Neurological Signs in Relation to Type of Cerebrovascular Disease in Vascular Dementia

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Background and Purpose—The aim of this study was to describe the prevalence of a number of neurological signs in a large population of patients with vascular dementia (VaD) and to compare the relative frequency of specific neurological signs dependent on type of cerebrovascular disease.

Methods—Seven hundred six patients with VaD (NINDS-AIREN) were included from a large multicenter clinical trial (registration number NCT00099216). At baseline neurological examination, the presence of 16 neurological signs was assessed. Based on MRI, patients were classified as having large vessel VaD (18%; large territorial or strategical infarcts on MRI), small vessel VaD (74%; white matter hyperintensities [WMH], multiple lacunes, bilateral thalamic lesions on MRI), or a combination of both (8%).

Results—A median number of 4.5 signs per patient was presented (maximum 16). Reflex asymmetry was the most prevalent symptom (49%), hemianopia was most seldom presented (10%). Measures of small vessel disease were associated with an increased prevalence of dysarthria, dysphagia, parkinsonian gait disorder, rigidity, and hypokinesia and as well to hemimotor dysfunction. By contrast, in the presence of a cerebral infarct, aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry, and hemiplegic gait disorder were more often observed.

Conclusions—The specific neurological signs demonstrated by patients with VaD differ according to type of imaged cerebrovascular disease. Even in people who meet restrictive VaD criteria, small vessel disease is often seen with more subtle signs, including extrapyramidal signs, whereas large vessel disease is more often related to lateralized sensorimotor changes and aphasia. (Stroke. 2008;39:317-322.)

Key Words: MRI ■ neurological signs ■ vascular dementia

Vascular dementia (VaD) is the second most common type of dementia worldwide. At present, the criteria of the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) are most often used to diagnose VaD. These criteria require the presence of dementia, defined as cognitive decline with interference in activities of daily living, and evidence of cerebrovascular disease. The latter includes both proof on brain imaging and the presence of focal signs on neurological examination. However, little is known about the relative prevalence of specific neurological signs in VaD. The NINDS-AIREN criteria suggest signs such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria. Other criteria for VaD requiring focal signs on neurological examination are the Diagnostic and Statistical Manual of Mental Disorders third and fourth edition (DSM III/IV) and the criteria of the International Statistical Classification of Diseases, tenth revision (ICD-10). The DSM III and IV mention neurological signs such as exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, or weakness of an extremity. The ICD-10 includes signs such as unilateral increased tendon reflexes, an extensor plantar response, or pseudobulbar palsy. Nonetheless, the prevalence of specific neurological signs in VaD patients is not known.

Cerebrovascular disease can be caused by large vessel disease, including large territorial or strategic infarcts, and small vessel disease, consisting of multiple lacunes, white matter hyperintensities (WMH), or bilateral thalamic lesions. It would be plausible that neurological signs differ according to the types of underlying vascular disease. The aim of this study was to investigate the relative prevalence of a number of specific neurological signs in a large population of patients with VaD according to the NINDS-AIREN criteria included in a clinical trial, and to compare neurological signs by type of underlying cerebrovascular disease.

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Methods

Study Design and Patients
Baseline data of 706 patients aged 50 to 85 years, included in the VantagE study, were used. The VantagE study was a large multicenter, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with VaD (registration number NCT00099216, Novartis International AG, Basel, Switzerland). Trial inclusion criteria included both fulfilment of the DSM-IV diagnostic criteria for VaD and fulfilment of the NINDS-AIREN criteria for probable VaD, with central assessment of the neuroimaging criteria at the Image Analysis Center (VU Medical Center, Amsterdam, the Netherlands).2,4 The NINDS-AIREN criteria for probable VaD were slightly modified: if neuroimaging criteria for subcortical VaD were met as assessed by the central neuroradiologist, patients were not required to have evidence of a temporal relationship between the dementia syndrome and the evidence of cerebrovascular disease. Accordingly, patients with cortical VaD entered the study with a clinical diagnosis of possible VaD by NINDS-AIREN criteria. Furthermore, focal signs, as evidence of cerebrovascular disease, were expanded to allow presence or history of any findings on neurological examination indicating cerebrovascular disease. Patients had to have a MMSE score of 10 to 24 to be included in the study. Excluded from entry into the study were patients with a history of stroke within the 3 months before baseline unless the patient was considered to have fully stabilized in function; a current diagnosis of any primary neurodegenerative disorder; and a current diagnosis of major depression. Patients with space-occupying lesions or lobar hemorrhages were excluded. All patients gave written informed consent. The study was approved by local Ethics Committees.

Baseline Clinical Assessment
Diagnostic evaluation included complete medical history, physical and neurological examination, laboratory tests, neuropsychological testing including Mini-Mental State Examination (MMSE),8 and MRI of the brain. For all patients, a standard neurological examination was performed, during which the presence of 16 specific neurological signs was assessed: aphasia, dysarthria, dysphagia, pseudobulbar signs (palmomental and snout reflexes), field cut/hemianopia, hemimotor dysfunction indicating upper motor neuron lesions, hemisensory dysfunction, reflex asymmetry, Babinski sign, bilateral increased deep tendon reflexes, hemiplegic gait disorder, atactic gait disorder (atactic gait defined as a broad based gait pattern indicative of cerebellar involvement), and Parkinsonian type gait disorder. Extrapyramidal signs shown by resting or postural tremor, nonspastic rigidity, or hypokinesia. All neurological signs were assessed as "none/absent," "mild," "moderate," "severe," or "very severe" and as such included, except for the signs hemianopia and reflex abnormalities which were graded as "none/absent" and "present." For this study, all signs were dichotomised as "none/absent"=0 and "present"=1, and as such used in the data analysis. The following 6 signs were regarded as "unilateral signs": aphasia, hemianopia, hemimotor dysfunction, sensory dysfunction, reflex asymmetry, hemiplegic gait. Furthermore, we considered "presence of extrapyramidal signs," determined as presence of 1 or more of the following: tremor, nonspastic rigidity, hypokinesia, or Parkinsonian type gait disorder.

MRI Protocol
All patients underwent MRI examination before randomization. MRI scanners operating between 0.5 and 1.5 Tesla were used. Axial spin-echo T2-weighted images (T2-WI; echo time [TE]: 80 to 120 ms; repetition time [TR]: 3000 to 4000 ms; slice thickness=5 mm); axial fluid-attenuated inversion recovery (FLAIR) images (TE: 110 to 150 ms; TR: 9000 to 10000 ms; inversion time: 2000 to 2200 ms; slice thickness=5 mm); and axial, sagittal, and coronal spin-echo T1-weighted images (T1-WI; TE: 11 to 20 ms; TR: 500 to 700 ms; slice thickness=5 mm) were acquired.

Table 1. Patient Demographics and Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>706</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>73 (8)</td>
</tr>
<tr>
<td>Sex, n (%women)</td>
<td>266 (38%)</td>
</tr>
<tr>
<td>Education, y</td>
<td>9 (4)</td>
</tr>
<tr>
<td>MMSE</td>
<td>19 (4)</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>Small vessel VaD, n (%)</td>
<td>522 (74%)</td>
</tr>
<tr>
<td>Large vessel VaD, n (%)</td>
<td>126 (18%)</td>
</tr>
<tr>
<td>Combination of small and large vessel VaD, n (%)</td>
<td>58 (8%)</td>
</tr>
<tr>
<td>ARWMC scale*</td>
<td>14.5 (6.2)</td>
</tr>
<tr>
<td>Multiple lacunes, n (%)</td>
<td>203 (29%)</td>
</tr>
<tr>
<td>Bilateral thalamic lesions, n (%)</td>
<td>269 (38%)</td>
</tr>
<tr>
<td>Cerebral infarct, n (%)</td>
<td>226 (32%)</td>
</tr>
</tbody>
</table>

*Data missing of 2 patients.

Data are presented as mean(SD) or n (percentage).

Image Assessment
Vascular abnormalities were evaluated by agreement of 2 experienced readers blinded to clinical information, with the use of digital image files. The items of the radiological NINDS-AIREN criteria for VaD were determined, according to operational definitions earlier proposed.6 Based on these criteria, patients were classified as having large vessel VaD, small vessel VaD, or a combination of both. For the fulfillment of large vessel disease both a topography and a severity criterion (=lesion of the dominant hemisphere or bilateral hemispheric strokes) has to be met. In case of small vessel disease, for white matter hyperintensities (WMH) both topography and severity criteria have to be met, for multiple lacunes and bilateral thalamic lesions only the topography criterion is sufficient. The degree of WMH severity was rated visually on axial FLAIR and T2-WI images using the Age Related White Matter Changes (ARWMC) scale.7 In short, WMH are ill-defined hyperintensities of >5 mm, rated on a 4-point scale ranging from 0 (no lesions) to 3 (diffuse involvement of the entire region), within 5 regions in each hemisphere. Here, we used the total degree of WMH (range 0 to 30) by summing the region-specific scores of both hemispheres. Lacunes were rated as presence or absence of multiple lacunes, defined as at least 2 lacunes in the basal ganglia and at least 2 lacunes in the fronto white matter. The presence of bilateral thalamic lesions was assessed, to meet the criterion, at least 1 lesion in each thalamus had to be present. In addition to assessment of large vessel VaD according to radiological NINDS-AIREN criteria, the presence of a cerebral infarct (of the anterior cerebral artery, in the territory of the posterior cerebral artery, in an association area of the medial cerebral artery or in the watershed area of the carotid territory) was also determined.

Statistical Analysis
All statistical analyses were performed using SPSS 14.0 (SPSS Inc). Associations between the number of neurological signs and MMSE score were assessed using partial correlations, controlling for age and sex. For comparison of neurological signs between the different types of VaD (small vessel VaD, large vessel VaD or a combination) χ² tests were used. Subsequently, to adjust for age and sex, we used logistic regression models with the individual neurological signs as dependent variables, and the different types of VaD as categorical
covariate. In addition, associations between neurological signs and specific MRI measures of cerebrovascular disease were assessed using logistic regression analysis, adjusting for age and sex. We used the individual neurological signs as dependent variables. Independent variables were dichotomized as follows: extensive WMH absent (ARWMC < 15) or present (ARWMC ≥ 15; determined using the median score of the whole population, ARWMC = 15), multiple lacunes and bilateral thalamic lesions absent or present, large vessel infarct—indeed of fulfilment of the criteria of large vessel VaD—absent or present. The associations between neurological signs and MRI measures of cerebrovascular disease were tested in separate models.

**Results**

The total study population of 706 VaD patients had a mean (±SD) age of 73±8 years (Table 1). On average, patients were mildly-to-moderately demented with a mean MMSE score of 19±4. On the basis of the operational definitions for the radiological part of the NINDS-AIREN criteria, 522 (74%) patients had small vessel VaD, 126 (18%) had large vessel VaD, and 58 (8%) had both small and large vessel VaD. The mean ARWMC score was 14.5±6.2 (median 15). There were 203 (29%) patients who showed multiple lacunes, 269 (38%) patients had bilateral thalamic lesions, and the presence of a cerebral infarct was demonstrated by 226 (32%) patients (n=4 anterior cerebral artery, n=52 posterior cerebral artery, n=57 association area of the medial cerebral artery, n=57 watershed area of the carotid territory, n=56>1 cerebral infarct).

A median (range) number of 4.5 (0–16) signs per patient were presented (see Figure 1; number of presented signs per patient). There were 19 patients who did not present any of the aforementioned selected neurological signs, however all had shown other neurological signs (eg, lower facial weakness), or symptoms not otherwise specified. We found a small negative correlation between the number of presented neurological signs and the MMSE (adjusted for age and sex, partial r = −0.14, P < 0.001). Prevalence of the 16 evaluated focal neurological signs in the total population is shown in Figure 2. Reflex asymmetry was the focal sign which was shown most often (49%), followed by hemimotor dysfunction (44%), dysarthria (43%), and aphasia (41%). The symptom which was most seldom presented was hemianopia (10%).

The relative prevalence of specific neurological signs appeared to be different between patients with small vessel and large vessel VaD (Table 2). Dysarthria, dysphagia, parkinsonian type gait disorder, and hypokinesia were more prevalent in patients with small vessel VaD compared with patients with large vessel VaD. Patients with large vessel VaD more frequently showed aphasia, hemianopia, hemisensory dysfunction, and reflex asymmetry. The results did not change after adjustment for age and sex. Other signs, including the babinski sign, atactic gait disorder, and tremor, were equally distributed between patients with small vessel or large vessel VaD.
In addition, the number of signs presented per patient did not differ between patients with small vessel VaD, large vessel VaD, or a combination (P/H11022 > 0.30). In an additional analysis, we compared the presence of at least 1 unilateral sign (presence of aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry, or hemiplegic gait) and presence of an extrapyramidal sign (parkinsonian gait, tremor, rigidity, or hypokinesia) according to type of cerebrovascular disease. The majority of patients with small vessel VaD (76%) showed at least 1 unilateral sign, but to a lesser extent (P/H11021 < 0.001) than patients with large vessel VaD, who almost invariably showed unilateral signs (large vessel VaD: 93%; large + small vessel VaD: 90%).

Conversely, presence of at least 1 extrapyramidal sign was highest in patients with small vessel disease (54%), but they were also shown by patients with large vessel disease (large vessel VaD: 41%; large + small vessel VaD: 33%; P = 0.001). Subsequently we related the various MRI measures of cerebrovascular disease (extensive WMH, multiple lacunes, bilateral thalamic lesions, presence of a cerebral infarct) to the presence of neurological signs (Table 3). Extensive WMH was associated with an increased risk of dysarthria, dysphagia, parkinsonian type gait disorder, and rigidity. The presence of multiple lacunes additionally showed an increased risk of hemimotor dysfunction. Bilateral thalamic lesions were associated with an increased risk of dysphagia, parkinsonian type gait disorder, and hypokinesia. Furthermore, these measures of small vessel disease were associated with a lower risk of aphasia and hemianopia. In contrast, the presence of a cerebral infarct was associated with a higher risk of hemimotor dysfunction, aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry, and hemiplegic gait disorder, whereas the risk of dysarthria, dysphagia, and extrapyramidal signs was lower in patients with a cerebral infarct.

### Discussion

In this large cohort of VaD patients we found that neurological signs of reflex asymmetry (49%), hemimotor dysfunction (44%), and dysarthria (43%) were most prevalent, whereas hemianopia was rarely observed (10%). Although the number of signs did not differ according to type of underlying cerebrovascular disease, the specific neurological signs differed by type of vascular abnormality.

Overall, little has been reported previously about the relative prevalence of specific neurological signs in VaD. Different criteria for VaD suggest different signs (DSM/ICD-10/NINDS-AIREN), and some criteria don’t require the presence of neurological signs at all (Alzheimer Disease Diagnostic and Treatment Centers [ADDTC]). However, the criterion of presence of focal neurological signs is nowhere clearly specified, neither in the NINDS-AIREN criteria nor in other criteria of VaD. The NINDS-AIREN criteria only give a suggestion of symptoms that might be
Previous findings. Furthermore, we found associations between small vessel disease and more subtle neurological signs would be expected. The acute signs, the onset of small vessel VaD is often insidious contrast to large vessel infarcts which are likely to produce pseudobulbar signs, which were equally prevalent among the focal signs which are most often mentioned in criteria for VaD, suggesting that a broad definition of neurological signs according to the localization of the infarcts. These signs are sensorimotor changes and aphasia, a result one would expect in gait pattern between small vessel and large vessel VaD patients, with a hemiplegic type gait disturbance in large vessel disease and parkinsonian type gait disturbance in small vessel disease.

Strengths of the present study include the large study population, as it is one of the largest clinical series of patients affected by VaD to date. Additionally, the screening for fulfillment of radiological criteria for probable VaD was performed carefully by central assessment. To diagnose patients with VaD the NINDS-AIREN criteria were used, widely used, and generally considered accurate criteria, although the criteria have been shown not to be interchangeable with other diagnostic methods for VaD.

A limitation includes the study design of a cross-sectional cohort study, which precludes the assessment of causality or the evolution of symptomatology. Another limitation is possible interrater variability attributable to the performance of neurological examination in several centers by several assessors. Ideally, reliability data should have been provided, but for the present study, these were not available. Furthermore, setting, entry criteria, and other design features of a randomized clinical trial may have introduced a selection bias on the inclusion of patients.

Finally, the unavoidable circularity of studying neurological signs in VaD patients—that by definition are required to encountered. We examined 16 signs, but there are many other possible signs we did not assess, like the presence of lower facial weakness. On the other hand, our study shows that in addition to signs of localization, nonfocal signs such as extrapyramidal signs have been reported before. None-theless, none of the criteria for VaD suggest the presence of extrapyramidal signs as a qualifying neurological sign. Gait disorders are common in VaD, and in the NINDS-AIREN criteria specified as clinical feature consistent with the diagnosis. In small vessel disease, gait disturbances have traditionally been classified as "marche à petit pas," an apraxic-atactic, or Parkinsonian gait. We demonstrated a difference in gait pattern between small vessel and large vessel VaD patients, with a hemiplegic type gait disturbance in large vessel disease and parkinsonian type gait disturbance in small vessel disease.

Table 3. Neurological Signs in Relation to Vascular MRI Measurements

<table>
<thead>
<tr>
<th>Sign</th>
<th>WMH</th>
<th>Multiple Lacunes</th>
<th>Bilateral Thalamic Lesions</th>
<th>Cerebral Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aphasia</td>
<td>0.62 (0.46–0.84)</td>
<td>0.53 (0.37–0.76)</td>
<td>0.56 (0.41–0.77)</td>
<td>1.86 (1.35–2.58)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>1.45 (1.05–1.98)</td>
<td>1.60 (1.13–2.27)</td>
<td>1.28 (0.93–1.76)</td>
<td>0.55 (0.39–0.77)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1.69 (1.14–2.51)</td>
<td>2.71 (1.81–4.05)</td>
<td>1.56 (1.07–2.99)</td>
<td>0.52 (0.34–0.81)</td>
</tr>
<tr>
<td>Pseudobulbar signs</td>
<td>1.28 (0.91–1.79)</td>
<td>1.30 (0.90–1.87)</td>
<td>0.94 (0.67–1.33)</td>
<td>0.83 (0.58–1.18)</td>
</tr>
<tr>
<td>Hemianopia</td>
<td>0.34 (0.20–0.57)</td>
<td>0.33 (0.17–0.66)</td>
<td>0.47 (0.27–0.83)</td>
<td>6.63 (3.83–11.48)</td>
</tr>
<tr>
<td>Hemimotor dysfunction</td>
<td>0.95 (0.70–1.28)</td>
<td>1.49 (1.06–2.09)</td>
<td>0.94 (0.69–1.29)</td>
<td>1.73 (1.25–2.39)</td>
</tr>
<tr>
<td>Hemisensory dysfunction</td>
<td>0.92 (0.63–1.34)</td>
<td>0.84 (0.54–1.29)</td>
<td>0.75 (0.51–1.11)</td>
<td>1.66 (1.13–2.44)</td>
</tr>
<tr>
<td>Reflex asymmetry</td>
<td>0.91 (0.67–1.23)</td>
<td>0.85 (0.61–1.20)</td>
<td>0.84 (0.61–1.14)</td>
<td>1.89 (1.37–2.61)</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>0.79 (0.58–1.07)</td>
<td>1.12 (0.79–1.58)</td>
<td>1.23 (0.90–1.68)</td>
<td>1.16 (0.84–1.61)</td>
</tr>
<tr>
<td>Bilateral increased deep tendon reflexes</td>
<td>1.07 (0.78–1.45)</td>
<td>0.97 (0.68–1.38)</td>
<td>1.22 (0.89–1.67)</td>
<td>0.76 (0.55–1.07)</td>
</tr>
<tr>
<td>Hemiplegic gait</td>
<td>1.14 (0.80–1.63)</td>
<td>1.22 (0.83–1.80)</td>
<td>1.38 (0.97–1.96)</td>
<td>1.68 (1.17–2.41)</td>
</tr>
<tr>
<td>Atactic gait</td>
<td>1.08 (0.78–1.51)</td>
<td>0.82 (0.56–1.19)</td>
<td>1.04 (0.74–1.45)</td>
<td>0.88 (0.62–1.26)</td>
</tr>
<tr>
<td>Parkinsonian type gait</td>
<td>1.45 (1.03–2.03)</td>
<td>2.10 (1.45–3.03)</td>
<td>1.42 (1.01–1.98)</td>
<td>0.44 (0.30–0.66)</td>
</tr>
<tr>
<td>Tremor</td>
<td>0.83 (0.53–1.29)</td>
<td>0.99 (0.60–1.63)</td>
<td>0.73 (0.45–1.16)</td>
<td>0.61 (0.37–1.02)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>1.53 (1.04–2.25)</td>
<td>1.63 (1.09–2.43)</td>
<td>1.27 (0.87–1.86)</td>
<td>0.68 (0.45–1.04)</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>1.32 (0.95–1.82)</td>
<td>1.41 (0.99–2.00)</td>
<td>1.40 (1.01–1.94)</td>
<td>0.65 (0.46–0.92)</td>
</tr>
</tbody>
</table>

Data presented as OR (95% CI). Univariate logistic regression analysis with adjustment for age and sex.

WMH indicates white matter hyperintensities, dichotomised by ARWMC<15=0, ARWMC≥15=1; Multiple lacunes, at least 2 lacunes in the basal ganglia and at least 2 lacunes in the frontal white matter; Cerebral infarct, presence of an infarct, independent of fulfillment of the criteria of large vessel VaD.
have neurological signs—is a complex issue. However, we feel that the description of the relative frequency of a large number of specific neurological signs indeed adds to the field. Moreover, we showed that specific signs were related to specific types of imaged vascular damage. Further studies should endeavor to avoid this inherent circularity, for example by studying presence of neurological signs in relation to MRI abnormalities in a broader group of patients with dementia, irrespective of the specific nosological diagnosis.

Disclosures

Dr Lane is an employee of Novartis. Please note that this was a posthoc analysis using baseline data only, bearing no relation to possible treatment whatsoever.

References

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