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Quantitative magnetic resonance analysis in vascular dementia

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Abstract The potential role of magnetic resonance imaging (MRI) in differentiating between specific causes of cognitive decline in patients with vascular dementia (VD) has not yet been fully established. We therefore decided to assess the supratentorial cerebral contents in 24 patients with a diagnosis of probable VD and in 24 normal subjects, matched for age and education level, using MRI volumetric parameters obtained by means of a quantitative method. The volumes of subarachnoid and ventricular spaces, cerebral tissue, and hyperintense areas on T2-weighted images were calculated. In order to reduce interindividual variability caused by differences in intracranial size, each absolute measurement was normalized to the relative size of the intracranial volume. In addition, we calculated the ratio between the areas of the corpus callosum (CC) and supratentorial brain at the same level on the T1-weighted image midsagittal plane. The MRI data were correlated with the deterioration of cognitive functions. Patients with VD showed significantly lower cerebral tissue volume and CC area,

and higher ventricular space volume than normal subjects. Furthermore, the total volume of the T2 signal alterations was higher in VD patients than in normal subjects. In VD patients, this volume was found to be proportional to the increase in the volume of the ventricular space. On the other hand, no correlation was found between the volume of the T2 signal alterations and the area of the CC. The degree of global cognitive dysfunction and the score of each neuropsychological test did not show any correlation with the MRI data. Our results suggest that ventricular enlargement in VD patients is correlated with the increase in volume of the T2 signal abnormalities, but that the degree of global cognitive dysfunction is not influenced by the volume of these T2 signal abnormalities. Furthermore, the CC atrophy does not influence the score of any neuropsychological test or the degree of global cognitive dysfunction.

Key words Vascular dementia · Magnetic resonance imaging · Neuropsychological assessment

Introduction

Vascular dementia (VD) is the second most common cause of dementia in the elderly after Alzheimer's disease. However, surprisingly little is known about the factors

that lead to dementia following stroke. In this regard, the potential role of magnetic resonance imaging (MRI) in differentiating between specific causes of cognitive decline has not yet been established. Conflicting results have been reported on the association of white matter hy-

perintensities (WHM) with cognitive functioning [2, 8, 21, 23]. Another frequent MRI finding in elderly persons that has also been related to cognitive decline is an increase in ventricular volume [9, 17, 24, 25]. It is generally assumed that this ventricular enlargement occurs, *ex vacuo*, by shrinkage of periventricular structures [11]. Although a large number of neuroimaging studies have been conducted both on healthy elderly and demented subjects, very few MRI studies have investigated the relevance of volumetric parameters of the supratentorial cerebral contents, obtained by using a quantitative method, on cognitive performance.

Corpus callosum (CC) atrophy has proven to be a sensitive indicator of cognitive dysfunction in multiple sclerosis [19, 28]. Results of an autopsy study indicated that the loss of nerve fibres in the CC might also play a role in inducing cognitive deficits in progressive subcortical vascular encephalopathy [36]. However, no MRI study has yet investigated the relevance of CC atrophy on cognitive performances in VD.

The aim of this study, was to assess the supratentorial cerebral contents in patients with VD and in normal subjects, using MRI volumetric parameters obtained by means of a quantitative method, and to correlate MRI data with the deterioration of cognitive functions. The relationship between CC area and cognitive performances was also evaluated.

Patients and methods

Twenty-four patients [17 male and 7 female; mean age (SD), 71.9 (6) years] with a diagnosis of probable VD and 24 normal subjects [14 male and 10 female; mean age (SD) 73.8 (5.3) years] underwent a brain MRI and neuropsychological test battery. The mean (SD) duration of the disease was 21.4 (6.6) months. Education level was similar in the two groups of subjects [7.7 (3.1) vs 7.3

(2.9) years, respectively]. Our control cohort was composed of age-matched community volunteers, invited to participate in the study after normal cerebral CT and preliminary neuropsychological evaluation. The NINDS-AIREN criteria was used to define VD [31]. Dementia was defined as a cognitive decline from a previously higher level of functioning, manifested by impairment of memory and two or more cognitive functions, as established by clinical examination and documented by neuropsychological tests. The cognitive deficits had to be severe enough to interfere with activities of daily living. The diagnosis of probable VD was substantiated on the basis of the case history, neurological findings, laboratory data including thyroid profile, serum folate and vitamin B12, and CT findings [10]. Single ischaemic stroke occurred in 8 patients, while the remaining 16 patients showed two or more ischaemic strokes and/or transient ischaemic attacks. All the patients showed a temporal relationship between the cerebrovascular disease and the cognitive deficits, with the onset of dementia occurring within 6 months of ischaemic attacks. Twenty-two of 24 patients showed focal neurological signs. However, their disability did not preclude neuropsychological evaluation. All the patients showed subcortical lacunes on CT. In 10 patients, lacunes were associated with major vessel infarcts involving cortical and subcortical areas.

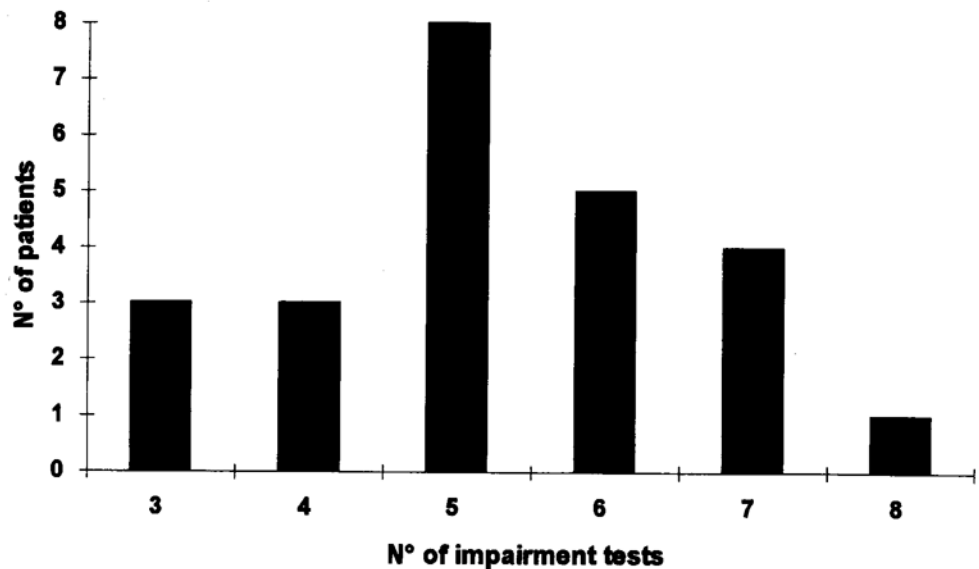
We excluded patients with disturbance of consciousness, major depression, agitation or psychosis. Moreover, patients with systemic disorders or other brain diseases that could cause cognitive impairment were excluded, as were those with a Mini Mental State Examination (MMSE) score < 12 and > 24.

Neuropsychological assessment

All the subjects underwent the following neuropsychological tests, administered by a neuropsychologist (A.G.): Block Design (WAIS subtest) [35] for general intelligence, reflecting the ability to solve logical problems; Controlled Oral Word Association [5] and Token "short version" [13] for language; Digit Span (forward and backward) [35] and Rey Auditor Verbal Learning [30] for verbal memory; Complex Figure [26] for visuospatial constructional ability and visual memory; Street Completion [33] for visuospatial abilities; Benton Visual Retention "Administration C" (copy trial) [4] for constructive apraxia.

The 11 items version of the Street Completion test was given. The Auditor Verbal Learning, consisting of a list of 15 stimulus

Fig. 1 Bar graph of the total number of neuropsychological test impairments, indicating the global cognitive dysfunction in 24 patients with vascular dementia



names of common objects, was read to the subject five times by the examiner. We assigned two different scores to this test: (1) short-term memory score (number of words recalled after the first presentation); (2) long-term memory score (number of words correctly recalled 15 min after the last presentation).

In VD patients, the neuropsychological test with a score of > 2 standard deviations from the mean value of the normal subjects was considered as significant impairment. The global cognitive performance in each patient was calculated by MMSE and by a global score calculated by totalling the number of neuropsychological test impairments (Fig. 1). The degree of global cognitive dysfunction was classified as mild (global score of ≤ 5) or severe (global score ≥ 6).

MR imaging

All the patients underwent MRI using a 0.2 T imager (Ansaldo MPR 4000). We obtained axial T2-weighted (TR = 2500; TE = 30–110; 2 measures, 256×192 matrix) images, 7.5 mm slice thickness with no gap, and sagittal T1-weighted images (TR = 400; TE = 25; 4 measures, 256×192 matrix) to calculate CC area.

Volumes of subarachnoid and ventricular spaces, cerebral tissue and hyperintense areas on T2-weighted images were calculated using a quantitative method. The MR images were independently analysed by two neuroradiologists (C.G. and A.P.) unaware of the

cognitive and clinical status of the patients. The MRI regions of interest were identified directly from the computer screen, and a consensus was reached. In cases of disagreement, a third senior neuroradiologist also reviewed the images, and a final consensus was reached. Prior to the study, the neuroradiologists were trained to minimize interobserver variability, which was less than 5%. The operators drew around the regions of interest using a mouse-controlled cursor on a computer display. As the segmentation method operates on individual slices, the results were defined and analysed as areas rather than volume. Subsequently, the areas were multiplied by the slice thickness for a straightforward estimate of volume. In order to reduce interindividual variability caused by differences in intracranial size, each absolute volumetric measurement was normalized to the value relative to the intracranial volume, using the following ratio [34]: absolute volumetric measurement/intracranial volume. Intracranial volume was calculated by adding the volumes of cerebral tissue, subarachnoid and ventricular spaces. In addition, we calculated the ratio between the areas of the CC and supratentorial brain at the same level on midsagittal T1-weighted images.

Statistics

Means were compared using Student's *t*-test. Spearman's non-parametric rank correlation was used to show correlations between variables. Statistical significance was taken at $P < 0.05$.

Table 1 Normalized volumetric data of the supratentorial contents and corpus callosum/brain ratio in patients with vascular dementia (VD) and in normal subjects. Values are mean (SD). *Subarachnoid space* subarachnoid space volume/intracranial volume; *ventricular space* ventricular space volume/intracranial volume; *cerebral tissue* cerebral tissue volume/intracranial volume; *corpus callosum* corpus callosum area/supratentorial brain area at the same level

	VD patients (<i>n</i> = 24)	Normal subjects (<i>n</i> = 24)	<i>P</i> value (Student's <i>t</i> -test)
Subarachnoid space (ratio)	12.2 (2)	12.3 (1.9)	NS
Ventricular space (ratio)	5.1 (2)	3.7 (1)	$P < 0.001$
Cerebral tissue (ratio)	81.6 (2.8)	84.3 (1.9)	$P < 0.001$
Corpus callosum (ratio)	0.08 (0.01)	0.1 (0.01)	$P < 0.001$

Fig. 2 Scatterplot displaying the values of the ventricular space volume, expressed as normalized data (ventricular space volume/intracranial volume), and age for 24 normal subjects ($P < 0.01$; Spearman's rank correlation)

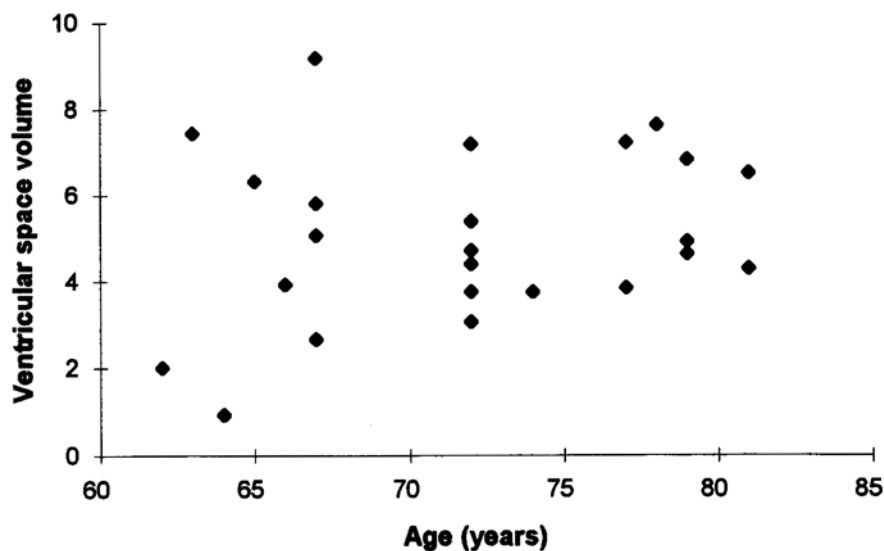


Fig. 3 Scatterplot displaying the values of the ventricular space volume, expressed as normalized data (ventricular space volume/intracranial volume), and T2 signal alteration volume (T2 signal alteration volume/intracranial volume) for 24 patients with vascular dementia ($P < 0.01$; Spearman's rank correlation)

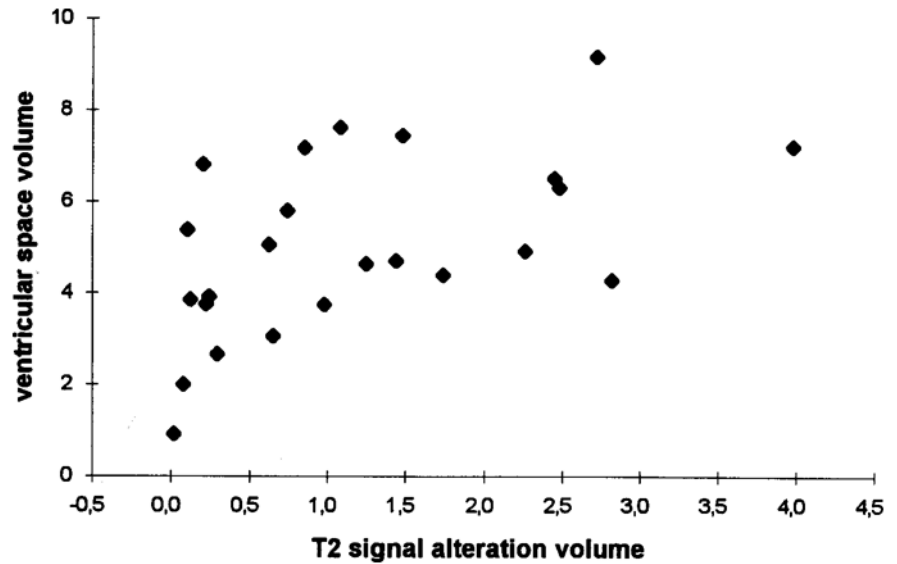


Table 2 Neuropsychological test scores [mean (SD)] in patients with VD and normal subjects (RAVLT Rey auditory-verbal learning test, COWA controlled oral word association)

	VD patients (n = 24)	Normal subjects (n = 24)	P value (Student's t-test)
RAVLT: short-term memory	2.7 (1.3)	4.0 (1.5)	$P < 0.001$
RAVLT: long-term memory	2.4 (2.4)	9.5 (2.9)	$P < 0.0001$
Digit Span (WAIS subtest)	7.6 (1.5)	10.5 (2.6)	$P < 0.0001$
COWA	13.4 (8.5)	37.2 (6.8)	$P < 0.0001$
Token	26.6 (3.8)	32.8 (2.9)	$P < 0.0001$
Street	4.2 (2)	7.0 (2.5)	$P < 0.001$
Complex Figure (Copy)	12.9 (10.1)	32.0 (2.0)	$P < 0.0001$
Complex Figure (Recall)	3.4 (3.6)	12.6 (7.5)	$P < 0.0001$
Block Design (WAIS subtest)	11.7 (8.5)	28.2 (1.8)	$P < 0.0001$
Benton Visual Retention "C"	4.4 (2.8)	9.0 (1.0)	$P < 0.0001$

tion of cerebral tissue volume. No correlation was found between age and the supratentorial cerebral contents in VD patients.

The total volume of the T2 signal alterations on MRI was higher in VD patients than in normal subjects [mean (SD) 1.2 (1.09) vs 0.23 (0.29)] ($P < 0.0001$). In VD patients, this volume was proportional to the increase in the volume of the ventricular space ($P < 0.01$; Spearman's rank correlation) (Fig. 3). This correlation did not change when the values were adjusted for age. No correlation was found between the volume of the T2 signal alterations and the area of the CC.

MMSE score was significantly lower in patients with VD [19.4 (3.5)] than in normal subjects [26.1 (1.5)] ($P < 0.0001$). Table 2 shows neuropsychological test scores in VD patients and normal subjects. In VD patients, the volume of the T2 signal alterations on MRI, of the subarachnoid and ventricular space, and of the cerebral tissue did

Table 3 Normalized volumetric data of the supratentorial contents and corpus callosum/brain ratio in VD patients with mild and severe global cognitive dysfunction. Values are mean (SD). Subarachnoid space subarachnoid space volume/intracranial volume; ventricular space ventricular space volume/intracranial volume; cerebral tissue cerebral tissue volume/intracranial volume; corpus callosum corpus callosum area/supratentorial brain area at the same level; T2 signal alteration T2 signal alteration volume/intracranial volume

	Mild global cognitive dysfunction (n = 14)	Severe global cognitive dysfunction (n = 10)	P value (Stu- dent's t-test)
Subarachnoid space (ratio)	12.3 (1.9)	12 (2.1)	NS
Ventricular space (ratio)	5.2 (1.8)	4.8 (2.2)	NS
Cerebral tissue (ratio)	81.3 (2.4)	81.9 (3.4)	NS
Corpus Callosum (ratio)	0.08 (0.01)	0.08 (0.01)	NS
T2 signal alteration (ratio)	1.1 (1)	1.3 (1.3)	NS

not show any correlation with the score of any of the neuropsychological tests. No correlation was found between the various MRI volume measures and global cognitive dysfunction, as evaluated by both MMSE and global score. MRI volume measures were similar in patients with mild and severe global cognitive dysfunction (Table 3). Finally, the cognitive performances were not influenced by the reduction in CC area.

Discussion

Our study shows that patients with VD have a cerebral atrophy characterized by a reduction in cerebral tissue and an increase in the volume of the ventricular space. The absence of differences in the volume of the subarachnoid space between VD patients and normal subjects suggests

that this atrophy is localized above all in subcortical areas. With regard to ventricular size, a question that remains to be answered is what factors contribute to the process of cerebral atrophy that causes the enlargement of the lateral ventricles. In patients with multiple infarcts, the accompanying dilatation of the ventricular system is thought to be secondary to the white matter changes [18, 24, 25]. Our results lend support to this hypothesis. We, in fact, found a correlation in our VD patients between the volume of the T2 signal abnormalities and that of the ventricular space.

T2 signal abnormalities on MRI are described as reflecting ischaemic tissue damage [18]. Hyperintense periventricular caps and a smooth halo, however, are of non-ischaemic origin and constitute areas of demyelination associated with subependymal gliosis [14]. Conflicting results have been reported with regard to the effects of WMH on cognitive functions. Some studies have failed to find any correlation between WMH and cognitive performance in non-demented elderly individuals [15, 29] and negative results have also been reported with demented patients [8, 20, 23]. Other studies, however, have found that WMH are related to cognitive deficiencies both with regard to general [6] and specific effects [2, 21]. Boone et al. [7] suggest that a "threshold" of WMH area must be present before cognitive deficits develop in healthy aged individuals. If this observation is true for non-demented subjects, in VD patients we found that the volume of the T2 signal abnormalities is not correlated with the global cognitive dysfunction. A potential problem in our method is the use of the 0.2 T MRI system. It could be argued that WMH might be underestimated. However, our data are in agreement with those of Almkvist et al. [1] who, using quantitative measurements, did not find any correlation between WMH and global cognitive performance in demented patients. However, in contrast to our results, they found that specific regional WMH may determine specific neuropsychological impairment, a result which may be explained if we assume that infarction location is the most critical factor in the development of dementia following stroke. In our study, we included only demented patients

with multiple cerebral infarcts. Therefore, the high number of infarcts in our VD patients might have influenced the results of the specific neuropsychological tests. It could be argued that we did not classify the site of T2 abnormalities on MRI, but our study was designed to evaluate the influence of total volume of the T2 signal abnormalities on global cognitive performance.

Our data show a CC reduction in VD patients compared with normal subjects of the same age. This atrophy is probably a secondary change due to lesions in the cerebral hemispheres. The role of CC in cognition is controversial [22, 37]. A relationship between callosal degeneration and dementia has been reported in patients with multiple sclerosis [3, 19]. However, callosotomy does not produce a clinical state of dementia [16]. In accordance with the latter evidence, we did not find any correlation between CC atrophy and the score of each neuropsychological test or the degree of global cognitive impairment. However, some authors have argued that the CC is important in the development of cerebral asymmetries [12, 32]. In this regard, recent studies have shown a significant association between CC atrophy and impairment of left hemisphere cognitive functions in patients with multiple sclerosis [27, 28]. If this is true also for VD patients, we cannot exclude the possibility that a specific battery of neuropsychological tests, designed to evaluate left hemisphere cognitive functions, might be influenced by CC atrophy.

In conclusion, despite the potential biases related to observer variability, the well-known diagnostic problems related to VD, the MRI system used and the small sample size, our results suggest that ventricular enlargement in VD patients is correlated with the increase in the volume of T2 signal abnormalities, but that the cognitive dysfunctions are not influenced by the volume of these abnormalities. A larger study with a more sophisticated MRI system is required.

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