>
</tr>
<tr>
<td>Symbol digit modalities</td>
<td>1 -0.03 (0.86)</td>
<td>-0.80 (1.00)</td>
<td>-2.20 (0.79)‡</td>
<td>-3.40 (0.77)‡</td>
</tr>
<tr>
<td></td>
<td>2 -1.83 (1.00)</td>
<td>-0.58 (1.01)</td>
<td>-2.71 (0.92)‡</td>
<td>-3.23 (0.77)‡</td>
</tr>
<tr>
<td>Digits backwards</td>
<td>1 -0.39 (0.18)*</td>
<td>0.12 (0.21)</td>
<td>-0.02 (0.16)</td>
<td>-0.32 (0.16)</td>
</tr>
<tr>
<td></td>
<td>2 -0.56 (0.21)†</td>
<td>0.04 (0.21)</td>
<td>-0.29 (0.19)</td>
<td>-0.31 (0.16)</td>
</tr>
<tr>
<td>Maze</td>
<td>1 8.64 (4.00)*</td>
<td>-5.85 (4.70)</td>
<td>-2.70 (3.72)</td>
<td>2.94 (3.63)</td>
</tr>
<tr>
<td></td>
<td>2 9.34 (4.80)</td>
<td>-3.86 (4.87)</td>
<td>2.47 (4.43)</td>
<td>2.99 (3.63)</td>
</tr>
<tr>
<td>Digit cancellation</td>
<td>1 -1.30 (0.51)*</td>
<td>-0.67 (0.60)</td>
<td>-0.70 (0.47)</td>
<td>-1.84 (0.45)‡</td>
</tr>
<tr>
<td></td>
<td>2 -2.51 (0.59)‡</td>
<td>-0.92 (0.60)</td>
<td>-1.67 (0.55)†</td>
<td>-1.81 (0.45)‡</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>1 -0.02 (0.44)</td>
<td>-1.17 (0.52)*</td>
<td>-0.63 (0.41)</td>
<td>-1.24 (0.40)†</td>
</tr>
<tr>
<td></td>
<td>2 -0.69 (0.52)</td>
<td>-1.18 (0.53)*</td>
<td>-0.68 (0.48)</td>
<td>-1.23 (0.40)†</td>
</tr>
</tbody>
</table>

Model 1: single MRI measure (each MRI measure is a different model) corrected for age, sex, education, and duration of dementia. Model 2: all 3 MRI measures simultaneously entered corrected for age, sex, education, and duration of dementia. Values represent unstandardized regression coefficients plus standard errors.

* $P<0.05$; † $P<0.01$; ‡ $P<0.001$.

MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer’s disease assessment scale.
Figure. Box plots displaying significant interactions between the occurrence of extensive WMH and considerable MTA. These interactions were found to influence results of the symbol digit modalities (SDM) and digit cancellation (DC) tests and suggest that the contribution of WMH for executive dysfunction is specific for patients without considerable MTA. A, Patients without considerable MTA but without extensive WMH. B, Patients without considerable MTA and extensive WMH. C, Patients with considerable MTA but without extensive WMH. D, Patients with considerable MTA and extensive WMH.

central assessment. A limitation results from the selection bias secondary to the requirement that all the included patients had to fulfill the NINDS-AIREN criteria. Another limitation is the cross-sectional design of the current study, which precludes the assessment of causality.

In conclusion, both MTA and large vessel disease contribute only to executive dysfunction specific for patients without considerable MTA. A, Patients without considerable MTA and without extensive WMH, B, Patients without considerable MTA but with extensive WMH, C, Patients with considerable MTA but without extensive WMH, D, Patients with considerable MTA and extensive WMH.

Disclosures

None.

References

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