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Identification of Alzheimer and vascular lesion thresholds for mixed dementia

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To explore the pathological substrates of mixed dementia, we performed a detailed analysis of lacunar and microvascular pathology in 156 autopsied, elderly individuals with various degrees of Alzheimer's disease (AD) pathology. Cognitive status was assessed prospectively using the Clinical Dementia Rating (CDR) scale; neuropathological evaluation included Braak neurofibrillary tangle (NFT) and Aß-protein deposition staging and bilateral semi-quantitative assessment of microvascular ischaemic pathology and lacunes; statistics included univariate and multiple regression models controlling for age, and receiver-operating characteristic analysis. Sensitivity analysis was performed in a randomized derivation sub-sample and tested in a validation sub-sample. White matter lacunes, periventricular and diffuse white matter demyelination and focal and diffuse cortical gliosis were not associated with cognition. Braak NFT, Aß deposition, cortical microinfarcts (CMI) and thalamic and basal ganglia lacunes (TBGL) predicted 27% of CDR variability and 49% of the presence of dementia. Braak NFT, CMI and TBGL thresholds determined in a derivation sample yielded 0.88 sensitivity, 0.79 specificity and 0.85 correct classification rate for dementia in a validation sample. The same thresholds distinguished three groups of demented cases consistent with mixed dementia, pure vascular dementia and AD. These findings indicate that the clinical expression of the vascular component in mixed cases is highly dependent on lesion type and location as well as severity of concomitant AD-related pathology. Proposed thresholds for vascular and degenerative lesions predict the presence of dementia with great accuracy and provide a basis for distinguishing pure vascular dementia or AD from mixed cases.

Keywords: Alzheimer's disease; cognition; lacunar infarction; subcortical dementia; vascular dementia

Abbreviations: NFT = neurofibrillary tangles; CMI = cortical microinfarcts; CAA = cerebral amyloid angiopathy

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Introduction

Brain ageing is characterized by the progressive development of both AD-related lesions and vascular pathology within the cerebral cortex of cognitively intact individuals. Clinically, these neuropathological changes remain silent in the vast majority of elderly people. Since Tomlinson's first observations (Tomlinson *et al.*, 1968), several neuropathological studies have confirmed that neurofibrillary tangles (NFT) and amyloid deposits may be present in restricted regions of the cerebral cortex in the absence of cognitive decline [for review see (Price and Morris, 1999; Knopman *et al.*, 2003)]. Classical neuropathological studies in the past two decades have also pointed to the cardinal role of massive NFT formation within adjacent components of the medial and inferior aspects of the temporal cortex in clinically overt AD [for review see (Giannakopoulos *et al.*, 2007)]. Contrasting with the Braak's hierarchical scheme of NFT development which makes it possible to predict at least partly the transition between normal ageing and dementia (Braak and Braak, 1991; Gold *et al.*, 2000; Giannakopoulos *et al.*, 2003), relating structural changes to cognitive findings has proven quite difficult with regard to vascular lesions (Pantoni *et al.*, 2006; Jellinger and Attems, 2007). Although early studies have acknowledged the negative impact of large macrovascular lesions on

Table 1 Demographic data and CDR scores in the entire sample and both sub-samples

	Derivation		Validation		All	
CDR	Number of cases (F/M)	Mean age, years ± SD	Number of cases (F/M)	Mean age, years ± SD	Number of cases (F/M)	Mean age, years ± SD
0	9 (8/1)	80.2 ± 9.7	11 (5/6)	78.6 ± 9.8	20 (13/7)	79.4 ± 9.5
0.5	14 (6/8)	81.0 ± 9.6	17 (10/7)	87.4 ± 6.6	31 (16/15)	84.5 ± 8.6
1	7 (4/3)	84.9 ± 5.2	7 (3/4)	87.6 ± 6.0	14 (7/7)	86.2 ± 5.5
2	19 (11/8)	87.8 ± 6.8	18 (9/9)	89.0 ± 6.8	37 (20/17)	88.4 ± 6.7
3	29 (23/6)	88.8 ± 6.4	25 (14/11)	89.3 ± 6.3	54 (37/17)	89.0 ± 6.3
All cases	78 (52/26)	85.8 ± 8.1	78 (41/37)	87.1 ±7.7	156 (93/63)	86.5 ± 7.9

cognition (Tomlinson *et al*., 1970; Hachinski *et al*., 1974), cognitive impairment of vascular origin is to date thought to be mostly related to the frequent presence of lacunes and other microvascular pathology such as cortical microinfarcts (CMI) and white matter lesions (WML) in the brains of elderly individuals (Vinters *et al*., 2000; Roman *et al*., 2002; Kalaria *et al*., 2004; Jellinger, 2006). However, since these lesions may frequently occur in cognitively intact individuals, the interpretation of their clinical significance is fraught with difficulty (Ylikoski *et al*., 1995; Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study, 2001; Roman *et al*., 2002; Vermeer *et al*., 2003; van der Flier *et al*., 2005).

The concept of mixed dementia covers a wide spectrum of combinations between AD and vascular pathology including at one extreme, cases with minimal AD-related pathology and substantial small macrovascular and microvascular changes and at the other cases with severe AD pathological changes and only slight vascular involvement. Mixed dementia was initially diagnosed in the presence of both AD pathology and large infarcts (Jellinger, 2005), yet the importance of lacunes and small vessel disease for the development of clinically overt dementia in individuals who also presented with AD lesions is also well documented (Snowdon *et al*., 1997; Esiri *et al*., 1999). Despite considerable efforts, to date there are no widely accepted neuropathological criteria for this condition. Two main reasons may explain this lack. First, the marked heterogeneity of the type and location of microvascular lesions renders difficult the development of a simple and reliable approach to assess them in routine neuropathological settings. Second, the definition of threshold values for AD and microvascular lesions that may predict dementia needs the analysis of large autopsy series. We had the opportunity to investigate a series of 156 prospectively documented cases with various degrees of AD pathology, lacunes and different types of microvascular pathology (i.e. CMI, diffuse and focal gliosis, periventricular and deep white matter demyelination). Using systematic semi-quantitative assessment of various types of vascular lesions and multivariate models that control for the possible confounding effect of age, we report here the identification of threshold values for AD and microvascular pathology that permits a highly accurate diagnosis of mixed dementia.

Patients and Methods

Patients

The initial autopsy series included 1355 patients who were autopsied at the Geriatric and Psychiatric Hospitals of the University of Geneva during the period 1993–2003. Three criteria were used to define the final sample. First, a cognitive assessment including the Clinical Dementia Rating (CDR) Scale had to be performed at most three months prior to death. The CDR is a validated scale that is widely used for the clinical staging of dementia.(Hughes *et al*., 1982) It assigns cognitive function to five levels defined as no dementia (CDR 0), questionable dementia (CDR 0.5), mild dementia (CDR 1), moderate dementia (CDR 2) and severe dementia (CDR 3). The rating is based on both intellectual functions and abilities to perform activities of daily living. It includes six subscores (memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care). An algorithm is applied to the subscores to yield the total score (Morris, 1993). Second, cases with other central nervous system disorders (i.e. tumours, inflammation, Parkinson's disease, Lewy body disease) were excluded from the present study. Third, all cases with macroscopic infarcts or non-AD-related pathology such as Lewy bodies, Pick bodies, α-synuclein and ubiquitin-positive inclusions as well as argyrophilic grains in the routine neuropathological examination were also excluded from the present series. The final sample included 156 patients aged 73 to 101 years. Gender and age distribution of the cases according to CDR score are listed in Table 1. All CDR 0 and 0.5 patients, 10 CDR1 and 25 CDR2 cases were admitted to the Geneva Geriatric Hospital for acute medical conditions such as bronchopneumonia (40%), cardiovascular (46%) and gastrointestinal disorders (14%). The remaining demented cases were admitted to the Psychiatric Hospital because of the presence of major behavioural disturbances such as psychomotor agitation, feeding difficulties, marked aggressiveness and delusional thoughts. There was no case with past history of psychiatric illnesses such as schizophrenia, major depression and bipolar disorder. The main causes of death were infectious disorders (38.7%), heart failure (37.7%), pulmonary embolism (15%) and cancer (8.6%).

Tissue processing

Brains obtained at autopsy were fixed in 15% formaldehyde for at least 4 weeks and cut into 1-cm-thick coronal slices. Lacunes,

defined as small definitive ischaemic necrosis, ranging from 1 mm to 1.5 cm, located in the white matter or basal ganglia and thalamus, were identified on macroscopic examination and controlled on Luxol–van Gieson (LVG)-stained coronal sections (see later). To visualize CMI as well as focal cortical and white matter gliosis, 1-cm-thick tissue blocks from the anterior hippocampus, inferior temporal cortex (area 20), frontal cortex (area 9), and parietal cortex (area 40) bilaterally were cut into 20 µm-thick serial sections of approximately $3 \times 2\,cm^2$. Every 50 sections, one section was stained with Globus silver impregnation for a total of 10 sections per area which have been subsequently considered for semi-quantitative analysis (Vallet *et al.*, 1992). To assess diffuse white matter and periventricular demyelination, whole coronal sections at the level of anterior commissure were embedded in paraffin, cut into 20 µm-thick sections and stained with LVG. Adjacent sections stained with Bodian silver stain demonstrated the relative preservation of axon integrity in our cases. In order to keep variation in LVG staining to a minimum, all cases were processed by the same highly experienced technical assistant under the same standard conditions. To visualize AD-type lesions, Pick bodies, ubiquitin-positive inclusions of frontotemporal dementia, argyrophilic grains and Lewy bodies, additional blocks from hippocampus, temporal, frontal, parietal and occipital cortex were embedded in paraffin, and 12 µm-thick sections were processed with highly specific and fully characterized antibodies to the phosphorylation-dependent tau AT8 (1/1000, Immunogenetics) (Goedert *et al.*, 1995), core amyloid ß protein A4 4G8 (1/1000, Signet Laboratories) (Bussière *et al.*, 2002), α-synuclein (1/20 000 courtesy of Dr Y. Charnay) and ubiquitin (1/100, Sigma). The tissues were incubated overnight at 4°C. Following incubation, sections were processed by the PAP method using 3,3′-diaminobenzidine as a chromogen (Vallet *et al.*, 1992). As a part of the routine neuropathological analysis, the presence or absence of cerebral amyloid angiopathy (CAA) was assessed on 20 µm-thick Globus silver stained sections in all cases.

Subsequently, all cases were classified neuropathologically according to Braak–NFT staging system (Braak and Braak, 1991). Aß-protein deposition staging was performed according to the amyloid nomenclature proposed by Thal and collaborators (Thal *et al.*, 2000). Lacunes, CMI and focal cortical gliosis were assessed semiquantitatively in 10 sections per area using the following score: 0 (absence of such lesions), 1 (<3 lesions per slide), 2 (3–5 lesions per slide), 3 (>5 lesions per slide). Semi-quantitative assessment of white matter gliosis was made in the same number of sections using the following rating scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Although we cannot exclude that additional pathology may be present mainly in neocortical areas, the use of a high number of sections limits this possibility. For each of these lesions, a total score was obtained by adding the scores of each area. The severity of diffuse white matter and periventricular demyelination in each hemisphere was estimated in LVG-stained sections using the same semi-quantitative scale. Scores for each hemisphere were added to obtain a total score. The same semi-quantitative assessment of lacunes and microvascular pathology has already been used in our previous studies with a high inter-rater reliability (Fig. 1; Kövari *et al.*, 2004; Gold *et al.*, 2005). In the present study, both vascular pathology, Braak NFT, Aß-protein deposition staging (Braak and Braak, 1991; Thal *et al.*, 2000) and CAA were assessed by two independent investigators (EK and CB), blind to the clinical findings, with a high inter-rater reliability (kappa values ranging from 0.88 to 0.95 for the different neuropathological variables). In case of disagreement between the two raters, the final determination was defined in a consensus meeting between both the raters.

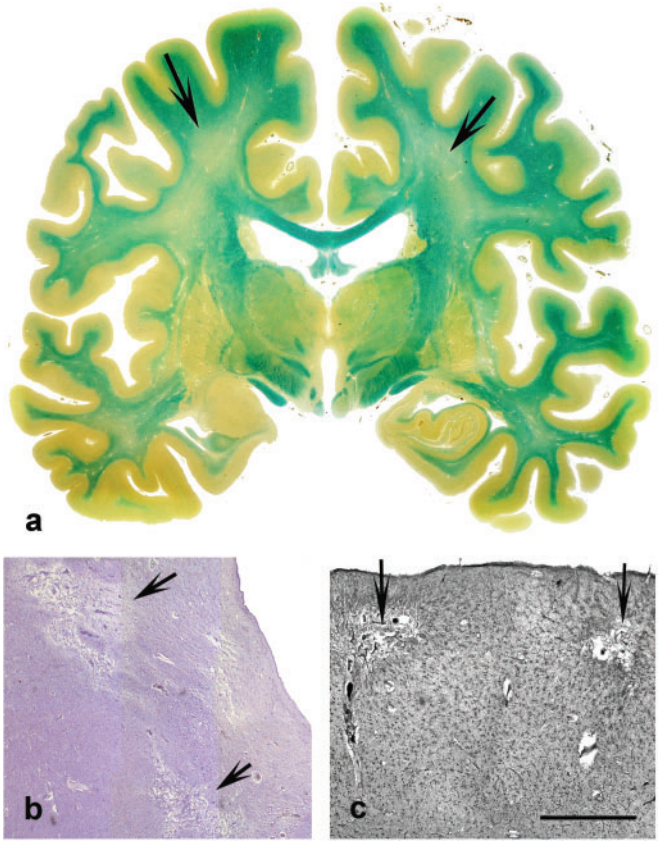

Fig. 1 Representative examples of microvascular lesions assessed in the present study. Macroscopic view of deep white matter demyelination (arrows, a). Histological view of thalamic lacunes (arrows, b). Multiple cortical microinfarcts in frontal cortex (arrows, c). Material was stained with LVG (a), haematoxylin–eosin (b) and Globus silver staining (c). Scale bar: a: 1.5 cm, b and c: 1000 µm.

Statistical analysis

Maximal likelihood ordered logistic regression with proportional odds was used to evaluate the association between CDR scores (the dependent variable) and neuropathological parameters (Braak NFT staging, Aß-protein deposition staging, presence of CAA and lacunes and microvascular pathology scores) in a univariate model. Subsequently, the same method was applied in a multiple model to take into account the effect of age as well as the interaction between the neuropathological variables. In addition, cases were dichotomized as demented (CDR 1 to 3) or non-demented (CDR 0 to 0.5) to build logistic regression models exploring the impact of lacunes and microvascular pathology on the presence of dementia. Braak NFT and Aß staging were entered as dummy variables in all regression models. A predictive model was derived from a randomized derivation sub-sample (50% of the cases, $N = 78$). Sensitivity analysis was performed in

Table 2 Distribution of neuropathological findings in the total sample

Neuropathological findings	*N*	%
Braak NFT I-II	72	46.2
Braak NFT III-IV	55	35.3
Braak NFT V-VI	29	18.6
Aβ I-II	80	51.3
Aβ III-IV	76	48.7
Cortical microinfarcts	65	41.7
Lacunes thalamus	12	7.7
Lacunes basal ganglia	36	23.1
Lacunes white matter	39	25.0
Periventricular demyelination	80	51.3
Diffuse white matter demyelination	121	77.6
Focal gliosis	47	30.1
Subcortical gliosis	47	30.1
Cerebral amyloid angiopathy	10	6.4

this sub-sample and corresponding receiver-operating characteristic (ROC) curves were constructed. The best threshold determined through this analysis of the derivation sub-sample, was then similarly tested in the validation sub-sample (remaining 50% of the cases, $N = 78$). Statistical analyses were performed using the Stata software package, release 9.2 (College Station, TX).

Ethical considerations

The present study has received the formal approval of the Local Ethics Committee of the University of Geneva Hospitals.

Results

Table 2 summarizes the distribution of AD-related pathology, lacunes and microvascular changes in the present series. In univariate analyses, five independent variables were significantly related to CDR scores. These included Braak NFT staging ($P < 0.001$), Aß deposition staging ($P < 0.001$), CMI score ($P < 0.01$) thalamic and basal ganglia lacune score (TBGL; $P < 0.05$) and age ($P < 0.05$). In contrast, presence of CAA, as well as white matter lacunes, periventricular and diffuse white matter demyelination scores as well as focal and diffuse cortical gliosis scores were not significantly related to CDR scores. We then tested a multiple model including all five variables that proved significant in the univariate approach. Four of the variables, Braak NFT staging, Aß deposition staging, CMI and TBGL scores remained significant predictors of cognitive status (Table 3). The concomitant assessment of these neuropathological variables predicted 27% of the CDR variability.

We then evaluated the relationship between the most important clinical outcome (presence or absence of dementia) and neuropathological parameters. In univariate analyses, the same five independent variables, Braak NFT staging, Aß deposition staging, CMI and TBGL scores and age, proved to be significant predictors of the presence of clinical dementia. Importantly, a multiple model which included these five variables revealed that age was no longer a significant predictor and that the four remaining neuropathological scores explained 48.9% of the presence of dementia. In a stepwise approach, the vascular scores (CMI and TBGL) explained 15% of the variability of the outcome variable (presence of dementia), Braak NFT staging 30.4% and Aß deposition staging 3.5%.

Table 3 Multiple analysis of AD and vascular pathology impact on CDR scores in the present series (maximum likelihood ordered logistic regression)

		OR	CI	*P*-value
NFT Braak	I	1.00	–	–
	II	0.81	[0.30, 2.12]	0.672
	III	1.84	[0.63, 5.37]	0.265
	IV	11.82	[3.17, 44.15]	<0.001
	V-VI	32.79	[2.39, 145.04]	<0.001
Aβ staging	1	1.00	–	–
	2	2.13	[0.90, 5.01]	0.085
	3	4.40	[1.79, 10.85]	0.001
	4	4.93	[1.33, 18.30]	0.017
Age		1.03	[0.98, 1.08]	0.221
CMI		1.21	[1.12, 1.31]	<0.001
TBGL		1.82	[1.73, 2.50]	<0.001

OR = odds ratio; CI = confidence interval; CMI = cortical microinfarct score; TBGL = thalamic and basal ganglia lacune score.

ROC curves were constructed using the vascular score (CMI + TBGL) and Braak NFT staging to determine the threshold value with the best combination of sensitivity and specificity. In the derivation sample, this corresponded to cut-off scores of 2 (>2) for both the vascular score and Braak NFT staging. The performance of this model was as follows: sensitivity 0.93, specificity 0.52, positive predictive value 0.82, negative predictive value 0.75 and correct classification rate of 0.81. The area under the ROC curve was 0.90 (Fig. 2A).

The same model was applied in the validation sample yielding an area under the ROC curve of 0.92. Use of the cut-off scores developed in the derivation model led to 0.88 sensitivity, 0.79 specificity, 0.88 positive predictive value, 0.79 negative predictive value and 0.85 correct classification rate (Fig. 2B).

When the above threshold scores were applied to the entire study population, 90% of the demented cases were correctly classified. These could be divided into three distinct groups (Fig. 3). The first includes cases with a vascular score >2 and a Braak NFT score ≤2 in whom dementia is associated with vascular lesions. The second includes cases with a Braak NFT score >2 and a vascular score ≤2 and represents cases in whom dementia is associated with neurofibrillary tangle formation. The third groups consists of neuropathologically mixed cases, with both a Braak NFT score >2 and a vascular score >2, in whom dementia may be related to both vascular and degenerative disease.

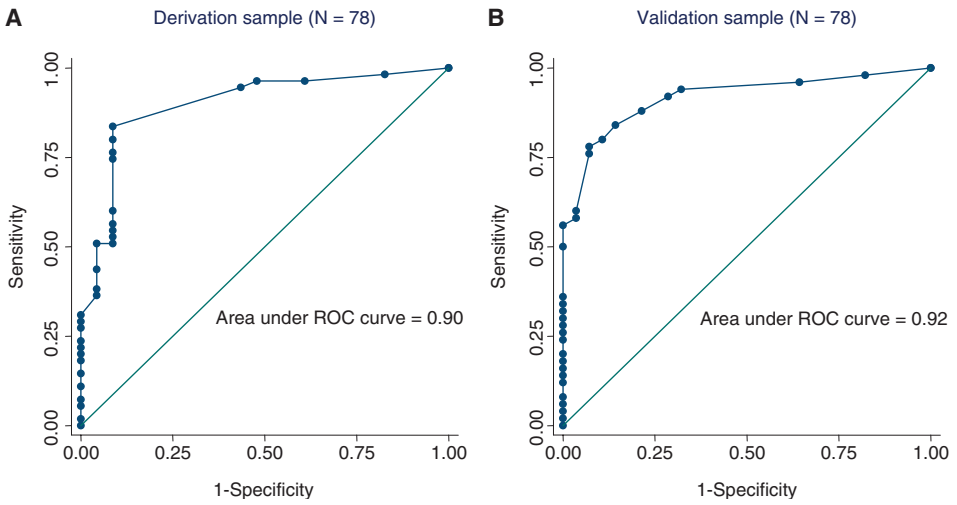

Fig. 2 Receiver-operating characteristic curves in the derivation and validation sub-samples.

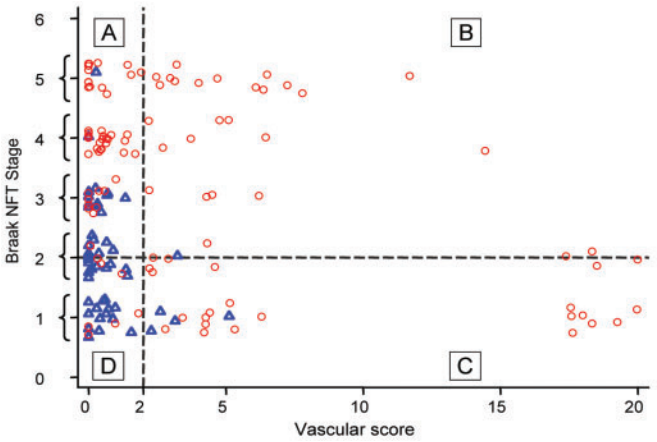

Fig. 3 Scatterplot of demented (red circle) and non-demented (blue triangle) cases according to Braak NFT stage and vascular score. The thresholds determined by sensitivity analysis (dotted lines) delineate four sectors. Demented cases are consistent with pure Alzheimer disease in sector A, pure vascular dementia in sector C and mixed dementia in sector B; most cases in sector D are not demented. In order to avoid superimposition of multiple cases random noise was applied to all points; brackets on the *y*-axis indicate the magnitude of the jitter (all points within the bracketed range correspond to the exact CDR value indicated to the left of the bracket).

Discussion

Completing our previous observations in cases with minimal to moderate NFT pathology [Braak NFT staging <4 (Kövari *et al.*, 2004; Gold *et al.*, 2005; Kövari *et al.*, 2007)], the present data show that the cognitive impact of CMI is still present even when cases with concomitant severe AD pathology were considered. In fact, a one-point increase in the semi-quantitative scale of CMI used in this study was associated with a 1.2-fold increase of the risk for higher CDR scores. Unlike CMI, other forms of microvascular pathology have no cognitive repercussions when the entire spectrum of AD pathology is taken into account. This observation is of particular importance in respect to periventricular and diffuse white matter demyelination, two types of lesions thought to be closely related to mixed dementia at least on the basis of earlier neuroimaging studies (Barber *et al.*, 1999; Garde *et al.*, 2000; de Groot *et al.*, 2000, 2001, 2002). We previously reported that in cases with pure microvascular pathology, periventricular demyelination is a better correlate of dementia than diffuse white matter demyelination (Kövari *et al.*, 2004). Although weaker, the negative influence of this neuropathological parameter was still present in Braak NFT III mixed cases (Kövari *et al.*, 2007) but does not persist in higher Braak NFT stages suggesting that the assessment of periventricular demyelination in mixed dementia should be confined to cases with intermediate stages of NFT pathology. However and as usual in neuropathological studies, both types of demyelination were assessed only at the level of the anterior commissure in the present cohort. We cannot thus formally exclude that the total volume of white matter lesions may be a more robust predictor of cognitive decline in this particular group.

Another significant determinant of cognition in mixed cases is the development of TBGL. The Nun study has first demonstrated that cognitive function was markedly influenced by thalamic, basal ganglia and deep white matter lacunes in individuals with AD neuropathology (Snowdon *et al.*, 1997). More recent studies challenged this point of view showing that many lacunes may have no cognitive repercussions (Jellinger and Attems, 2003; Vermeer *et al.*, 2003). Giving additional support to the recent notion of subcortical vascular dementia (Reed *et al.*, 2001; Erkinjuntti, 2002; Roman *et al.*, 2002), one recent neuropathological study of cases with minimal AD lesions revealed that the assessment of TBGL may predict as much

as 17% of the cognitive variability (Gold *et al.*, 2005). In our series, a one-point increase in the 6-point semiquantitative scale used for the assessment of TBGL corresponded to a 1.8-fold increase in the risk for higher CDR scores, indicating that, in terms of cognition, the disruption of subcortical frontal circuits must be considered in mixed cases.

Given the unusually high number of autopsy cases in the present series, it was possible to define randomly two independent samples: that of derivation where the clinicopathological correlations and thresholds were established and that of validation in order to test the performance of the proposed semi-quantitative neuropathological approach. Based on a simple model that includes only Braak NFT staging and CMI + TBGL scores, we were able to identify correctly the vast majority of demented cases. The areas under the ROC curve reached 90% in the derivation sample and 92% in the validation sample implying that the concomitant consideration of these neuropathological variables is sufficient for a highly accurate discrimination of demented cases. Although significantly associated with cognitive decline, Aß deposits contributed only marginally to this discrimination since their assessment explained only an added 3.5% of the cognitive variability.

In routine neuropathological settings, the identification of a single cut-off value that can separate demented from non-demented cases in mixed conditions is a very challenging issue. We report here sensitivity values of 0.93 in the derivation sample and 0.88 in the validation sample when using a single cut-off point corresponding to Braak NFT II stage or CMI + TBGLs score of 2. The extremely high sensitivity value obtained with the simple semi-quantitative approach applied in the present study is encouraging in the perspective of developing widely accepted neuropathological criteria for mixed dementia. This is further supported by the quite high positive and negative predictive values in both derivation and validation samples that ranged from 0.75 to 0.88. Of course, it should be remembered that these latter values are also related to dementia prevalence.

Based on these observations, one can propose an operational definition of mixed dementia within the spectrum of degenerative and vascular changes occurring in brain ageing. Demented cases with Braak NFT staging >II and CMI + TBGL score >2 may be classified as having mixed dementia. Demented cases with Braak NFT staging ≤II and CMI + TBGL score >2 should be considered pure vascular dementia. Finally, a CMI + TBGL score ≤2 in the presence of substantial NFT pathology (Braak NFT staging >II) characterizes pure AD cases.

Several limitations should be considered when interpreting these data. First, our hospital-based neuropathological sample cannot be considered as fully representative of the whole spectrum of mixed dementia. Second, we excluded cases with macroinfarcts that correspond to a rarer and different type of vascular pathology and can make no conclusion in such cases. Third, although we carefully assessed microvascular changes in several neocortical association areas bilaterally, the obtained results are based on the sampling strategy used and needs further validation in other neuropathological centres. Fourth, the specificity values of the proposed cut-off values (i.e. 0.52 in the derivation sample and 0.79 in the validation sample) are suboptimal. Finally, a small number of patients were demented in the absence of both significant vascular and degenerative pathology (CMI + TBGL score ≤2 and Braak NFT staging ≤II), and the assessment of AD and vascular pathology explained ~50% of the presence of dementia in our series. Methodological biases related to the semi-quantitative approach used may partly account for this (Giannakopoulos *et al.*, 2003). Alternatively, other neuropathological variables such as neuronal and synaptic loss or microvascular morphometry may also contribute to cognitive decline in these cases. In this respect, a recent stereological analysis of capillary morphometric parameters demonstrated that cortical capillary diameters may be a powerful and independent predictor of cognitive impairment in the elderly (Bouras *et al.*, 2006).

In conclusion, the present findings demonstrate that a systematic semi-quantitative assessment of CMI and TBGL coupled with the traditional Braak NFT staging not only makes it possible to predict with a high sensitivity the presence of dementia in cases with various combinations of vascular and degenerative changes but can serve to distinguish mixed dementia from AD and pure vascular dementia. Additional studies in independent prospectively assessed autopsy series are needed to confirm the validity of the proposed approach and define easily applicable and consensual neuropathological procedures to improve its specificity.

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