Infratentorial Abnormalities in Vascular Dementia
António J. Bastos Leite, Wiesje M. van der Flier, Elisabeth C. W. van Straaten, Philip Scheltens and Frederik Barkhof

Stroke 2006;37;105-110; originally published online Dec 8, 2005;
DOI: 10.1161/01.STR.0000196984.90718.8a

Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 2006 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/cgi/content/full/37/1/105

---

Subscriptions: Information about subscribing to Stroke is online at http://stroke.ahajournals.org/subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail: journalpermissions@lww.com

Reprints: Information about reprints can be found online at http://www.lww.com/reprints
Infratentorial Abnormalities in Vascular Dementia

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

Background and Purpose—Infratentorial abnormalities may cause cognitive deficits, but current research criteria for vascular dementia (VaD) do not consider them. Our purposes were to determine the prevalence of infratentorial abnormalities in VaD, their relation with supratentorial abnormalities, and whether they are relevant to cognition.

Methods—We examined 182 patients (120 men, mean age = 73 years, SD = 8) with probable VaD at inclusion into a multicenter clinical trial. MRI scans were evaluated for infratentorial vascular abnormalities, midbrain atrophy, cerebellar atrophy, basilar artery diameter and tortuosity, and supratentorial abnormalities. Cognitive testing included the mini–mental state examination (MMSE) and the vascular dementia assessment scale (VaDAS-cog).

Results—One hundred forty-one (77.5%) patients had infratentorial abnormalities: 119 (65.4%) had focal infratentorial vascular lesions, 65 (35.7%) had diffuse pontine vascular abnormalities hyperintense on T2-weighted images, 20 (11.0%) had midbrain atrophy, and 16 (8.8%) had cerebellar atrophy. Significant correlations were found between number of infratentorial vascular lesions and basilar artery diameter (r = 0.26; P < 0.0001), infratentorial and basal ganglia (including thalamus) vascular abnormalities (r = 0.30; P < 0.0001), as well as between midbrain atrophy and global supratentorial atrophy (r = 0.27; P < 0.0001). Infratentorial vascular abnormalities and cerebellar atrophy were not significantly associated with cognitive impairment. Patients with midbrain atrophy performed worse on cognitive tests than those without midbrain atrophy. After correction for sex, age, education, supratentorial abnormalities, and center, midbrain atrophy remained significantly associated with lower MMSE scores (P < 0.05).

Conclusions—Infratentorial abnormalities often occur in patients with VaD, but only midbrain atrophy was found to be relevant to cognition. (Stroke. 2006;37:105–110.)

Key Words: cognition • infratentorial • MRI • vascular dementia

In the late eighties, it became accepted that besides motor function, the neocerebellum contributes to sensory, cognitive, linguistic, and emotional aspects of human behavior. In addition, animal studies provided evidence that the basilar pons and certain brain stem nuclei may also be involved in cognitive processes.

Therefore, infratentorial abnormalities may be associated with cognitive deficits, and subjects with several pathologies restricted to the cerebellum were found to have a pattern of behavioral abnormalities characterized by disturbances in executive function, spatial cognition, language, and emotional regulation of behavior, the so-called cerebellar cognitive affective syndrome. Furthermore, impairment of attention and visuospatial skills were found in patients with isolated infratentorial infarcts.

Although MRI studies have shown that midbrain atrophy is a main feature of progressive supranuclear palsy and that brainstem lesions occur in almost half of the patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), not much is known about the prevalence and relevance of infratentorial abnormalities in other types of dementia. Current research criteria for vascular dementia (VaD) do not consider infratentorial involvement.

The purposes of this study were to describe the type, extent, and location of infratentorial abnormalities in patients with VaD using MRI, to assess the possible associations between infratentorial and supratentorial abnormalities, and to determine whether infratentorial abnormalities may influence cognitive function.

Materials and Methods

Patients

Baseline data of 182 patients (120 men, 62 women) were available for this study. The cases were the first batch involved in a large multicenter, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with VaD, the VantagE study (Novartis International AG, Basel, Switzerland). Trial inclusion criteria included fulfillment of the clinical and radiological parts of the National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche
et al.'Enseignement en Neurosciences (AIREN) criteria for probable VaD,\textsuperscript{13} with central assessment of the neuroimaging criteria at the Image Analysis Center (VU University Medical Center, Amsterdam, the Netherlands). Patients with space-occupying lesions or lobar hemorrhages were excluded.

To evaluate cognitive function, patients were submitted to a set of tests, which included the mini–mental state examination (MMSE)\textsuperscript{13} (possible range of scores: 0 to 30), and the vascular dementia assessment scale (VaDAS-cog), a battery of tests comprising the Alzheimer disease assessment scale (ADAS-cog)\textsuperscript{16} (possible range of scores: 0 to 85) and 5 additional subtests covering neuropsychological areas (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 backwards 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). Based on the MMSE, patients were classified as having mild to moderate (MMSE scores ≥10) or severe (MMSE scores <10) dementia.

MRI Protocol
All patients underwent an 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.

Image Assessment
Image assessment was performed by a single reader blinded to clinical information, with the use of digital image files. The assessment of vascular abnormalities included the items of the radiological NINDS-AIREN criteria for VaD,\textsuperscript{13} according to operational definitions recently proposed.\textsuperscript{15} Based on these criteria, patients were classified as having large vessel VaD, small vessel VaD, or a combination of both.

The age-related white matter changes (ARWMC) scale\textsuperscript{18} was used to rate vascular abnormalities (including diffuse signal abnormalities hyperintense on T2-WI, as well as number and size of focal lesions: complete infarcts, incomplete infarcts, and hemorrhages) in the following 5 regions: frontal lobes, parietal and occipital lobes, temporal lobes, basal ganglia (including thalamus), and infratentorial structures (possible range of scores for each region: 0 to 6). Large vessel territorial infarcts were identified by means of templates based on imaging and anatomical studies.\textsuperscript{19,20} Lesions hyperintense on T2-WI and hypointense on T1-WI were considered complete infarcts. Complete infarcts of deep small vessels were defined as ischemic lacunae. Lesions hyperintense on T2-WI and isointense on T1-WI were considered incomplete infarcts.\textsuperscript{21} Lesions hypointense on T2-WI were considered hemorrhages and defined as microbleeds when measuring <5 mm.\textsuperscript{22}

The location and side of each infratentorial vascular abnormality was registered according to anatomical location: mesencephalon, pons (basilar or tegmental), cerebellar peduncles, cerebellar hemispheres and vermis (cortical-subcortical or deep), and medulla oblongata. For each focal infratentorial lesion, the greatest dimension was determined on axial T2-WI. We also measured the basilar artery diameter on axial T2-WI and rated the basilar artery tortuosity according to the following scale: non-tortuous basilar artery (score 0), tortuous basilar artery medial to the lateral border of pons (score 1), tortuous basilar artery reaching or going beyond the lateral border of pons (score 2), and dolicho-ectasia of the basilar artery (score 3). In addition, we used visual rating scales to evaluate medial temporal lobe atrophy (MTA),\textsuperscript{23} (possible range of scores for each side: 0 to 4), and global cortical atrophy (GCA),\textsuperscript{24} (possible range of scores: 0 to 3). Midbrain and cerebellar atrophy were considered, respectively, when the anteroposterior diameter of the mesencephalon was <15 mm\textsuperscript{25} and the left/right average width of the largest cerebellar sulci, measured approximately at the midpoint of their longitudinal extension, was ≥2 mm.

Table 1. Baseline Characteristics of the Patients (n=182)

Including Age and Clinical Data, ARWMC, MTA, and GCA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.1 (7.5)</td>
<td>49–88</td>
</tr>
<tr>
<td>Education (y)</td>
<td>8.3 (4.1)</td>
<td>0–20</td>
</tr>
<tr>
<td>Duration of dementia (mo)</td>
<td>35.7 (35.2)</td>
<td>1–325</td>
</tr>
<tr>
<td>MMSE†</td>
<td>19.2* (3.9)</td>
<td>10–26</td>
</tr>
<tr>
<td>Alzheimer disease assessment scale‡</td>
<td>32.5* (11.5)</td>
<td>11–80</td>
</tr>
<tr>
<td>Symbol digit modalities‡</td>
<td>9.5 (8.7)</td>
<td>0–43</td>
</tr>
<tr>
<td>Digits backwards‡</td>
<td>3.2 (1.8)</td>
<td>0–9</td>
</tr>
<tr>
<td>Maze (s)‡</td>
<td>35.6 (42.3)</td>
<td>4–240</td>
</tr>
<tr>
<td>Digit cancellation†</td>
<td>8.8 (5.4)</td>
<td>0–29</td>
</tr>
<tr>
<td>Verbal fluency†</td>
<td>8.2 (4.6)</td>
<td>0–30</td>
</tr>
<tr>
<td>ARWMC frontal‡</td>
<td>5.0* (1.4)</td>
<td>1–6</td>
</tr>
<tr>
<td>ARWMC parieto-occipital‡</td>
<td>5.0* (1.5)</td>
<td>0–6</td>
</tr>
<tr>
<td>ARWMC basal ganglia (including thalamus)‡</td>
<td>2.4* (1.7)</td>
<td>0–6</td>
</tr>
<tr>
<td>ARWMC temporal‡</td>
<td>3.4* (1.8)</td>
<td>0–6</td>
</tr>
<tr>
<td>ARWMC infratentorial‡</td>
<td>2.0* (1.8)</td>
<td>0–6</td>
</tr>
<tr>
<td>MTA (left/right average)‡</td>
<td>2.1* (1.0)</td>
<td>0–4</td>
</tr>
<tr>
<td>GCA‡</td>
<td>1.8* (0.7)</td>
<td>0–3</td>
</tr>
</tbody>
</table>

*Please note that means of scores are presented because of lack of variability in the medians; †Lower values indicate greater severity; ‡Higher values indicate greater severity.
(9.9%) had both small and large vessel VaD. There was an overlap of findings suggestive of small vessel disease: 139 (76.4%) of the 182 patients had extensive supratentorial periventricular white matter lesions, which in 129 (70.9%) involved at least 25% of the white matter; 77 (42.3%) had multiple basal ganglia, thalamic, and frontal white matter lacunae; and 70 (38.5%) had bilateral thalamic lesions.

**Infrafateral Abnormalities**

One hundred forty-one (77.5%) of the VaD patients had infratentorial abnormalities: 119 (65.4%) had focal infratentorial vascular lesions (Figure 1), 65 (35.7%) had diffuse signal abnormalities occurring in the pons (Figure 2), 20 (11.0%) had midbrain atrophy (Figure 3), and 16 (8.8%) had cerebellar atrophy (Figure 4).

Focal infratentorial vascular lesions occurred more frequently among patients with small vessel VaD (either isolated or associated with large vessel VaD), than in patients with large vessel VaD (Pearson \( \chi^2 = 4.39; P < 0.05 \)). No significant differences between those groups were found for diffuse pontine signal abnormalities, midbrain atrophy, or cerebellar atrophy.

The total number of focal infratentorial vascular lesions detected, not including diffuse pontine abnormalities, was 399 (Table 2). The number of lesions per patient ranged from 0 to 25 (mean = 2.2; SD = 3.1), but only 56 (30.8%) patients had >2 lesions. The size of infratentorial vascular lesions ranged from 2 to 28 mm (mean = 6.2; SD = 4.8), but only 37 (20.3%) patients had lesions larger than 10 mm.

Of the 399 focal lesions, 306 (76.7%) were ischemic lesions and 93 (23.3%) were hemorrhages. Most (78.5%) of the hemorrhages were microbleeds. The majority (74.2%) of ischemic lesions involved the cerebellar cortex or the basilar pons, and the vast majority (86.0%) of hemorrhages were deep cerebellar or basilar pontine (Figure 1). We found only 1 infratentorial large vessel infarct occurring in the right posteroinferior cerebellar artery territory.
The mean basilar artery diameter was 4.1 mm (SD = 0.8; range: 2 to 9 mm), and the mean basilar artery tortuosity score was 0.9 (SD = 0.8; range: 0 to 3). A significant correlation was found between basilar artery diameter and number of infratentorial vascular lesions ($r_s = 0.26; P < 0.0001$), but not between basilar artery diameter and size of lesions. No significant correlations were found between basilar artery tortuosity and number or size of lesions, nor between basilar artery diameter or tortuosity and infratentorial ARWMC.

**Associations Between Infratentorial and Supratentorial Abnormalities**

A significant correlation was found between infratentorial and basal ganglia (including thalamus) ARWMC ($r_s = 0.30; P < 0.0001$), but not between infratentorial and other supratentorial regions. With respect to atrophy, a significant correlation was found between midbrain atrophy and GCA ($r_s = 0.27; P < 0.0001$), but not between midbrain atrophy and MTA, nor between cerebellar atrophy and GCA or MTA. No significant correlations were found between midbrain or cerebellar atrophy and ARWMC.

**Clinical-Radiological Associations of Infratentorial Abnormalities**

Neither focal infratentorial vascular lesions, nor diffuse pontine signal abnormalities or cerebellar atrophy were significantly associated with cognitive impairment.

Patients with midbrain atrophy performed worse on MMSE ($P < 0.01$), ADAS-cog ($P < 0.05$), digit cancellation test ($P < 0.01$), and verbal fluency test ($P < 0.05$). No significant differences were found between patients with and without infratentorial lesions in terms of age, sex, education, or severity of cognitive impairment.

**TABLE 2. Presumed Pathology, No., Location, and Side of Focal Infratentorial Lesions in Patients With VaD**

<table>
<thead>
<tr>
<th>Side</th>
<th>Location</th>
<th>Large Vessel Complete Infarcts</th>
<th>Small Vessel Complete Infarcts</th>
<th>Small Vessel Incomplete Infarcts</th>
<th>Hemorrhages</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Mesencephalon</td>
<td>8 (2.0%)</td>
<td>1 (0.3%)</td>
<td>2 (0.5%)</td>
<td>11 (2.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basilar pons</td>
<td>42 (10.5%)</td>
<td>9 (2.3%)</td>
<td>26 (6.5%)</td>
<td>77 (19.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tegmental pons</td>
<td>5 (1.3%)</td>
<td>1 (0.3%)</td>
<td></td>
<td>6 (1.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Middle cerebellar peduncles</td>
<td>2 (0.5%)</td>
<td>1 (0.3%)</td>
<td></td>
<td>3 (0.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (cortical-subcortical)</td>
<td>69 (17.3%)</td>
<td>5 (1.3%)</td>
<td>3 (0.8%)</td>
<td>77 (19.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar vermis (cortical-subcortical)</td>
<td>1 (0.3%)</td>
<td></td>
<td></td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (deep)</td>
<td>20 (5.0%)</td>
<td>7 (1.8%)</td>
<td>22 (5.5%)</td>
<td>49 (12.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medulla oblongata</td>
<td></td>
<td>1 (0.3%)</td>
<td></td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Subtotal left</td>
<td></td>
<td>147 (36.8%)</td>
<td>24 (6.0%)</td>
<td>54 (13.5%)</td>
<td>225 (56.4%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>Mesencephalon</td>
<td>2 (0.5%)</td>
<td>1 (0.3%)</td>
<td>3 (0.8%)</td>
<td>7 (1.8%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td></td>
<td>Basilar pons</td>
<td>24 (6.0%)</td>
<td>13 (3.3%)</td>
<td>13 (3.3%)</td>
<td>50 (12.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tegmental pons</td>
<td>7 (1.8%)</td>
<td></td>
<td></td>
<td>7 (1.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Middle cerebellar peduncles</td>
<td>1 (0.3%)</td>
<td></td>
<td></td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (cortical-subcortical)</td>
<td>1* (0.3%)</td>
<td>57 (14.3%)</td>
<td>7 (1.8%)</td>
<td>5 (1.3%)</td>
<td>70 (17.5%)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemispheres (deep)</td>
<td></td>
<td>17 (4.3%)</td>
<td>57 (14.3%)</td>
<td>7 (1.8%)</td>
<td>19 (4.8%)</td>
</tr>
<tr>
<td>Subtotal right</td>
<td></td>
<td>1 (0.3%)</td>
<td>107 (26.8%)</td>
<td>27 (6.8%)</td>
<td>39 (9.8%)</td>
<td>174 (43.6%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1 (0.3%)</td>
<td>254 (63.7%)</td>
<td>49 (12.3%)</td>
<td>93 (23.3%)</td>
<td>399 (100%)</td>
</tr>
</tbody>
</table>

*Posteroinferior cerebellar artery infarct.
Infratentorial pathology (eg, large vessel cerebellar infarcts, abnormal results when used in subjects with predominant supratentorial pathology.\footnote{1,2,5} The association between midbrain atrophy and lower MMSE scores persisted even after correction for abnormalities representing degenerative and vascular supratentorial pathology. These findings suggest that the midbrain contributes to cognition independently of the supratentorial structures, and that assessment of midbrain atrophy should be included in the MRI evaluation of patients with dementia.

There is an increasing awareness that vascular and degenerative pathology may coexist.\footnote{11} Additionally, neuropathological studies have reported involvement of the cerebellum and midbrain by Alzheimer disease pathology.\footnote{12,13} Therefore, it is conceivable that cerebellar and midbrain atrophy observed in this sample of VaD patients may represent concomitant Alzheimer pathology, and that its occurrence in the periaqueductal gray matter may explain the association between midbrain atrophy and cognitive impairment by disruption of mesencephalic connections.\footnote{14} More work is needed to determine whether midbrain atrophy actually represents degenerative pathology and whether its presence in patients fulfilling diagnostic criteria for VaD is a marker for mixed dementia (Alzheimer and vascular).

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 central assessment. Limitations include the fact that MRI images were acquired on a wide range of scanners and sequences, which may have hampered the qualitative assessment of the abnormalities, and that gradient-echo T2*-weighted images were not available, which may have underestimated the number of hemorrhages detected.\footnote{15} In the present sample, we also lack information on neurological sequelae of the lesions.

Our study shows the high prevalence of infratentorial vascular lesions in patients with probable VaD. Current research criteria for VaD\footnote{16,17} do not require such lesions to be present, and our results seem to support this notion. However, apart from the relevance of midbrain atrophy, it is not ruled out that infratentorial vascular lesions may contribute to the clinical picture of VaD, by interacting with strategic supratentorial (basal ganglia and thalamic) vascular lesions.

**References**


