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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_s=0.26; P<0.0001), infratentorial and basal ganglia (including thalamus) vascular abnormalities (r_s=0.30; P<0.0001), as well as between midbrain atrophy and global supratentorial atrophy (r_s=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.[1,2] In addition, animal studies provided evidence that the basilar pons and certain brain stem nuclei may also be involved in cognitive processes.[3–6]

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.[7] Furthermore, impairment of attention and visuospatial skills were found in patients with isolated infratentorial infarcts.[8–10]

Although MRI studies have shown that midbrain atrophy is a main feature of progressive supranuclear palsy[11] and that brain stem lesions occur in almost half of the patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL),[12] not much is known about the prevalence and relevance of infratentorial abnormalities in other types of dementia. Current research criteria for vascular dementia (VaD)[13,14] 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

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From the Department of Radiology and Image Analysis Center (A.J.d.B.L., F.B.), VU University Medical Center, Amsterdam, the Netherlands; the Department of Neuroradiology (A.J.d.B.L.), Hospital Geral de Santo António, Oporto, Portugal; and the Department of Neurology and Alzheimer Center (W.M.v.d.F., E.C.W.S., P.S.), VU University Medical Center, Amsterdam, the Netherlands.

Correspondence to António José de Bastos Leite, VU University Medical Center, Department of Radiology, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. E-mail A.bastosleite@vumc.nl

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et al'Enseignement en Neurosciences (AIREN) criteria for probable VaD,[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)[15] (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)[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,[13] according to operational definitions recently proposed.[17] 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[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.[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.[21] Lesions hypointense on T2-WI were considered hemorrhages and defined as microbleeds when measuring <5 mm.[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: nontortuous 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 dolichoectasia of the basilar artery (score 3).

In addition, we used visual rating scales to evaluate medial temporal lobe atrophy (MTA)[23] (possible range of scores for each side: 0 to 4), and global cortical atrophy (GCA)[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[25] and the left/right average width of the largest cerebellar sulci, measured approximately at the midpoint of their longitudinal extension, was ≥2 mm.

Focal infratentorial abnormalities measuring <2 mm were not included, nor were punctate or linear foci of abnormal signal (isointense with the cerebrospinal fluid) suggestive of enlarged perivascular spaces, regularly occurring near the substantia nigra.[26] Care was taken to avoid the inclusion of pulsation artifacts, recognizable by linear patterns of signal banding attributable to phase misregistration.[27] Abnormalities suggestive of Wallerian degeneration of the corticospinal tract in the brain stem were excluded because they represent axonal degeneration secondary to supratentorial lesions.[28]

Statistical Analysis

Statistical analysis was performed by means of SPSS 11.0 (SPSS Inc). We used χ^2 tests to compare categorical variables and the Mann-Whitney U test to compare scores. For comparisons of continuous variables, the independent sample Student *t* test and the Mann-Whitney U test were used, according to the distribution of data. Correlations were tested using the Spearman rank correlation coefficient (r_s). We used stepwise multiple linear regression analyses to determine whether infratentorial abnormalities independently influenced cognitive function after correction for sex, age, education, duration of dementia, supratentorial ARWMC, MTA, and GCA. Because at least 50 different centers participated in the trial, center of origin was additionally corrected for. Statistical significance was considered when probability values were <0.05.

Results

Patient Sample

Table 1 summarizes baseline characteristics of the patients. All patients had VaD of mild to moderate severity.

Based on the operational definitions for the radiological part of the NINDS-AIREN criteria, 142 (78.0%) patients had small vessel VaD, 22 (12.1%) had large vessel VaD, and 18

TABLE 1. Baseline Characteristics of the Patients (n=182) Including Age and Clinical Data, ARWMC, MTA, and GCA

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

*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.

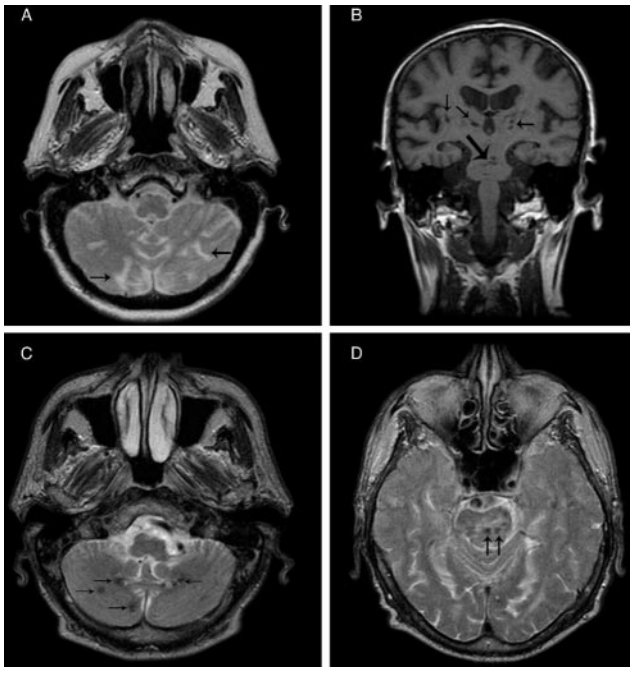

Figure 1. A, Axial T2-WI of a 78 year-old patient showing multiple bilateral small vessel cerebellar infarcts, some involving the cerebellar cortex (arrows). B, Coronal T1-WI of an 80 year-old patient showing multiple infratentorial lacunae in the basilar pons (large arrow), and supratentorial lacunae occurring in the right basal ganglia region and in both thalami (small arrows). C, D, Axial T2-WIs of a 66 year-old patient showing multiple deep cerebellar and pontine microbleeds (arrows).

(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.

Infratentorial Findings

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.

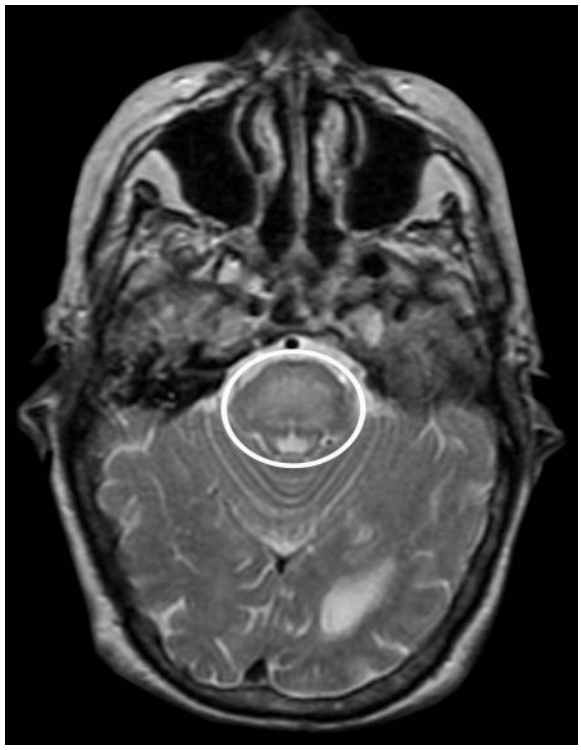

Figure 2. Axial T2-WI showing diffuse hyperintensity occurring in the pons (round overlay), suggestive of small vessel ischemic pathology.

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.

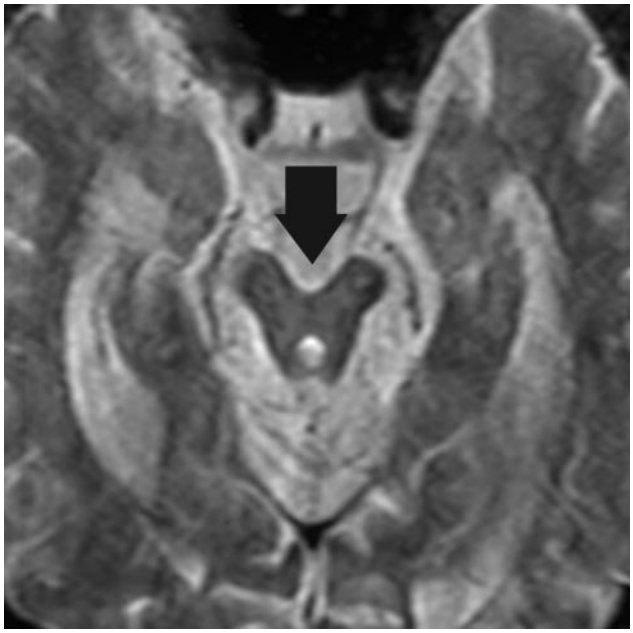

Figure 3. Axial T2-WI showing midbrain atrophy (arrow), and the consequent dilatation of the cerebral aqueduct.

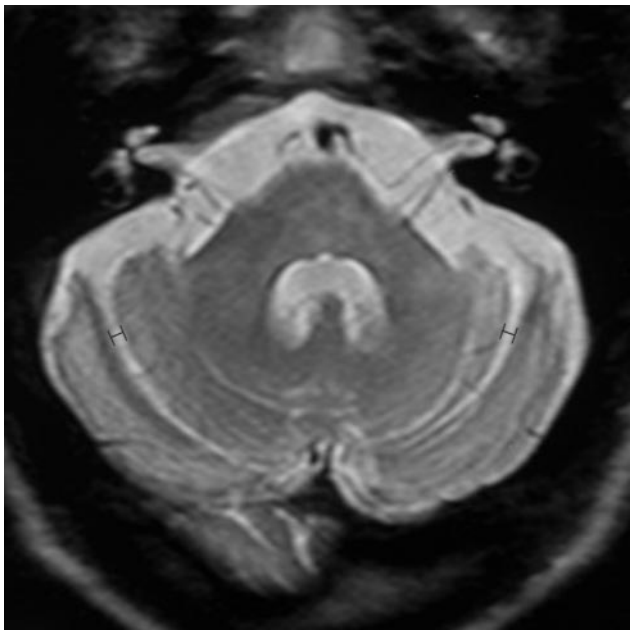

Figure 4. Axial T2-WI showing enlarged cerebellar sulci bilaterally (measurement overlays), indicative of cerebellar atrophy.

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

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

Side	Location	Large Vessel Complete Infarcts	Small Vessel Complete Infarcts	Small Vessel Incomplete Infarcts	Hemorrhages	Total
Left	Mesencephalon		8 (2.0%)	1 (0.3%)	2 (0.5%)	11 (2.8%)
	Basilar pons		42 (10.5%)	9 (2.3%)	26 (6.5%)	77 (19.3%)
	Tegmental pons		5 (1.3%)	1 (0.3%)		6 (1.5%)
	Middle cerebellar peduncles		2 (0.5%)		1 (0.3%)	3 (0.8%)
	Cerebellar hemispheres (cortical-subcortical)		69 (17.3%)	5 (1.3%)	3 (0.8%)	77 (19.3%)
	Cerebellar vermis (cortical-subcortical)		1 (0.3%)			1 (0.3%)
	Cerebellar hemispheres (deep)		20 (5.0%)	7 (1.8%)	22 (5.5%)	49 (12.3%)
	Medulla oblongata			1 (0.3%)		1 (0.3%)
Subtotal left			147 (36.8%)	24 (6.0%)	54 (13.5%)	225 (56.4%)
Right	Mesencephalon		2 (0.5%)		1 (0.3%)	3 (0.8%)
	Basilar pons		24 (6.0%)	13 (3.3%)	13 (3.3%)	50 (12.5%)
	Tegmental pons		7 (1.8%)			7 (1.8%)
	Middle cerebellar peduncles				1 (0.3%)	1 (0.3%)
	Cerebellar hemispheres (cortical-subcortical)	1* (0.3%)	57 (14.3%)	7 (1.8%)	5 (1.3%)	70 (17.5%)
	Cerebellar hemispheres (deep)		17 (4.3%)	7 (1.8%)	19 (4.8%)	43 (10.8%)
Subtotal right		1 (0.3%)	107 (26.8%)	27 (6.8%)	39 (9.8%)	174 (43.6%)
Total		1 (0.3%)	254 (63.7%)	49 (12.3%)	93 (23.3%)	399 (100%)

*Posteroinferior cerebellar artery infarct.

($P<0.01$), and verbal fluency ($P<0.05$) tests than patients without midbrain atrophy. No significant associations were found between midbrain atrophy and symbol digit modalities, digits backwards, or maze time to completion.

Stepwise multiple linear regression analyses revealed the following independent variables significantly associated with MMSE: MTA (B=−0.97; SE=0.28; $P<0.01$), education (B=0.20; SE=0.06; $P<0.01$), GCA (B=−1.10; SE=0.42; $P<0.05$), and midbrain atrophy (B=−1.77; SE=0.88; $P<0.05$). After additional correction for center, midbrain atrophy remained significantly associated with MMSE (B=−2.10; SE=0.99; $P<0.05$). Stepwise multiple linear regression analyses also revealed that midbrain atrophy was significantly associated with digit cancellation (B=−2.39; SE=1.19; $P<0.05$), but this association no longer demonstrated statistical significance after correction for center.

Discussion

Our study shows that infratentorial abnormalities often occur in patients fulfilling the NINDS-AIREN criteria for VaD. Focal infratentorial vascular lesions are especially frequent among patients with small vessel type of VaD, which is in agreement with the view that these patients have more widespread cerebrovascular pathology than those with isolated large vessel VaD. In addition, patients with large basilar artery diameter were found to have more infratentorial vascular lesions, which may result from atheroembolic events associated with vascular ectasia. We also found diffuse signal abnormalities in the pons, probably representing diffuse ischemic small vessel pathology.[29] Moreover, we found that infratentorial vascular abnormalities are associated with basal ganglia and thalamic lesions. Because both infratentorial structures and the thalami are perfused by the vertebrobasilar system,[19,20] this association may be partially explained. Furthermore, we found midbrain and cerebellar atrophy occurring in a minority of patients.

The observed infratentorial vascular lesions were mainly located in the cerebellum and basilar pons, structures currently considered relevant to cognitive processes,[1,2,5] although the clinical scales that we used for VaD, selected to test general cognitive and executive functions, did not confirm that such lesions indeed contribute to cognitive impairment. However, the amount of supratentorial vascular lesions occurring in our patients may have masked the cognitive relevance of infratentorial lesions, and it is also possible that more specific neuropsychological tests might have shown other subtle cognitive effects. Actually, neuropsychological batteries including tests for visuospatial skills[30] showed abnormal results when used in subjects with predominant infratentorial pathology (eg, large vessel cerebellar infarcts, Friedreich ataxia, and olivopontocerebellar atrophy).[8–10,31]

On the other hand, we found that patients with midbrain atrophy had worse general cognitive and executive functions than the other VaD patients. Although midbrain atrophy was found to be related with GCA, most probably attributable to axonal degeneration secondary to supratentorial pathology, 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.[32] Additionally, neuropathological studies have reported involvement of the cerebellum and midbrain by Alzheimer disease pathology.[33,34] 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.[34] 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.[35] 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[13,14] 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.

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