Acta Neuropathol (2002) 103:481–487
DOI 10.1007/s00401-001-0493-5

REGULAR PAPER

**Dina Zekry · Charles Duyckaerts · Robert Moulias
Joël Belmin · Caroline Geoffre · François Herrmann
Jean-Jacques Hauw**

# Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly

Received: 9 June 2001 / Revised, accepted: 29 October 2001 / Published online: 6 February 2002
© Springer-Verlag 2002

**Abstract** The relative importance of vascular and Alzheimer's disease (AD) lesions, their interaction in the development of cognitive impairment and the very existence of mixed dementia induced by the potentiation of both mechanisms remain controversial. The aim of this study was to assess whether the patients with infarcts and lacunes have fewer plaques and tangles than those without vascular lesions, for similar severity of clinical dementia. We performed a prospective clinicopathological study in elderly patients of a long-stay care unit. The severity of clinical dementia was assessed by psychometry performed according to standardized methods less than 6 months before death. A volumetric study of cerebral vascular lesions was performed at post-mortem study of the brain. The density of neuritic plaques (SP), Amyloid β focal deposits (Aβ FD), and neurofibrillary tangles (NFT) in the temporal and frontal isocortex was quantified. According to DSM III criteria, 28 of the 33 patients for whom autopsies were performed had dementia. Twenty-four of the included patients had degenerative or vascular lesions, or both. The volume of infarcts and lacunes was significantly correlated with the severity of cognitive impairment. The density of SP, Aβ FD and NFT in the temporal and frontal isocortex was significantly lower when vascular lesions were present. For similar clinical severity of dementia, there were fewer AD lesions in patients with vascular lesions than in those without vascular lesions.

D. Zekry · C. Duyckaerts · J.-J. Hauw (✉)
Laboratoire de Neuropathologie Raymond Escourolle,
Hôpital de la Salpêtrière, INSERM U 106 and 360,
Association Claude Bernard, Pierre et Marie Curie University,
47 Bd de l'Hôpital, 75013 Paris, France
Tel.: +33-1-42161880, Fax: +33-1-44239828

R. Moulias · C. Geoffre
Hôpital Charles Foix, Ivry-sur-Seine, France

J. Belmin
Hôpital René Muret, Sevran, France

F. Herrmann
Hôpitaux Universitaires de Genève, Thônex, Switzerland

**Keywords** Alzheimer's disease · Multiple infarct dementia · Mixed dementia · Neuropathology · Morphometry

## Introduction

Despite the considerable degree of accuracy in diagnosing Alzheimer's disease (AD), the distinction between isolated AD, multiple infarct dementia and mixed dementia, when the patient suffers from both diseases simultaneously, remains controversial and has been one of the most difficult diagnostic challenges [5, 22] since the first description of mixed dementia by Delay and Brion [12]. This is not simply an academic problem, as the prognosis and treatment of these disorders are different [10].

The highly variable frequency of diagnosis of mixed dementia on neuropathological examination is evident from the diversity of the prevalence values reported in post-mortem studies (from 2% to 38%). This cannot be due only to recruitment biases or geographic factors, and is probably at least partly related to differences in diagnostic criteria. According to some authors, mixed dementia should be diagnosed only if there are sufficient vascular and degenerative lesions to make each diagnosis independently [2, 4, 16, 21, 23, 27, 37, 38]. Others suggest that the diagnosis of mixed dementia requires only a diagnosis of AD in addition to ischemic lesions [26]. Still others believe that there is an interaction between the two types of lesion, with degenerative and vascular lesions each insufficient to account for dementia alone, but able to account for dementia when associated [11, 28, 36]. Thus, the relative contributions of degenerative and vascular lesions to the development of the various types of dementia are difficult to evaluate. Degenerative or vascular lesions may be incidental, contributory, or the primary cause of dementia. This has been dealt with differently in the various diagnostic criteria. The CERAD [27] does not take mixed dementia into account, and the presence or absence of other pathological lesions likely to cause dementia does not interfere with the diagnosis of definite, possi-

ble or probable AD. In the ADDTC criteria [8], a second systemic or brain disorder in addition to AD must be shown to be causally related to dementia for mixed dementia to be recognized. For the NINDS-AIREN criteria [34], the term AD with cerebrovascular disease is reserved for patients fulfilling the clinical criteria for possible AD who also have clinical or brain-imaging signs of relevant cerebrovascular disease, and the term "mixed dementia" should be avoided. There is even doubt as to whether mixed dementia actually exists as a clinical entity, and some authors have recently recommended the reevaluation and more detailed redefinition of this term [9, 33].

We carried out a prospective cliniconeuropathological study among elderly patients institutionalized in a long-stay care unit to assess the relationship between AD pathology and large vascular lesions in the mechanism of clinical dementia.

## Material and methods

### Clinical assessment

A prospective study was carried out 13 years ago, in a long-stay care unit at Charles Foix Hospital, Ivry-sur-Seine, near Paris. A consecutive series of patients over 75 years old cared for at this unit between January and August 1989 were studied. Exclusion criteria were disorders interfering with psychometric assessment (deafness, blindness and psychiatric disorders). The patients included were intellectually normal or affected by cognitive impairment of various causes. The patients' histories were recorded and physical examinations were performed by a geriatrician, who noted the results on a standardized form. The patients were followed up over 2 years.

Patients were classified as intellectually normal or demented according to DSM III criteria [1]. To assess the severity of clinical dementia, the following tests and scales were applied every 6 months: the mini mental state examination (MMSE) [18], a test of visual memory (Benton) [3], the vocabulary test from the Wechsler adult intelligence scale (WAIS) [40], a cognitive battery evaluation (BEC 96) [35], the global deterioration scale (GDS) [32], the rating scale for primary depressive illness [20], and Kuntzmann's dependence scale [24]. The education level was measured according to the Poitrenaud scale [31]. The data analyzed were those collected closest to the time of death. However, if the last psychometric assessment was carried out more than 6 months before death, the patient was excluded from the study. We analyzed the correlation between psychometry results (MMSE, Benton, WAIS, BEC 96) and neuropathological data. As the correlation coefficients were very similar for all the psychometric tests, and for the sake of simplicity, only the results for correlation with the MMSE are presented here.

### Post-mortem neuropathological study

Autopsies were performed when possible, according to French legislation. We carried out a macroscopic and microscopic study of the cerebral hemispheres, brain stem and cerebellum, to identify lesions that might be related to cognitive impairment. Brains were fixed in 10% formalin for at least 2 months. Both hemispheres were cut coronally after section of the midbrain at the geniculate bodies. If vascular lesions were detected on macroscopic examination of the brain, they were studied by microscopy, and the contralateral hemisphere was systematically sampled. If no vascular lesion was detected on macroscopic examination, the left or right hemisphere was chosen at random and studied by microscopy.

### Macroscopic morphometry

Colored marks were made on the external surface of the hemisphere to facilitate the precise recognition of the different lobes on the coronal sections. Sections (1 cm thick) of the whole hemisphere were photographed. A volumetric study (absolute volume expressed in $cm^3$) of cerebral structures and all large vascular lesions identified was performed by planimetry using a semiautomatic image analyzer and point counting method [41]. The picture of the brain section (always taken with a ruler) was examined on a video screen. An array of regularly spaced points (20 mm for all measurements, except for lacunes =1 mm) was applied to the screen and rotated to a random angle. The number of points falling on the evaluated area, multiplied by the area surrounding each point and a scaling factor depending on the magnification of the picture, allowed the calculation of the surface of the studied structure.

We also quantified the severity of atherosclerosis of the basal arteries on a scale of 0 (absent) to 3+ (occlusion of at least one basal artery).

### Microscopic morphometry

In all cases, sections from the hippocampus at the level of the geniculate bodies, the parahippocampus gyrus, the superior temporal gyrus (Brodmann's [7] area 22), the middle frontal gyrus (Brodmann's area 9), the white matter of the frontal portion of the centrum semi-ovale and the substantia nigra were examined. Samples were stained with hematoxylin and eosin (H&E), Congo red and Bodian silver combined with Luxol fast blue (Bodian), and if required, other specific stains for molecules such as ubiquitin, to identify possible causes of dementia. Immunohistochemistry was systematically performed using a mouse anti-β-amyloid protein (Aβ) monoclonal antibody (Dako) and a rabbit anti-human tau protein antibody (Dako).

Senile plaques of the neuritic type (SP) and neurofibrillary tangles (NFT) detected by tau immunohistochemistry, and Aβ diffuse and focal deposits (Aβ FD) detected by Aβ immunohistochemistry, were counted in ten adjacent columns of contiguous fields (160 μm×240 μm=0.384 $mm^2$, magnification ×400). The numbers of these lesions were assessed in the temporal and frontal isocortex from the pial surface to the white matter, perpendicularly to the respective gyrus axis. Mean lesion densities per $mm^2$ were calculated. The diagnosis of AD was made according to CERAD criteria and the severity of AD was assessed by the Braak staging procedure [6] (stages 1 and 2 = entorhinal; stages 3 and 4 = limbic; and stages 5 and 6 = neocortical).

The following neuropathological features were assessed semiquantitatively: (1) small vessels hyalinosis; (2) microinfarcts (i.e., those not grossly visible); and (3) cribriform changes (dilation of perivascular spaces) in the white matter of the centrum semi-ovale on H&E-stained sections; (4) amyloid angiopathy in the white matter of the centrum semi-ovale on sections stained with Aβ immunohistochemistry; and (5) hippocampal sclerosis [13] on sections stained by H&E and Bodian. Severity of hyalinosis, cribriform changes and amyloid angiopathy was evaluated on a scale of 0 (absent) to 2+ (severe). The hippocampal population of pyramidal cells was assessed on a three point scale: 0, within normal limits; +, mild depopulation; and 2+, marked depopulation.

The same physician carried out all clinical evaluations, the same neuropsychologist performed all neuropsychological assessments, and the same neuropathologist made all neuropathological examinations, each blinded to the findings of the others.

### Statistics

The Mann-Whitney U test was used to compare the distribution of quantitative measurements between cases with and without vascular lesions. Relationships between cognitive impairment (MMSE) and morphometric results were evaluated by calculating Spearman's rank correlation coefficient. Continuous variables were ex-

pressed as medians and means ± SD. Differences were considered to be significant if $P \leq 0.05$. Statistical analyses were performed using Statview 4.0 software for Macintosh.

## Results

We initially included 101 patients in this study. We were able to conduct the neuropathological study for 33 of these patients, all of whom had undergone psychometric assessment less than 6 months before death (mean 88±44 days). According to DSM III criteria, 28 of the 33 patients had dementia and 5 did not. For the 28 patients with dementia, neuropathological examination revealed 15 cases of AD (CERAD criteria), with the following Braak's stages: 1 case of entorhinal stage, 6 cases of limbic stage and 8 cases of neocortical stage. Other disorders (1 case of Parkinson's disease, 1 case of dementia with Lewy bodies, and 2 cases of frontal lobe degeneration lacking distinctive histology) were excluded from the analysis. We found vascular lesions (infarcts and lacunes) on neuropathological examination in 18 of the 24 brains. Lacunes alone were not found in any of the demented patients. Thus, our analysis was based on 24 demented patients with degenerative, vascular lesions, or both. These 24 patients comprised 19 women and 5 men (sex ratio women/men=3.8), aged from 79 to 101 years (mean age 87±6 years). There were no significant differences in age, mean education level and severity of clinical dementia between patients with and without vascular lesions. Among the 5 non-demented cases, only one had moderate atherosclerosis, 2 had lacunes, 1 had moderate cribriform changes and 1 had moderate hyalinosis. None had amyloid angiopathy.

Details concerning demented cases, including macroscopic and microscopic morphometry of brain lesions, are presented in Table 1.

### Macroscopic morphometry

There was a significant correlation between the volume of vascular lesions and the severity of cognitive impairment ($P$=0.015, $r^2$=24.1%). Atherosclerosis affecting the large arteries at the base of the brain was notable in 8 cases. No arterial occlusion was observed. Four of the 11 cases in which large infarcts were observed had severe cerebral atheromatous disease.

**Table 1** Summary of macroscopic and microscopic morphometry of brain lesions in demented cases. The absolute volume of vascular lesions was expressed in $cm^3$. Densities of AD lesions were expressed per $mm^2$ in the superior temporal gyrus (Brodmann's area 22).Severity of atherosclerosis of the basal arteries was evaluated on a scale from *0* (absent) to *3+* (occlusion of at least one basal artery). Severity of hyalinosis, amyloid angiopathy and cribriform changes was evaluated on a scale of *0* (absent) to ++ (severe). The hippocampal population of pyramidal cells was assessed on a three point scale: *0,* within normal limits; +, mild depopulation; and ++, marked depopulation (*MMS* Mini mental state examination, *Aβ FD* Aβ focal deposits, *NFT* neurofibrillary tangles, *SP* neuritic plaques, *AT* atherosclerosis, *HY* hyalinosis, *AA* amyloid angiopathy, *HpScl* hippocampal sclerosis, *CC* cribriform changes)

| Case no. | MMS | Vascular lesions | Aβ FD | NFT | SP | AT | HY | AA | HpScl | CC |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 14 | 80.0 | 0 | 0 | 0 | 0 | ++ | 0 | ++ | ++ |
| 2 | 6 | 0 | 13.5 | 44.8 | 33.8 | 0 | + | ++ | ++ | ++ |
| 3 | 5 | 10.0 | 5.5 | 7.4 | 4.8 | + | + | + | ++ | ++ |
| 4 | 17 | 3.3 | 4 | 13.0 | 7.0 | 0 | + | 0 | 0 | 0 |
| 5 | 19 | 107.5 | 7.3 | 5.0 | 8.9 | 0 | + | 0 | 0 | + |
| 6 | 10 | 0 | 11.7 | 59.2 | 29.1 | 0 | + | ++ | + | 0 |
| 7 | 3 | 37.0 | 1.1 | 31.0 | 6.4 | 0 | ++ | 0 | 0 | ++ |
| 8 | 10 | 53.2 | 0 | 0.5 | 0.2 | ++ | ++ | 0 | + | ++ |
| 9 | 8 | 124.0 | 7.8 | 45.0 | 8.5 | 0 | + | ++ | + | ++ |
| 10 | 18 | 224.0 | 0.3 | 0 | 0 | ++ | 0 | 0 | 0 | + |
| 11 | 9 | 15.0 | 3.0 | 1.2 | 2.7 | 0 | + | 0 | 0 | + |
| 12 | 0 | 82.0 | 1.9 | 0 | 1.0 | 0 | + | + | 0 | + |
| 13 | 8 | 0 | 21.9 | 50.5 | 13.1 | 0 | ++ | ++ | ++ | + |
| 14 | 13 | 0 | 2.2 | 34.5 | 23.4 | 0 | + | ++ | ++ | 0 |
| 15 | 8 | 52.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ++ |
| 16 | 3 | 41.4 | 8.5 | 14.0 | 12.5 | ++ | ++ | + | 0 | + |
| 17 | 17 | 169.0 | 5.2 | 33.1 | 7.1 | ++ | + | 0 | 0 | + |
| 18 | 19 | 166.0 | 0 | 0 | 0 | 0 | + | 0 | 0 | ++ |
| 19 | 5 | 0 | 8.9 | 33.6 | 25.1 | ++ | ++ | ++ | ++ | 0 |
| 20 | 9 | 12.0 | 5.8 | 4.0 | 4.0 | 0 | + | + | ++ | + |
| 21 | 5 | 9.0 | 9.2 | 36.9 | 18.9 | 0 | + | ++ | + | 0 |
| 22 | 9 | 196.0 | 0 | 0 | 0 | ++ | + | ++ | + | + |
| 23 | 5 | 0 | 14.8 | 16.8 | 13.9 | ++ | 0 | ++ | + | 0 |
| 24 | 23 | 94.0 | 0 | 0 | 0 | 0 | + | 0 | 0 | ++ |

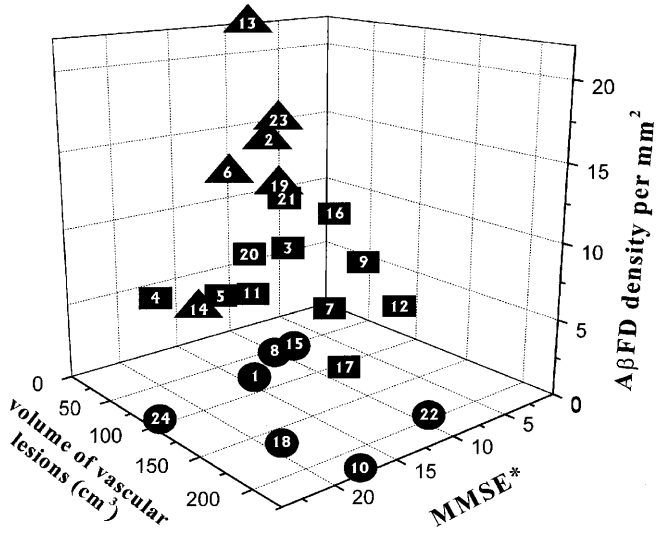


**Fig. 1** Three-dimensional scatter plot of AD lesion densities: Aβ focal deposits (*Aβ FD*) as a function of vascular lesions and MMSE score for the superior temporal gyrus. *Each number* identifies a case. Three groups were identified: (i) *filled triangles* demented patients with AD lesions alone: points were distributed in a triangular plane crossing the volume-of-vascular-lesions axis at zero (case nos. 2, 6, 13, 14, 19 and 23), (ii) *filled circles* demented patients with vascular lesions but no AD lesions: threshold of 52 $cm^3$ of cerebral tissue loss, AD lesions axis coordinate at zero (case nos. 1, 8, 10, 15, 18, 22 and 24), and (iii) *filled squares* demented patients with both AD and vascular lesions: widely scattered across the AD lesions and volume-of-vascular-lesions axes (case nos. 3, 4, 5, 7, 9, 11, 12, 16, 17, 20 and 21) (*MMSE* Mini mental state examination)

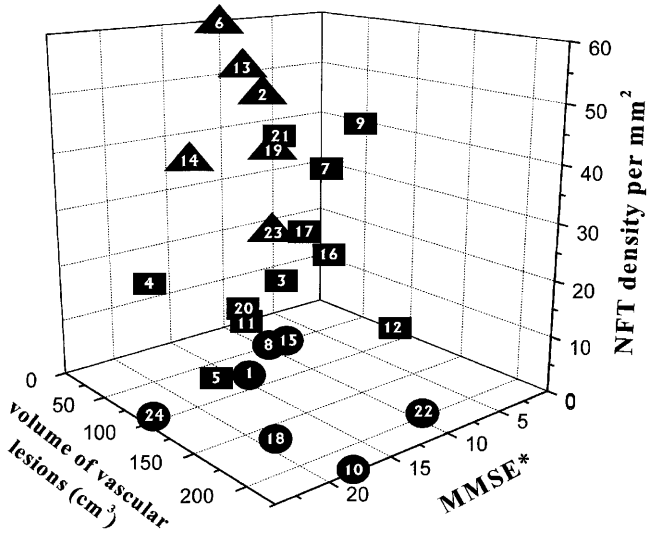


**Fig. 2** Three-dimensional scatter plot of AD-lesion densities: neurofibrillary tangles (*NFT*). Aβ focal deposits (*Aβ FD*) as a function of vascular lesions and MMSE score for the superior temporal gyrus. *Each number* identifies a case. Three groups were identified: (i) *filled triangles* demented patients with AD lesions alone: points were distributed in a triangular plane crossing the volume-of-vascular-lesions axis at zero (case nos. 2, 6, 13, 14, 19 and 23), (ii) *filled circles* demented patients with vascular lesions but no AD lesions: threshold of 52 $cm^3$ of cerebral tissue loss, AD lesions axis coordinate at zero (case nos. 1, 8, 10, 15, 18, 22 and 24), and (iii) *filled squares* demented patients with both AD and vascular lesions: widely scattered across the AD lesions and volume-of-vascular-lesions axes (case nos. 3, 4, 5, 7, 9, 11, 12, 16, 17, 20 and 21) (*MMSE* Mini mental state examination)

## Microscopic morphometry

### *Senile changes of the Alzheimer type*

The densities of Aβ FD, NFT and SP in the temporal and frontal isocortex were not correlated with the severity of cognitive impairment.

Figures 1, 2, and 3 are three-dimensional scatter plots of the number of AD lesions (Aβ FD, NFT and SP) in the superior temporal gyrus and of the volume of vascular lesions according to the severity of dementia assessed with the MMSE for each patient. Similar graphs were obtained for the middle frontal gyrus. We identified three populations: (1) demented patients with only AD lesions gave points distributed in a triangular plane crossing the volume-of-vascular-lesions axis at zero, (2) demented patients with only vascular lesions gave points arranged in a plane, in every case higher than 52 $cm^3$ on the volume-of-vascular-lesions axis, with a coordinate on the AD lesions axis of zero, and (3) demented patients with both AD and vascular lesions gave points widely scattered on the AD lesions and volume-of-vascular-lesions axes.

The density for each category of AD lesions for the two topographies [the superior temporal gyrus (Brodmann's area 22) and the middle frontal gyrus (Brodmann's area 9)] was significantly lower when vascular lesions were present (Table 2).

### *Microvascular disease*

Hyalinosis of small vessels was very common among the brains examined. Moderate to severe hyalinosis was noted in 6/24 cases and mild to moderate in 15/24. Amyloid angiopathy of some degree was found in 13/24 cases (9/24 moderate to severe; 4/24 mild to moderate). Among the 21 cases with hyalinosis, amyloid angiopathy was found in 11 cases. In these cases, there was no significant correlation either between the severity of cognitive impairment and the small vessel hyalinosis ($P$=0.5) or between the severity of hyalinosis and that of amyloid angiopathy ($P$=0.3) On the contrary, there was a significant correlation between the severity of cognitive impairment and that of the amyloid angiopathy ($P$=0.001).

### *Hippocampal sclerosis*

The depopulation of hippocampal pyramidal cells was also very frequent in this cohort (marked in 7/24 case; severe in 6/24 cases). There was no significant correlation between the hippocampal sclerosis and the severity of cognitive impairment ($P$=0.5).

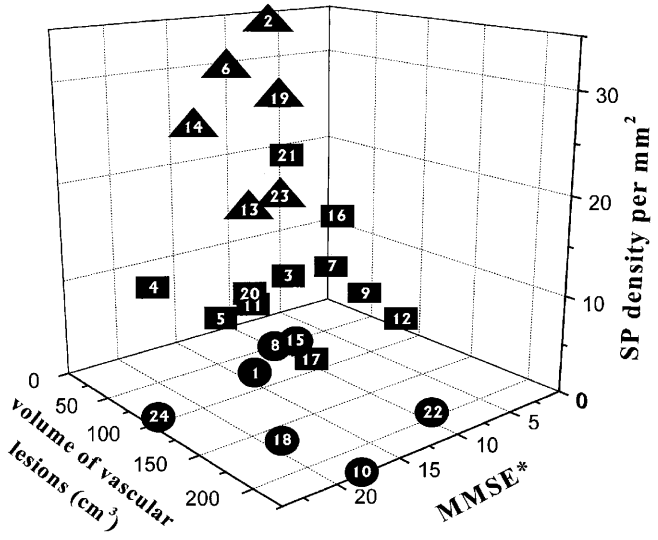


**Fig. 3** Three-dimensional scatter plot of AD-lesion densities: neuritic plaques (SP). Aβ focal deposits (*Aβ FD*) as a function of vascular lesions and MMSE score for the superior temporal gyrus. *Each number* identifies a case. Three groups were identified: (i) *filled triangles* demented patients with AD lesions alone: points were distributed in a triangular plane crossing the volume-of-vascular-lesions axis at zero (case nos. 2, 6, 13, 14, 19 and 23), (ii) *filled circles* demented patients with vascular lesions but no AD lesions: threshold of 52 $cm^3$ of cerebral tissue loss, AD lesions axis coordinate at zero (case nos. 1, 8, 10, 15, 18, 22 and 24), and (iii) *filled squares* demented patients with both AD and vascular lesions: widely scattered across the AD lesions and volume-of-vascular-lesions axes (case nos. 3, 4, 5, 7, 9, 11, 12, 16, 17, 20 and 21) (*MMSE* Mini mental state examination)

**Table 2** Median and mean densities of AD lesions per $mm^2$ in two cortical areas in the two groups of patients (with and without vascular lesions) with a similar average degree of severity of clinical dementia. The densities of AD lesions in the superior temporal gyrus and in the middle frontal cortex, expressed as median (mean ±SD), were significantly different in AD with and without associated vascular lesions (*ST* superior temporal gyrus, *MF* middle frontal gyrus)

| | Vascular lesions | | |
|---|---|---|---|
| | Present | Absent | *P* |
| Aβ FD (ST) | 2.2 (3.3±3.4) | 12.6 (12.2±6.5) | 0.0030 |
| NFT (ST) | 2.6 (10.6±15.1) | 39.7 (39.9±14.9) | 0.0030 |
| SP (ST) | 3.3 (4.6±5.3) | 24.2 (23.1±8.2) | 0.0005 |
| Aβ FD (MF) | 0.8 (1.5±1.9) | 11.0 (10.4±4.3) | 0.0005 |
| NFT (MF) | 3.3 (4.6±5.3) | 19.9 (19.7±6.2) | 0.0010 |
| SP (MF) | 0.8 (2.5±4.3) | 14.2 (16.7±7.9) | 0.0010 |

### *Microinfarcts*

We did not find any microscopic infarcts in the white matter of the centrum semi-ovale. All patients who manifested large infarcts had at least mild to moderate cribriform changes. There was no significant correlation between the cribriform changes and the severity of cognitive impairment ($P$=0.7).

## Discussion

This series of elderly institutionalized patients (mean age 87 years) is probably not representative of the general population due to recruitment bias. The prevalence of dementia (85%) was very high. The Canadian Study of Health and Aging reported a prevalence of dementia of 56.1% in subjects over 85 years of age [14] and a Swedish study reported a prevalence of dementia of 55% in institutionalized patients aged over 74 years [19].

The present demented patient groups, with and without vascular lesions, were similar in age, mean education level and severity of cognitive impairment. This homogeneity of the two groups allowed further comparisons. In this series, the volume of damaged tissue was correlated with the severity of cognitive impairment. Tomlinson et al. [38] compared a group of 50 demented patients with 28 controls with no intellectual impairment. They suggested a threshold of 100 ml as the minimum volume of brain tissue destruction likely to cause dementia, independently of the location of the lesion. Few measurements of the volume of infarcts on neuropathological examination have subsequently been reported. Erkinjuntti et al. [15] described 26 demented patients, and reported a mean loss of cerebral tissue of 39 ml (range 1–229 ml). They concluded that the extent of destruction was correlated with the degree of cognitive impairment. Del Ser et al. [11] compared 28 demented patients with 12 normal controls and found that the volume of tissue loss was more than 3.32% of total brain volume in the demented subjects. Lesion volume was greater than 100 ml in only three patients. Tomlinson et al. [38] stressed, however, that there was no direct relationship between the volume of tissue destroyed and cognitive impairment. Two individuals in their control group presented infarcts larger than 50 ml (91 ml in one case), whereas the infarcts found in three patients with purely multiple infarct dementia were smaller than 100 ml. They concluded that the threshold depends on the site of the lesions in the brain and proposed the concept of strategic sites. These strategic sites included the hippocampus (limbic area) and corpus callosum. Del Ser et al. [11] described lesions involving predominantly the frontal and occipital cortex and the basal ganglia.

In the present series, patients with the same degree of severity of clinical cognitive impairment had fewer Aβ FD, NFT and SP in the temporal and frontal isocortex when large vascular lesions were present (Table 1). These findings are consistent with the data of Nagy et al. [29], who measured the density of microscopic lesions in pathological processes associated with AD (frontal lobe dementia, Huntington's disease, Pick's disease, progressive supranuclear palsy, glioma, vascular dementia, Parkinson's disease and vascular disease). They found that, for any given level of cognitive deficit, the densities of either all plaques, or of neuritic plaques alone in the neocortex was significantly lower in cases of AD concomitant with other central nervous system pathology than in AD with

no other central nervous system pathology. For vascular lesions associated with AD, Nagy et al. [29] distinguished three groups: cases in which the pathologist thought that the vascular lesions would have no effect (15), cases in which these lesions were thought to make a minor contribution (1), and cases in which they were thought to make a major contribution (5) to the cognitive deficit of the patients. In patients in whom the vascular lesions were thought to make a major contribution, the cerebrovascular disease consisted of multiple infarcts and/or status cribriformis accompanied by rarefaction of the surrounding tissue and gliosis or myelin pallor. The densities of plaques and tangles were significantly lower in the neocortex of these patients than in that of the patients pooled from the other two groups. In terms of plaque and tangle densities, the difference between subjects with AD lesions alone and those who had minimal or mild vascular disease was not significant, but there was a trend toward lower densities in patients with minimal vascular damage.

In the present cohort of demented cases, we did not find microinfarcts, and we quantified the severity of small vessel lesions and hippocampal sclerosis. We did not find significant correlations between the severity of dementia and that of these lesions, which were present in a large number of cases. This allowed considering only infarcts and lacunes on one hand, and AD lesions on the other hand to study their relationships. Our quantitative data confirm information provided by the Nun study [36], the Oxford project to investigate memory and aging (OPTIMA) [17], the longitudinal study of ischemic-vascular dementia of California [39], and the Medical research council cognitive function and aging study (MRC CFAS) [30]. The Nun study [36] showed that among 61 participants meeting the neuropathological criteria for AD, those with brain infarcts had poorer cognitive function and a higher prevalence of dementia than those without infarcts. In the OPTIMA [17] cohort, Esiri et al. presented evidence that cerebrovascular disease significantly worsened cognitive performance in the earliest stages of AD, but had no significant effect on cognitive deficit in advanced stages. Vinters et al. [39] showed that subcortical lacunes are seldom responsible for dementia, and suggested that a semiquantitative analysis of vascular lesions might be of interest in evaluating cerebral vascular disease. More recently, the MRC CFAS [30], in a prospective study, reported that Alzheimer-type and vascular pathology were the major pathological correlates of cognitive decline on the first 209 individuals who have come to necropsy, as expected, but most patients had mixed disease. There were no clear thresholds of these features that predicted dementia status. Lee et al. [25], in a retrospective study, proposed that concomitant small cerebral infarcts with a total volume of less than 10 $cm^3$ do not significantly influence the overall rate of global cognitive decline in patients with AD. In the present study, similar levels of dementia severity were exhibited by AD patients who had no vascular lesions and AD patients who had associated vascular lesions, but fewer plaques and NFT. This provides support for the validity of the mixed dementia concept and suggests that the pathological processes involved in AD and multiple infarct dementia are synergistic and cumulative.

**Acknowledgements** We would like to thank Dr. V. Sazdovitch for assistance with the neuropathological work, Mrs. C. Zunz's team for technical assistance and Mr. C. Nzé for the preparation of photographs. Dina Zekry received a grant from Association France Alzheimer and from CAPES – Brasilia/Brazil. This work was supported by grant BV194036 of Projet Hospitalier de Recherche Clinique.

## References

1. American Psychiatric Association (1980) Diagnostic and statistical manual of mental disorders, 3rd edn. American Psychiatric Association Washington
2. Barclay L, Zemcov A, Blass JP (1985) Survival in Alzheimer's disease and vascular dementia. Neurology 35:834–840
3. Benton AL (1960) Manuel pour l'application du test de rétention visuelle. Centre de Psychologie appliquée, Paris
4. Boller F, Lopez OL, Moossy J (1989) Diagnosis of dementia: clinicopathologic correlations. Neurology 39:76–79
5. Bowler J, Hachinski VC (1998) Vascular dementia. In: Ginsberg MD, Bogousslavsky J (eds) Cerebrovascular disease: pathophysiology, diagnosis and management, vol 2. Blackwell Science, Massachusetts, pp 1126–1144
6. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239–259
7. Brodmann K (1909) Vergleichende Lokalisationlehre der Grosshirnrinde in ihren Prinzipen dargestellt auf Grund des Zellenbaues. J A Barth, Leipzig
8. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R (1992) Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 42:473–480
9. Cohen CI, Araujo L, Guerrier R, Henry KA (1997) "Mixed dementia": adequate or antiquated? A critical review. Am J Geriatr Psychiatry 5:279–283
10. Cummings JL, Benson DF (1989) Dementia: a clinical approach. Butterworth-Heinemann, Boston
11. Del Ser T, Bermejo F, Portera A, Arredondo JM, Bouras C, Constantinidis J (1990) Vascular dementia: a clinicopathological study. J Neurol Sci 96:1–17
12. Delay J, Brion S (1962) Les démences tardives. Masson, Paris
13. Dickson DW, Davies P, Bevona C, Van Hoeven KH, Factor SM, Grober E, Aronson MK, Crystal HA (1994) Hippocampal sclerosis: a common pathological feature of dementia in very old (≥80 years of age) humans. Acta Neuropathol 88:212–221
14. Ebly EM, Parhad IM, Hogan DB, Fung TS (1994) Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. Neurology 44:1593–1600
15. Erkinjuntti T, Haltia M, Palo J, Sulkava R, Paetau A (1988) Accuracy of the clinical diagnosis of vascular dementia: a prospective clinical and post-mortem neuropathological study. J Neurol Neurosurg Psychiatry 51:1037–1044
16. Erkinjuntti T (1988) Differential diagnosis between Alzheimer's disease and vascular dementia – evaluation of common clinical methods. Acta Neurol Scand 76:433–442
17. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD (1999) Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. Lancet 364:919–920
18. Folstein MF, Folstein SE, MacHugh PR (1975) Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Pychiatr Res 12:189–198
19. Fratiglioni L, Forsell Y, Torres HA, Winblad B (1994) Severity of dementia and institutionalization in the elderly: prevalence data from an urban area in Sweden. Neuroepidemiology 13:79–88

20. Hamilton M (1967) Development of the rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296
21. Jellinger K, Danielczyk W, Fischer P, Gabriel E (1990) Clinicopathological analysis of dementia disorders in the elderly. J Neurol Sci 95:239–258
22. Kaye JA (1998) Diagnostic challenges in dementia. Neurology 51 [Suppl]:S45–S52
23. Kokmen E, Offord KP, Okasaki H (1987) A clinical and autopsy study of dementia in Olmsted Country, Minnesota, 1980–1981. Neurology 37:426–430
24. Kuntzmann F, Ebel M, Strubel D, Berthel M (1983) La dépendance des personnes âgées: validation et intérêt d'une méthode d'évaluation applicable à l'étude des populations institutionnalisées. Méd Hyg 41:1894–1898
25. Lee J-H, Olichney JM, Hansen LA, Hofstetter CR, Thal L (2000) Small concomitant vascular lesions do not influence rates of cognitive decline in patients with Alzheimer's disease. Arch Neurol 57:1474–1479
26. Mendez MF, Mastri AR, Sung JH, Frey WH (1992) Clinically diagnosed Alzheimer disease: neuropathologic findings in 650 cases. Alzheimer Dis Assoc Disord 6:35–43
27. Mirra SS, A Heyman, D McKeel, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, Belle G van, Berg L, and participating CERAD neuropathologists (1991) The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 41:479–486
28. Mölsä PK, Paljärvi L, Rinne JO, Rinne UK, Säkö E (1985) Validity of clinical diagnosis in dementia: a prospective clinicopathological study. J Neurol Neurosurg Psychiatry 48:1085–1090
29. Nagy Z, Esiri MM, Jobst KA, Morris JH, King EM-F, McDonald B, Joachim C, Litchfield S, Barnetson L, Smith AD (1997) The effects of additional pathology on the cognitive deficit in Alzheimer disease. J Neuropathol Exp Neurol 56:165–170
30. Neuropathology group of the medical research council cognitive function and aged study (MRC CFAS) (2001) Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 357:169–175
31. Poitrenaud J, Aman D (1978) La batterie D. 48 – vocabulaire. (Réflexions à propos de valeurs obtenues chez des adultes ou jeunes adultes appartenant à des niveaux culturels moyens ou inférieurs). Rev Psychol Appl 28:261–275
32. Reisberg B, Ferris SH, De Leon MJ, Crook KT (1988) Global Deterioration Scale. Psychopharmacol Bull 24:661–663
33. Rockwood K (1997) Lessons from mixed dementia. Int Psychogeriatr 9:245–249
34. Roman GC, Tatemichi TK, Erkinjuntti T, et al (1993) Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 43:250–260
35. Signoret JL, Bonvarlet M, Benoit N, Bolgert F, Eustache F, Leger JM (1988) Batterie d'estimation des états démentiels; description et validation. In: Leys D, Petit H (eds) La Maladie d'Alzheimer et ses limites. Masson, Paris, pp 265–270
36. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Marksbery WR (1997) Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 277: 813–817
37. Todorov AB, Go RCP, Constantinidis J, Elston RC (1975) Specificity of the clinical diagnosis of dementia. J Neurol Sci 26:81–98
38. Tomlinson BE, Blessed G, Roth M (1970) Observations on the brains of demented old people. J Neurol Sci 11:205–242
39. Vinters HV, Ellis WG, Zarow C, Zaias BW, Jagust WJ, Mack WJ, Chui HC (2000) Neuropathologic substrates of ischemic vascular dementia. J Neuropathol Exp Neurol 59:931–945
40. Wechsler D (1970) Manual for the Wechsler adult intelligence scale. The psychological corporation, New York
41. Weibel ER (1980) Stereological methods: practical methods for biological morphometry. Academic Press, New York