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Neuropathological analysis of lacunes and microvascular lesions in late-onset depression

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Abstract

Aims—Previous neuropathological studies documented that small vascular and microvascular pathology is associated with cognitive decline. More recently, we showed that thalamic and basal ganglia lacunes are associated with post-stroke depression and may affect emotional regulation. The present study examines whether this is also the case for late-onset depression.

Methods—We performed a detailed analysis of small macrovascular and microvascular pathology in the postmortem brains of 38 patients with late-onset major depression (LOD) and 29 healthy elderly controls. A clinical diagnosis of LOD was established while the subjects were alive using the DSM-IV criteria. Additionally, we retrospectively reviewed all charts for the presence of clinical criteria of vascular depression. Neuropathological evaluation included bilateral semiquantitative assessment of lacunes, deep white matter and periventricular demyelination, cortical microinfarcts and both focal and diffuse gliosis. The association between vascular burden and LOD was investigated using Fisher's exact test and univariate and multivariate logistic regression models.

Results—Neither the existence of lacunes nor the presence of microvascular ischaemic lesions was related to occurrence of LOD. Similarly, there was no relationship between vascular lesion scores and LOD. This was also the case within the subgroup of LOD patients fulfilling the clinical criteria for vascular depression.

Conclusions—Our results challenge the vascular depression hypothesis by showing that neither deep white matter nor periventricular demyelination is associated with LOD. In conjunction with our previous observations in stroke patients, they also imply that the impact of lacunes on mood may be significant solely in the presence of acute brain compromise.

Keywords

brain ischaemia; elderly; mood; neuropathology; vascular depression

Introduction

Clinically significant depressive syndromes can be found in 8% to 16% of community-dwelling, 25 % of primary care, and 23 % of hospitalized older adults [1,2], and are associated not only with functional disability and decline in global health but also with an increase in the use of medical services and in mortality rate [3-6].

Late-onset depression (LOD) is a heterogeneous and broad concept that includes both individuals with early-onset recurrent depression and those who developed a first depressive episode after the age of 60. In contrast with major depression at younger ages, which is thought to have a strong genetic background, subcortical vascular pathology has consistently been pointed as a possible key substrate of LOD [7-12].

The concept of “vascular depression” postulates that the disruption of frontostriatal circuits by vascular lesions predisposes, perpetuates, or exacerbates depressive symptoms in some elderly individuals. These patients display a significant increase in the frequency of cardiovascular risk factors such as hypertension, dyslipidaemia or a history of cerebrovascular disease and predominant dysexecutive syndrome [13]. Krishnan and colleagues reported the substantial development of white matter hyperintensities (WMH) in the deep white matter and subcortical grey matter [14] of patients older than 60 presenting with a first depressive episode after the age of forty and in the absence of psychotic symptoms. Early neuroimaging findings revealed that WMH tend to be more frequent and more severe in LOD patients compared both to elders with early-onset depression [15-18] and age-matched controls [18,19]. However, more recent contributions including the community-based Longitudinal Aging Study Amsterdam [20] challenged the validity of “vascular depression” as a clinically recognized subtype of depression phenotype [21]. In particular, the implication of cardiovascular risk factors in the pathogenesis of LOD remains controversial [22-27], and two recent studies failed to identify WMH burden differences between LOD and elderly controls [28,29]. One main methodological limitation of the concept of “vascular depression” resides in the heterogeneous character of WMH that correspond to several distinct neuropathological changes including arteriosclerosis, perivascular demyelination, dilated perivascular spaces, vascular ectasia, ischaemia, incomplete infarction, partial loss of myelin and axons, gliosis, and infarction with necrosis [30-35].

As recently stated by Smith and Alexopoulos [36], a rigorous neuropathological investigation in clinically well-documented autopsy cases is crucial to shed some light on the role of cerebrovascular lesions in late-life affective disorders. The only currently available clinicopathological analyses were performed by a single research group and led to conflicting conclusions [35,37-39]. Given the marked difficulty to obtain autopsy material from LOD cases, these observations have not been subsequently tested in an independent sample. To address this issue, we had the opportunity to examine in detail the small macrovascular and microvascular pathology in a postmortem series of 38 subjects having suffered from LOD and 29 age- and gender-matched controls.

Methods

Selection of cases

The initial autopsy series included 2,642 patients who were autopsied at the Department of Rehabilitation and Geriatrics and at the Department of Psychiatry of Geneva University Hospitals between 1998 and 2007 (see figure 1).

The final sample was defined in a three-step process. First, exclusion criteria were applied by reviewing the clinical files of autopsied cases. All patients with a clinical diagnosis of dementia were excluded. We also excluded all cases with neurological disorders, as well as those presenting with psychiatric co-morbidities (19 cases with schizophrenia and 3 cases with chronic alcoholism). From the remaining 1,717 cases, 224 had a prospectively documented diagnosis of major depression [40].

Second, on the basis of the routine neuropathological assessment of these 224 cases, we excluded those presenting with macroscopic vascular pathology other than lacunes (brain infarcts, haemorrhage, venous sinus thrombosis), clinically silent but substantial Alzheimer type pathology (Braak neurofibrillary tangle staging >3), other neurodegenerative lesions (Pick bodies, ubiquitin-positive inclusions of frontotemporal dementia, argyrophilic grains and Lewy bodies), as well as traumatic brain lesions, tumours and inflammation. An intermediate series of 167 cases was considered for the last step of the inclusion process.

Third, subjects with a first depressive episode before age 65, minor, subsyndromal or subthreshold [40] depression or without DSM-IV diagnosis established by a certified psychiatrist were also excluded. The final sample of LOD cases included 38 patients aged 65 to 89 (16 men, mean age: 79 years; and 22 women, mean age: 80 years).

Twenty-nine age- and gender-matched control subjects (without history of depression) were selected from the initial autopsy series of the Department of Rehabilitation and Geriatrics (1,715 subjects). They also satisfied the exclusion criteria applied in the two first steps of the inclusion process for depressed cases (15 men aged 68 to 95, mean age 80 years old; and 14 women aged 66 to 95, mean age: 79 years old).

Clinical assessment

A fully trained senior resident established the clinical diagnosis while the subjects were alive, according to DSM-IV criteria for major depression. His assessment was confirmed by the independent evaluation of the senior attending. This diagnosis was confirmed in all of the cases by a Geriatric Depression Scale score higher than 5 [41]. Similarly, the clinical diagnosis of dementia was assessed according to the DSM-IV criteria and confirmed by a Clinical Dementia Rating score > 0.5 [42]. Cardiovascular risk factors (hypertension, diabetes and smoking) in LOD patients and controls were identified by retrospective chart review in all cases. In order to identify the presence of vascular depression we applied retrospectively the set of criteria proposed by Alexopoulos et al. [13]. This clinical definition requires an onset of depression after 65 years of age and clinical and/or laboratory evidence of vascular disease or vascular risk factors.

Our final sample included 38 cases with LOD autopsied cases and 29 age- and gender-matched controls. All procedures involving the use of postmortem human brain were conducted with the written consent of the next of kin and were approved by the relevant ethics committee of the University Hospitals of Geneva.

Neuropathological assessment

Brains obtained at autopsy were fixed in 15 % formaldehyde for at least 4 weeks, cut into 1-cm-thick coronal slices and examined for macroscopic vascular lesions including brain infarcts, cerebral haemorrhage and lacunes (table 1). The latter were defined as small definitive areas of ischaemic necrosis, ranging from 1 to 15 mm, located in the white matter, basal ganglia or thalamus (Fig. 2a). They were identified on macroscopic examination and confirmed on Luxol-van Gieson (LVG) stained coronal sections. Histologically, lacunes (Fig. 2b) were recognized as irregular cavities containing parenchymal fragments and lipid- or haemosiderin-laden macrophages [43]. To assess deep white matter and periventricular

demyelination, whole coronal sections at the level of the anterior commissure were embedded in paraffin, cut into 20- μ m-thick sections and stained with LVG (Fig. 2c). Cortical microinfarcts were defined as small areas of ischaemic necrosis in the cerebral cortex seen only on histological examination (Fig. 2d). In order to visualize cortical microinfarcts, focal cortical and diffuse white matter gliosis (Figs 2e, f), 1cm-thick tissue blocks from the anterior hippocampus, inferior temporal cortex (area 20), prefrontal cortex (area 9), parietal cortex (area 40) and anterior cingulate cortex (area 24) bilaterally were cut into 20- μ m-thick serial sections of approximately 3 \times 2cm (Fig. 2a). Every 50 sections, one section was stained with Globus silver impregnation for a total of ten sections per area which were subsequently considered for semiquantitative analysis [44].

To assess the severity of Alzheimer type pathology and exclude other degenerative lesions such as 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- μ m-thick sections were processed with highly specific and fully characterized antibodies to the phosphorylation-dependent tau AT8 (1:1,000, Innogenetics) [45], to the amino acid residues 17-24 of the human amyloid β protein (Clone 4G8, 1:1000, Signet Laboratories) [46], alpha-synuclein (1:20,000 courtesy of Dr Y. Charnay) and ubiquitin (1:100, Sigma) as previously described [44]. The assessment of NFT and A β pathology was made according to the Braak and Braak [47] and Thal A β phase [48] staging systems. In routine neuropathological evaluation, the exclusion of argyrophilic grains and alpha-synuclein pathology was based on the procedure described by the DLB Consortium [49] and that of Pick bodies and ubiquitin pathology on the criteria of the Consortium for FLD [50].

The mean lacune severity in thalamus, basal ganglia and white matter was assessed semiquantitatively 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). The same score was applied in ten sections per area studied for cortical microinfarcts and focal cortical gliosis. Semiquantitative assessment of diffuse white matter gliosis was made in the same number of sections using the following rating scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. For these three microvascular lesions, an individual total score was obtained by adding the scores of each area. Subsequently, the scores of cortical microinfarcts, focal cortical and diffuse white matter gliosis for each hemisphere were added to obtain a total microvascular score for each case. The severity of deep white matter and periventricular demyelination in each hemisphere was estimated in Luxol-van Gieson stained sections using the following rating scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Scores for each hemisphere were added to obtain a total score for each type of demyelination. This semi-quantitative assessment of lacunes and microvascular pathology has already been used in our previous studies with a high inter-rater reliability [51,52].

Statistics

Univariate analysis was performed to identify independent risk factors associated with the outcome (LOD), using Student's *t* tests or Fisher exact test as appropriate. Demographic variables assessed as possible predictors of LOD were age, gender and main CVRF (hypertension, diabetes, and smoking). The relationship between survival time after the first episode of depression, number of depressive recurrences and vascular scores were assessed by Spearman's rho correlation coefficient. All variables were coded as dichotomous except survival time after the first episode of depression, number of depressive episodes and age. For univariate regression analyses, Odds Ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the relationship between vascular scores and the clinical outcome. Multiple logistic regression models were built to explore the association between possible predictors and the presence of LOD and vascular depression. Only the predictors

closer to significance in univariate analysis were used in this part of the statistical analysis. In order to limit statistical errors due to multiple comparisons, only P values < 0.01 were considered as statistically significant. Statistical analyses were performed with Stata software version 11.

Results

The demographic and clinical characteristics in our series are summarized in table 2. Among the 38 patients with LOD, 71 % survived at least one year after the first depressive episode and the average survival time was 3.3 years (Standard deviation, SD = 3.9). The average age at onset of depression was 75.8 years (SD = 7.6) and the average duration of the first depressive episode was one year (SD = 1.7). One third of the LOD patients had at least one recurrence of major depression and the average number of recurrences was 1 (SD = 0.8). Among the LOD patients, 14 were untreated (refusal of pharmacological treatment in the context of severe episodes of major depression but no suicidal thoughts) and 24 were treated with serotonin reuptake inhibitors or tricyclic antidepressants. No control cases received psychotropic medication. Within the 38 LOD cases, 25 (66%) fulfilled Alexopoulos et al. criteria for vascular depression [13]. There were no statistically significant differences in the frequency of hypertension ($p=0.07$), diabetes ($p = 0.34$) and smoking ($p = 0.69$) between the two diagnostic groups.

The frequency of all of the lesions studied did not differ between LOD and control groups (table 3). In LOD patients, the average length of survival after the first LOD episode and the number of subsequent depressive recurrences were not associated with the vascular scores (Spearman's rho coefficients ranging from 0.15 to 0.02, p ranging from 0.11 to 0.74).

In the present study, two independent investigators (EK and MS), blind to the clinical findings, assessed the severity of vascular pathology with a high inter-rater reliability (kappa values ranging from 0.88 to 0.95 for the severity score of the different neuropathological variables). In case of disagreement, the final determination was defined in a consensus meeting between the two raters.

The lacune scores (thalamic, basal ganglia, and white matter lesions) were not associated with the LOD diagnosis. Although controls displayed higher frequencies of deep white matter and periventricular demyelination compared to LOD cases, this difference did not reach the statistical significance threshold. No significant differences in focal gliosis, diffuse white matter gliosis or cortical microinfarcts' scores were found between LOD patients and controls (table 3). This was also the case within the LOD subgroups fulfilling or not previously described clinical criteria for vascular depression (OR ranging from 0.23 to 6.67, p values between 0.092 and 0.899). In multivariate models including all variables close to statistical significance in univariate models (hypertension, deep white matter and periventricular demyelination, table 4), no association was found between vascular lesion burden and LOD (OR/CI: 0.36/0.11-1.12, 0.27/0.08-0.92 and 0.15/0.02-0.98, respectively). This was also the case for the diagnosis of vascular depression (OR/CI: 0.53/0.14-1.75 for hypertension, 0.24/0.06-0.86 for deep white matter demyelination and 0.22/0.03-1.44 for periventricular demyelination).

Discussion

After the publications of O'Brien's group [35,37-39,53], this is the first neuropathological report attempting to validate the concept of vascular depression in the elderly in an independent autopsy series. The present autopsy study is based on a relatively large number of prospectively documented LOD cases, with careful exclusion of both clinical and

neuropathological conditions that could affect the specificity of the LOD sample, a systematic bilateral assessment of lacunes and each type of microvascular lesions, and controls for possible confounders such as survival time after the first episode of depression, number of depressive recurrences, and main CVRFs. Several limitations should, however, be considered. First, autopsy-related biases such as selection of younger, atypical or highly puzzling cases not representative of the whole spectrum of LOD cannot be formally ruled out. However, even the inclusion of such cases that usually display severe brain pathology [54] did not lead to positive clinicopathological correlations in the present series. Second, the temporal relationship between the occurrence of LOD and vascular pathology cannot be established on the basis of post-mortem observations. We thus cannot exclude the possibility that lacune and microvascular lesion formation may have taken place in part during the survival period after the first depressive episode biasing the relationship between vascular lesion scores and LOD onset. The fact that the survival time after first depressive episode and the number of depressive recurrences were not related to neuropathological parameters in LOD cases is, however, reassuring in this regard. Third, even though our previous work on Alzheimer's disease neuropathology demonstrated that the use of stereological principles in lesion quantification might lead to a substantial improvement of clinicopathological correlations [55], in the present study lacunes and microvascular lesions were assessed with a semi-quantitative severity scale. Fourth, the number of cases was not sufficient to determine whether the location of microvascular lesions modulated their effect on mood. In addition, even though dysfunction in several prefrontal areas has consistently been related to depression in both neuroimaging [56-62] and neuropathologic [63-67] studies, we did not assess separately the vascular burden in this frontal lobe subdivision. Finally, the present investigation focuses on small macrovascular and microvascular lesions and did not address possible changes in vascular structure (i.e., capillary integrity or changes in vascular endothelial cells) that may participate in the pathogenesis of LOD and deserve further quantitative analysis.

At a first glance, our results appear to contradict the observations of the O'Brien's group in 20 hospital-based LOD cases [35,37-39,53]. In these studies, radiologically confirmed deep WMHs were more frequent in LOD compared to control cases. However, the neuropathological assessment *per se* led to different conclusions. Amongst deep WMH, only those located in the dorsolateral prefrontal cortex were mainly of ischaemic origin and were associated with increased expression of intercellular cell adhesion molecule and glial fibrillary acidic protein in depressed patients compared to controls [39]. However, LOD was associated neither with small vascular or microvascular lesions [35,37] nor with an increase of vascular cell adhesion molecule [53]. There are two main methodological differences between the present study and these contributions. First, our hospital-based autopsy series included only cases with major depression from two primary care county hospitals whereas the cases analyzed by Thomas and coworkers were from referrals to a secondary care unit. Unlike these studies, we have examined separately each type of microvascular lesions and subcortical lacunes. Moreover, the bilateral assessment of microvascular pathology throughout the brain makes it possible to define semi-quantitative scores that reflect at least partly the global microvascular burden of each case. Our results complete the observations of Thomas et al. [35,37,39] in that they indicate that small macrovascular and microvascular burden is not a major determinant of LOD. One could argue that the paucity of the observed relationships may be due to the heterogeneity of the LOD group in respect of the presence of vascular co-morbidities. However, this is highly unlikely given that similar results were found in the subgroup of LOD patients that satisfied the clinical criteria for vascular depression [13].

The present observations should be interpreted in the light of the current debate regarding the deleterious role of lacunes and cortical microinfarcts in brain aging (for review see [68]).

Our earlier neuropathological work documented that cortical microinfarcts and, to a lesser degree, thalamic and basal ganglia lacunes are independent predictors of cognitive decline [51,52,69]. More recently, we found that the chronic accumulation of lacunar infarcts within the thalamus, basal ganglia and deep white matter was strongly related to the occurrence of post-stroke depression and explained 25% of the variability of this occurrence [70]. Based on these data we proposed that the development of subcortical lacunes may be a common denominator of cognitive and mood disorders in old age. In contrast to our initial expectations, the present data did not confirm this hypothesis in LOD cases, supporting the idea that the chronic accumulation of lacunes may exert a negative impact on mood exclusively in the presence of acute brain compromise. Furthermore, they indicate that both deep white matter and periventricular demyelination are not associated with LOD. Recent prospective studies have proposed a shift of focus towards clinical and psychological determinants of LOD such as global medical burden [22,23,71-73], intensity of treatment for depression [74], social support [75-78], functional disability [79,80], and personal characteristics such as resilience [81] and locus of control [76], comorbid anxiety [82], and psychiatric functional status [22,75]. Future neuropathological studies in large community-based autopsy series including rigorous assessment of vascular lesion volumes in mood regulation-related cortical areas, as well as morphological analyses of microvascular structure are warranted to explore the complex relationships between vascular burden and LOD.

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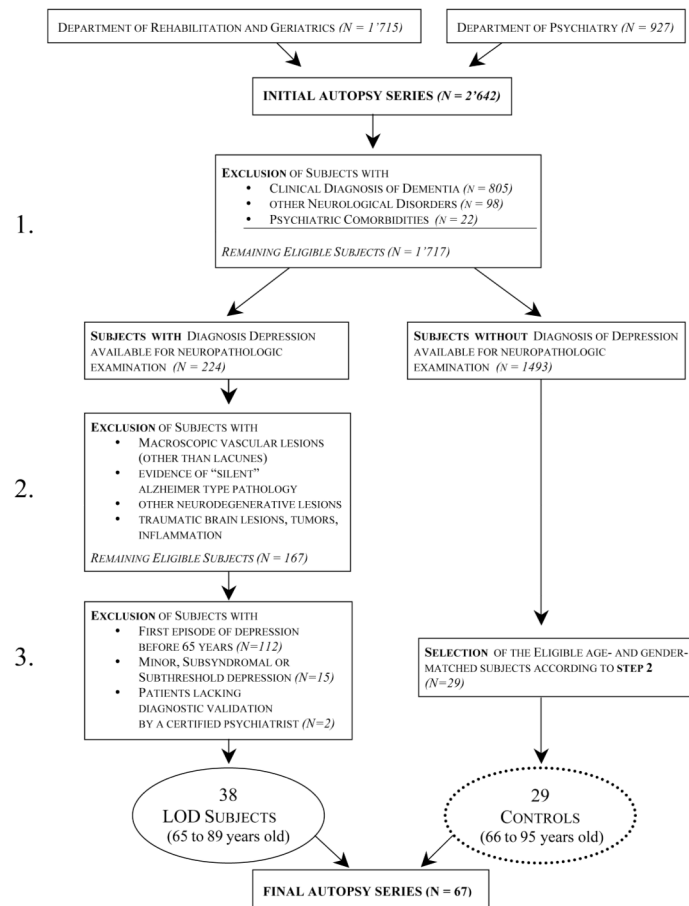


Figure 1.
Study profile and patient selection

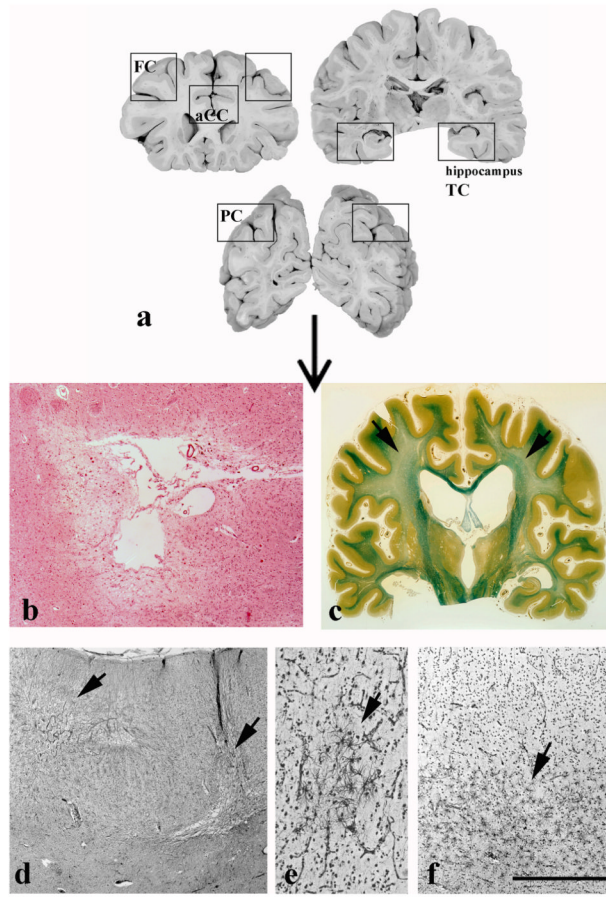


Figure 2.

Schematic representation of the assessed cortical areas (a) and representative examples of basal ganglia lacunes (b), deep white matter demyelination (c, arrow), multiple cortical microinfarcts in the frontal cortex (d, arrows), focal cortical gliosis (e, arrow), and diffuse white matter gliosis (f, arrow). Sections were stained with hematoxylin-eosin (b), Luxol-van Gieson staining (c), and Globus silver impregnation (d-f). Scale bar (on f): 1 mm (b and d), 250 μm (e), and 500 μm (f).

Table 1
Neuropathologic assessment of vascular lesions

Area	Lesions	Methods
Thalamus	Lacunes	Macroscopy Luxol-van Gieson (LVG)
Basal ganglia	Lacunes	Macroscopy LVG
White matter	Lacunes Demyelination Diffuse gliosis	Macroscopy LVG LVG Globus silver impregnation
Gray matter (Hippocampus, temporal, frontal, parietal and anterior cingulate cortex)	Cortical microinfarcts Focal cortical gliosis	Globus silver impregnation

Table 2
Characteristics of LOD patients and controls

	LOD N (%)	Controls N (%)
N	38	29
Age, years (SD)	79 (6.1)	80 (8.6)
Male gender (%)	16 (42)	15 (52)
Braak stage I for NFT [47]	25 (65.8)	13 (44.8)
Braak stage II for NFT [47]	12 (31.6)	15 (51.7)
Braak stage III for NFT [47]	1 (2.6)	1 (3.5)
Phase 1 for SP [48]	17 (44.7)	19 (65.5)
Phase 2 for SP [48]	12 (31.6)	7 (24.1)
Phase 3 for SP [48]	3 (7.9)	3 (10.4)
Phase 4 for SP [48]	6 (15.8)	0 (0)
Hypertension (%)	12 (32)	14 (48)
Diabetes (%)	6 (16)	7 (24)
Smoking (%)	5 (13)	2 (7)

NFT = neurofibrillary tangles; SP = senile plaques.

Table 3
Regional distribution of frequencies of small macrovascular and microvascular lesions in the present series

	<i>Univariate Analysis</i>		
	Late-onset depression	No Depression	Fisher exact p^1
	N = 38 (%)	N = 29 (%)	
Lacunes	53	45	
Thalamus	3	8	0.557
Basal ganglia	32	24	0.579
Deep white matter	18	20	1.000
Demyelination	55	86	
Deep white matter demyelination	50	76	0.065
Periventricular demyelination	5	24	0.050
Cortical microinfarcts	24	45	
Hippocampus	12	21	0.503
Temporal cortex	0	0	--
Frontal cortex	4	5	1.000
Parietal cortex	13	12	1
Anterior cingulate cortex	0	0	--
Focal Gliosis	37	21	
Hippocampus	3	0	1.000
Temporal cortex	4	3	1.000
Frontal cortex	18	16	1.000
Parietal cortex	5	0	0.514
Anterior cingulate cortex	8	4	1.000
Diffuse white matter gliosis	74	79	
Hippocampus	13	12	1.000
Temporal cortex	11	20	0.463
Frontal cortex	34	36	1.000
Parietal cortex	5	16	0.204
Anterior cingulate cortex	11	8	1.000

¹Data from both hemispheres were pooled; see text for details.

Table 4
Relationship between late-onset depression and vascular scores

	<i>Univariate Logistic Regression</i>		
	Crude Odds Ratio		
	OR	95% CI	<i>p</i>¹
Lacunes			
Thalamus	0.31	0.27-3.62	0.351
Basal ganglia	1.46	0.47-4.59	0.516
Deep white matter ^a	0.9	0.25-3.24	0.876
Demyelination			
Deep white matter demyelination	0.32	0.10-0.96	0.043
Periventricular demyelination	0.17	0.32-0.96	0.044
Cortical microinfarcts			
Hippocampus	1.96	0.46-8.22	0.360
Temporal cortex	--	--	--
Frontal cortex	1.33	0.11-15.5	0.818
Parietal cortex	1.11	0.24-5.13	0.893
Anterior cingulate cortex	--	--	--
Focal Gliosis			
Hippocampus	--	--	--
Temporal cortex	0.65	0.39-10.87	0.763
Frontal cortex	1.19	0.31-4.56	0.805
Parietal cortex	--	--	--
Anterior cingulate cortex	2.06	0.20-10.98	0.543
Diffuse white matter gliosis			
Hippocampus	1.11	0.24-5.13	0.893
Temporal cortex	0.47	0.11-1.96	0.300
Frontal cortex	0.92	0.32-2.66	0.884
Parietal cortex	0.29	0.05-1.73	0.175
Anterior cingulate cortex	1.35	0.23-8.01	0.739

¹Data from both hemispheres were pooled; see text for details.