Abstract We investigated if, in patients with vascular lesions, the variable that best discriminated demented from non-demented patients was the severity of the vascular pathology or the degree of hippocampal atrophy. A total of 39 patients multiple subcortical infarcts, who could be considered as possible vascular dementia with small vessel pathology, with underwent a neuropsychological study and brain magnetic resonance imaging (MRI) DSM IV criteria supported by neuropsychological data were used to distinguish demented from non-demented patients. The MRI study took into account the degree of hippocampal atrophy (hippocampal height and interuncal distance) and the severity of vascular pathology (number of brain infarcts). The distribution of lesions and a factor analysis showed that hippocampal atrophy is a better predictor of dementia than the number of brain infarcts. Multiple subcortical infarcts alone are probably not able to cause clinical dementia but the presence of vascular lesions increases the expression of concomitant Alzheimer’s disease.

Key words Multi-infarct dementia • Alzheimer’s disease • Brain infarcts • Hippocampal atrophy

Introduction

Epidemiological and neuropathological data have recently suggested a critical revision of the concept of vascular dementia (VD) and, in particular, of subcortical ischaemic vascular dementia, which is considered to be the most frequent form of VD [1, 2]. From the epidemiological point of view, it has become increasingly clear that the prevalence of VD is heavily dependent upon the diagnostic criteria used and that, accordingly, a low level of agreement exists among different authors on how to diagnose VD [3–5]. In these studies, the highest prevalence values have been obtained adopting the Hachinski ischemia scale [6] or the DSM-IV [7] diagnostic criteria and the lowest values have been obtained with the NINDS-AIREN [8] diagnostic criteria for VD. In the same studies, the level of agreement (k coefficient) in making a diagnosis of VD has been consistently low (ranging between 25% and 60%), whereas a much higher agreement (80%–90%) has been obtained in making a diagnosis of Alzheimer’s disease (AD).

From the neuropathological point of view, recent studies, conducted with semiquantitative methods, have shown that in the absence of extensive cortical infarcts, vascular lesions alone are insufficient to determine a clear syndrome of dementia [9, 10], although they certainly contribute to increase the clinical expression of a concomitant AD [11]. Therefore, the aim of the present study consisted in evaluating more closely the role of vascular and degenerative lesions in VD. We focused our attention on patients who could be considered to have vascular dementia with small vessel pathology, since they showed clinical and neuroradiological evidence of multiple subcortical infarcts. These patients underwent neuropsychological assessment and magnetic resonance imaging (MRI) of the brain, including the hippocampal formation. The neuropsychological assessment allowed us to distinguish patients who met DSM IV criteria [7] of dementia from those who did not. The MRI study allowed us to evaluate both the severity of cerebrovascular disease and the presence of hippocampal atrophy, considered by many authors to be a neuroradiological marker of AD [12–16]. The prediction of the study was that, if
Patients and methods

Subjects to be included in the study were selected from all the patients with possible vascular dementia with small vessel pathology, consecutively observed during a two-year period (from June 1999 to June 2001) at the Neuropsychology Service of the Catholic University of Rome. Patients were considered to have possible VD if they met the following criteria:

- A history suggesting cerebrovascular disease, e.g. a previous transient ischemic attack (TIA) or strokes and obvious risk factors for cerebrovascular diseases, and a possible cognitive impairment;
- An ischemia score on Hachisaki et al.'s scale [6] higher than 7;
- Two or more small subcortical ischemic lesions observed at standard neuroimaging investigations (MRI or computed tomography of the brain) in the absence of large cortical infarcts.

Patients who met these criteria were included in the study if they had no history of depression, alcoholism, or drug abuse, and no clinical evidence of other major medical illnesses.

These patients underwent a detailed neuropsychological assessment to distinguish demented from non-demented patients, and an MRI investigation to evaluate the severity of the vascular pathology and hippocampal atrophy. A double-blind procedure between neuropsychological and neuroradiological assessments was systematically used. Thirty-nine patients who completed the neuropsychological assessment and the MRI investigation constituted the final study sample. All patients gave their informed consent to the study, which was approved by the Ethical Committee of the Catholic University.

Neuropsychological examination

All patients enrolled in the study underwent the Mini-mental state examination (MMSE) [18] and a detailed neuropsychological battery exploring verbal memory (Rey’s auditory verbal learning test), language (phonological word fluency), visual-spatial memory ('immediate visual memory'), visual-spatial attention (lines cancellation and multiple features targets cancellation tasks), visual-spatial intelligence (Raven’s coloured matrices), ideomotor and constructional praxis (copying drawings with and without landmarks). These tests have been described in some detail in recent papers by our group [19, 20]. Here, we describe in some detail our version of Rey’s Auditory Verbal Learning Test [21], since results obtained on this test had a particular weight in distinguishing demented from non-demented patients.

In the Rey’s auditory verbal learning test (RAVLT), a list of 15 high-frequency, semantically unrelated words is read aloud by the examiner five consecutive times, at the rate of one word per second. After each reading, the patient has to recall as many words as possible in free order. The overall number of words correctly reproduced after the five consecutive administrations of the word list constitutes the immediate recall score. Fifteen minutes later, the patient is again requested to recall as many words as possible, without any further reading of the list. The overall number of correct items reproduced after this interval constitutes the delayed recall score. Finally, after 15 more minutes, the patient is requested to recognize the target words among 45 items (15 target words plus 30 distractors). The numbers of right and false recognitions obtained during this stage are used to obtain a delayed recognition score. This score, which measures recognition accuracy, was computed according to the procedure suggested by McNicol [22], and is based on the signal detection theory [23].

Criteria used to distinguish demented from non-demented patients

Patients were considered to be demented if their caregivers reported memory problems and difficulties of recent onset in their professional (or daily living) activities and if, in addition, they obtained:

1. A score (corrected for age and education) lower than 24 at the MMSE [24].
2. Pathological scores in at least 2 (out of 3) memory scores at the RAVLT and in at least one other test of the neuropsychological battery. This criterion was chosen because it corresponds in neuropsychological terms to the DSM-IV diagnostic criterion of considering as demented patients showing a defect of memory and of at least one other cognitive ability.

MRI Acquisition

Patients underwent imaging with a 1.5 T Horizon GE Medical System MR scanner. In all patients, we obtained conventional spin echo T1-weighted (TR/TE 600/15) and turbo spin echo T2-weighted (TR=4000 ms; TE=109 ms) brain images on sagittal, axial and coronal planes, using high-resolution and small thickness (2 mm) slices.

Assessment of severity of vascular pathology and of hippocampal atrophy

Since the main scope of our study consisted in evaluating if the presence of dementia in patients with multiple subcortical infarcts is related more to the severity of vascular pathology or to that of hippocampal atrophy, it was necessary to evaluate both these pathological phenomena with a similar methodology. Since it is difficult to evaluate the degree of vascular pathology with an objective quantitative method analogous to the volumetric study of the hippocampus, we evaluated both the severity of vascular pathology and the degree of hippocampal atrophy using similar semi-quantitative methods. The number of subcortical infarcts was used to measure vascular pathology. Linear measures of hippocampal height and inter-uncal distance were used to score the hippocampal atrophy. In particular, measurements of hippocampal height were obtained in a plane parallel to the brainstem axis plane, where the hippocampal formation (dentate gyrus, hippocampus proper, subiculum and parahippocampal gyrus) is highest. Hippocampal height was normal if ≥14 mm; the reduction in height was mild if <14 mm and marked if <11 mm. Measurements of the inter-uncal distance were obtained in a plane parallel to the bicommissural plane, at the level of the suprasellar cistern. Intercanal distance was mildly increased if >29 and markedly increased if >33

VD results from the number of brain infarcts, then this index should well distinguish patients with and without a clinical form of dementia. If, on the other hand, even in patients with multiple brain infarcts, dementia is mostly due to a concomitant AD, then atrophy of the hippocampus, which is highly susceptible to neurofibrillary degeneration [17], should be the MRI index which best distinguishes demented from non-demented patients with diffuse vascular lesions.