Neuropathological assessment of the lesions of significance in vascular dementia

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Abstract

***Objectives*—To better define the neuropathology of vascular dementia.**

***Methods*—The neuropathological findings in 18 elderly, undemented subjects free of cerebrovascular disease were compared with 19 elderly undemented subjects who had cerebrovascular disease (many of whom had had a "stroke") and 24 elderly demented subjects who had cerebrovascular disease, but no other pathology to account for dementia. Cases in all groups were selected for absence or no more than very mild Alzheimer type pathology.**

***Results*—Microvascular brain damage in the form of severe cribriform change and associated subcortical white matter damage and microinfarction were correlated with a history of dementia. Severe cribriform change was much more common and microinfarction somewhat more common in the demented group with vascular disease than the undemented group with vascular disease (P=0.0006 and P=0.031 respectively). Other findings of note were that congophilic angiopathy had a greater prevalence in the vascular dementia group than the control group, single cerebral infarcts were more common in the group who were undemented with vascular disease than in the group with dementia and vascular disease (P=0.0028), and the last group lacked evidence of macroscopic infarction more often than the first (P=0.034). There was a non-significant trend for the ratio of infarcted:uninfarcted tissue in one cerebral hemisphere to be higher in the group with dementia and vascular disease than in the group with vascular disease but no dementia.**

***Conclusions*—Microvascular disease, not macroscopic infarction, was the chief substrate of vascular dementia in this series of cases.**

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Although Alzheimer's disease, vascular disease, and dementia associated with Lewy bodies are the three most frequent causes of dementia most necropsy surveys of dementia have found that vascular disease is second only to Alzheimer's disease as a cause of dementia and that vascular disease and Alzheimer's disease not uncommonly coexist.[1–7] Vascular disease as a cause of dementia therefore merits close attention. Early studies of the subject emphasised the importance of the volume of cerebral tissue infarcted, with dementia being more common in those patients with cerebral infarction amounting to more than 50 ml than in those with smaller infarcts. However, more recent studies in dementia after stroke[2 8–10] have found most patients, whether demented or not, to have an infarct volume smaller than 50 ml, although there is some recent evidence from either necropsy or neuroimaging studies to suggest that volume, laterality, and location of infarct are determinants of dementia in those with cerebrovascular disease.[8 10–12] Rather more attention has been paid to the importance of small vessel disease of the cerebral white matter and deep grey matter as a cause of dementia; a concept with a long history extending back to Binswanger[13] and well reviewed by Fisher.[14]

We recently carried out a study of the influence of cerebrovascular disease on the clinicopathological correlations that can be made in Alzheimer's disease.[15] Vascular disease of varying severity had an incremental modifying effect on correlations between plaques, tangles, and dementia that were seen in pure Alzheimer's disease. In particular, in cases with vascular disease as well as Alzheimer's disease the amyloid load in the form of all argyrophilic plaques influenced severity of dementia whereas this was not the case in pure Alzheimer's disease, in which tangle density was the main determinant of dementia severity.[16] This suggests that in the presence of vascular disease there may be enhanced sensitivity to the potential dementia promoting effects of plaques. If this is so in cases that meet pathological criteria for Alzheimer's disease, it may also be true of the far more numerous cases of elderly subjects with plaque densities that are insufficient to meet pathological criteria for Alzheimer's disease. However, before attempting to explore further potential interactions between cerebrovascular disease and Alzheimer type pathology in the development of dementia it seemed important to try to define which vascular lesions were of particular significance in producing dementia on their own.

To further explore the relative importance of macroscopic infarcts and pathology associated with microscopic small vessels in the aetiology of dementia we have undertaken a necropsy study of three groups of cases:

(1) Elderly subjects known to have been undemented during life and found to have had neither cerebrovascular disease nor Alzheimer's

Table 1 Selected demographic and pathological features of controls (C), undemented cases with vascular disease (UDV) and cases with vascular dementia (DV)

	C n (%)	*UDV n (%)*	*DV n (%)*
Number	18	19	24
Men (n(%))	10 (55)	12 (63)	9 (38)
Women (n(%))	8 (45)	7 (37)	15 (62)
Age (y (SD))	80 (9)	83 (9)	76 (9)****
Brain WT (g (SD)):			
Men	1307 (149)	1337 (76)	1284 (219)
Women	1184 (78)	1127 (92)	1125 (107)
Fixed cerebral hemisphere wt:			
Men	599 (58)	590 (39)	540 (102)
Women	522 (37)	517 (82)	499 (29)
Circle of Willis atheroma:			
None	7	2	4
Any (score 1-3)	10	17*	20
Severe (score 2/3)	1	7**	8
Internal carotid atheroma:			
Present	6	9	7
Absent	3	7	5
Myocardial pathology:			
Infarction	3 (18)	11 (58)***	8 (40)
Left ventricular hypertrophy	7 (41)	6 (32)	8 (40)
AD pathology:			
No plaques or tangles	7	6	14
A few plaques and/or tangles	11	13	10

*P=0.029; **P=0.042; ***P=0.019 *v* C by Fisher's exact test; ****P=0.0008 *v* UDV by two tailed unpaired student *t* test, no significant difference from C.
AD = Alzheimer's disease.

disease on neuropathological assessment; (2) elderly patients known to have been undemented in life, but who had a history of stroke, or were found to have had cerebrovascular disease on neuropathological assessment; (3) elderly patients known to have been demented in life and who were found to have had only cerebrovascular disease as an explanation for their dementia.

We took particular care to exclude from any of the groups in this study cases that had had any more than minimal Alzheimer's disease type pathology as there is evidence that in stroke subjects without sufficient Alzheimer's disease type pathology to meet current pathological criteria for diagnosis of Alzheimer's disease, the presence of some argyrophilic plaques may contribute to the risk of having dementia.[10] (Ideally, we would have liked to have excluded from our study cases with even minimal Alzheimer's disease type pathology, but that would have reduced the number of cases available for study to unacceptably low numbers.) In this way we hoped to define the vascular pathology most likely to account for dementia, and to distinguish this from "stroke" pathology.

Material and methods

We studied brains collected in this department over a 20 year period from:

(1) 18 elderly subjects who were prospectively assessed and were undemented in life and had no cerebrovascular disease or any more than minimal Alzheimer's disease type pathology (referred to as C; eight women, 10 men); (2) 19 elderly patients who were prospectively assessed and were undemented, but had cerebrovascular disease of varying severity together with minimal or no Alzheimer's disease type pathology (referred to as UDV; seven women, 12 men). Many of these subjects had had clinical "stroke". A few had been clinically neurologically normal, but were found on neuropathological examination to have had mild cerebrovascular disease; (3) 24 elderly subjects with dementia who were found neuropathologically to have had cerebrovascular disease, but minimal or no Alzheimer's disease type pathology or any other pathology likely to have contributed to their clinically demented state (referred to as DV; 15 women, nine men).

Table 1 shows the ages of these cases. One patient had had a clinical diagnosis of mild diabetes mellitus. Hypertension had been clinically diagnosed in one control case, and two DV cases. Atrial fibrillation had been present in one control case, two UDV, and two DV cases. Myocardial infarction had been clinically diagnosed in one control and one DV case. In all cases a close relative of the deceased had given permission for necropsy examination and retention of tissue for research purposes.

The diagnosis of dementia was made on the basis of a clinical assessment of the patient by a geriatrician, neurologist, or psychiatrist, supplemented by the nursing and paramedical staff. In addition, formal assessment was undertaken using the Kew test.[17] In most cases this was performed during the patients' last hospital admission, usually within a month or two of death. In a few DV cases retrospective analysis of hospital notes provided the evidence for deciding that the patient had been demented.

Pathological findings were assessed blind to the disease category for each case. In almost all cases a full postmortem examination was performed and information from the report of this examination was obtained about the state of the heart (weight, presence of valvar abnormalities, presence of myocardial infarction, fibrosis, or hypertrophy) and the internal carotid arteries (this was not available in all cases). The brains were weighed and from some cases one cerebral hemisphere was dissected away and deep frozen for neurochemical studies. In these cases the remaining cerebral hemisphere and brain stem, and in other cases the intact brain, were fixed by suspension in a large volume of neutral 10% formalin for several weeks after which the material was sliced coronally at 1 cm intervals. The extent of atheroma of the circle of Willis was recorded on a semiquantitative 0-3 scale. A score of 1 was given if atheroma was present but no artery was more than 50% occluded, a score of 2 if one vessel was 50% or more occluded, and a score of 3 if more than one vessel was 50% or more occluded. Slices of cerebrum were overlaid by a grid in the form of an acetate sheet marked out with dots at the corners of 1 cm squares. The total number of dots falling over intact or infarcted grey or white matter of one or both cerebral hemispheres was recorded for each case and a ratio of infarcted: intact tissue recorded. Blocks were taken from hippocampus, frontal, parietal, and temporal lobe cortex, and white matter and embedded in paraffin wax and sectioned. Sections of basal ganglia and thalamus were available from those cases with macroscopic abnormalities in these regions. Sections were stained to show myelin (Luxol fast blue stain), nerve fibres (Palmgren stain), cells, amyloid (Congo

red stain) and argyrophilic plaques (Bielschowsky or von Braunmühl stains), and neurofibrillary tangles. Small vessel associated disease was semiquantitatively scored as follows.

0=No widening of perivascular spaces or hyaline thickening of arteriolar walls; no perivascular pallor of myelin staining, loosening of tissue, or attenuation of nerve fibres, or gliosis in white matter, or loss of nerve cells and gliosis in deep grey matter.

1=Widened perivascular spaces, or hyaline thickening of arteriolar walls, or a few perivascular macrophages, but none of the other features mentioned above, occurring in one or more sections of white matter or deep grey matter.

2=Widened perivascular spaces, or hyaline thickening of arteriolar walls plus mild or moderate perivascular pallor of myelin staining, or loosening with attenuation of nerve fibres with gliosis in white matter or loss of nerve cells and gliosis in deep grey matter in one or more sections.

3=Widened perivascular spaces, hyaline thickening of arteriolar walls, severe perivascular and some more widespread pallor of myelin staining and nerve fibre attenuation with gliosis in white matter or loss of nerve cells and gliosis in deep grey matter in more than one section. These findings are equivalent to those of Binswanger's disease.

Microinfarcts in the deep grey matter, white matter, or cortex were scored 0-3 depending on the number of lesions found. Microinfarcts in white matter took the form of microscopic cystic cavities with ragged edges. In grey matter they were either cystic or formed slit-like or triangular shaped gliotic foci, devoid of neurons.

Alzheimer's disease pathology was assessed by the Consortium to establish a Registry for Alzheimer's Disease (CERAD) protocol[18] on von Braunmühl or Bielschowsky stained sections. All cases fell into the 1-1a category (table 1).

Congophilic angiopathy was assessed in leptomeningeal and cortical vessels on a four point scale: 0=absent; 1=trace or occasional vessel affected; 2=one or a few vessels circumferentially affected; 3=widespread involvement of circumferentially affected vessels, 4=as 3, with secondary changes (haemorrhage, occlusion, recanalisation).

Table 2 Macroscopic cerebral infarction in a single cerebral hemisphere in UDV and DV groups and prevalence of microscopic vascular changes

	Undemented vascular disease (UDV)	*Demented vascular disease (DV)*
% Cerebral hemisphere infarcted	1.93	2.48
Single cerebral infarct present	11††	3
Multiple cerebral infarcts present	4	8
No macroscopic cerebral infarct present	4	13‡
Microscopic vascular changes:		
Any cribriform change (n (%))	12 (63)	22 (92)*
Severe cribriform change (score 2/3, n (%))	3 (16)	7 (71)**
Microinfarction (n (%))	5 (26)	15 (63) ***
Congophilic angiopathy (n (%))	4 (21)	8 (33)†

*P=0.03 *v* UDV group; **P=0.0006 *v* UDV group; ***P=0.031 *v* UDV group; †P=0.0067 *v* C group (nil congophilic angiopathy); ††P=0.014, more prevalent than in DV; ‡P=0.034, more prevalent than in UDV.
All analyses by Fisher's exact test.

Two tailed, unpaired Student's *t* test, Mann-Whitney non-parametric test, and Fisher's exact test were used to analyse the results as appropriate as indicated in the text and tables.

Results

The *mean ages of the cases* in each of the three groups ranged from 76 (DV) to 83 (UDV) years. The mean age of the control cases (80 years) was not significantly different from DV or UDV cases, but the DV cases were significantly younger than the UDV cases (P=0.008; table 1).

The *mean brain weights and cerebral hemisphere weights* (table 1) were not significantly different between the C, DV, and UDV groups. (These comparisons were made within sexes as brain weights of males and females are known to differ and the relative numbers of males and females differed between groups.)

Involvement of *the internal carotid arteries* at their origin in the neck with atheromatous narrowing did not differ in prevalence between any of the three groups. It was present on one side in more than 50% of cases in all groups. However, it should be noted that information about this was not available in several cases, particularly in group C, and the recording of this information is likely to have been biased in favour of recording it only when it was present (table 1).

Any atheroma and severe atheroma of circle of Willis arteries were just significantly less common in group C than group UDV, but the difference between group C and group DV on these measures just failed to reach significance (table 1).

Cerebral infarction (table 2) was, by definition, not present in group C. Comparing the cerebral hemisphere ratios of infarcted:uninfarcted tissue in the cerebral hemispheres analysed morphometrically, there was a slightly, but not significantly, higher ratio in the DV than the UDV group (percentage tissue infarcted 2.48 for DV and 1.93 for UDV; P=0.15 Mann-Whitney non-parametric test) (table 2). Single cerebral infarcts were more common in the UDV than the DV group (P=0.0028; table 2). There was no significant difference between the groups with respect to frequency of multiple macroscopic infarcts in one hemisphere but absence of macroscopic infarction was more common in the DV than the UDV group (P=0.034; table 2). We had insufficient whole brains to examine the frequency of bilateral infarction for DV and UDV groups.

Microscopic vascular changes showed highly significant differences between UDV and DV groups. Cribriform change of any severity was significantly more common in the DV than UDV groups (P<0.03) and a higher level of significance was obtained when severe cribriform change was compared in these groups (P=0.0006) (table 2). Microinfarction was also significantly more common in DV than UDV cases (P=0.031). Congophilic angiopathy was significantly more common in the DV than C group (P<0.0066) but there was no significant

difference between congophilic angiopathy prevalence in C and UDV or UDV and DV groups (table 2).

Left ventricular hypertrophy was quite common in all disease groups and showed no significantly increased prevalence in UDV or DV groups compared with controls (table 1) Myocardial infarction and fibrosis were significantly more common in the UDV group than in the controls. Prevalence was intermediate in DV cases, in which it was not significantly different either from the controls or the UDV cases.

Discussion

The chief finding that emerges from this study is that microvascular brain damage in the form of cribriform change and associated perivascular subcortical white matter damage and microinfarction is closely correlated with a history of dementia in cases of cerebrovascular disease, uncomplicated by any more than trivial Alzheimer's disease pathology. Although cribriform change was found in cases without dementia none of these cases achieved the maximum severity score (3) for cribriform change, whereas a third of the demented cases achieved this score and only 8% of demented cases had no cribriform change. By contrast, the extent of macroscopic infarction was not correlated significantly with dementia, and nor were brain weights or cerebral hemisphere weights. However, the comparisons concerning brain and hemispheric weights are unsatisfactory in that the disease groups turned out to be not evenly matched for age, the DV cases being younger than the UDV cases, and age is known to influence brain weight. Circle of Willis atheroma and myocardial infarction were both significantly more common in UDV than C cases. A similar trend was seen for DV cases but these trends failed to reach significance. Perhaps surprisingly, given the long recognised relation between Binswanger's disease and hypertension, left ventricular cardiac hypertrophy was not increased in the DV cases (or UDV cases). Congophilic angiopathy, which was not severe in any case, as might be expected in a series selected for the paucity of Alzheimer's disease pathology, was present to a mild extent significantly more often in DV than C cases. A similar, but not significant, trend was also seen in UDV cases. This difference was despite all groups having similar proportions of cases showing no plaques or a minimal number of plaques (table 1).

The present findings in DV cases need to be compared with those in previous studies of vascular dementia. There has been no exactly comparable study that includes both cases with vascular disease, known to have been undemented in life, and undemented cases with no cerebrovascular disease as well as cases of vascular dementia, but excluding cases with any more than very mild Alzheimer type pathology. Erkinjuntti *et al*[8] described the neuropathological findings in 23 cases of clinically diagnosed and neuropathologically confirmed cases of vascular dementia and compared them with cases due to Alzheimer's disease. The aim of this study was clinicopathological correlation, but the neuropathological examination was comparable with that in the present study. Cases of vascular dementia almost always had bilateral and multiple infarcts. In 91% of cases there was temporal lobe infarction and in 83% of the cases there was subcortical infarction. More infarction, cribriform change (present in 78% of cases), and circle of Willis atheroma characterised the vascular dementia group in comparison with cases of dementia due to Alzheimer's disease. Severity of dementia was correlated with total volume of infarcted tissue but not with severity of cribriform change which was assessed on a 0-3 scale. Alzheimer's pathology was very mild in these cases, probably comparable to that in the present study, except in a further three cases designated as mixed Alzheimer's disease and vascular dementia. This study concluded that major cerebral infarcts are of major importance in causing vascular dementia with subcortical lesions "a contributing factor". Emphasis on large macroscopic infarcts as a cause of vascular dementia was likewise made by Tomlinson *et al.*[2]

However, the concept of vascular dementia being determined primarily by the volume of infarcted tissue is oversimplistic, as has been recognised by several recent reviews.[12 19–24] Del Ser *et al*[10] carried out a study that compared neuropathological findings in demented and non-demented patients with cerebrovascular disease. These cases were comparable with our DV and UDV groups respectively. In this study bilaterality of infarction, the volume of frontal, occipital and basal ganglia infarction, lacunar state, and white matter lesions were significantly greater in demented cases, although there was a considerable overlap between the two groups. In our study we found a non-significant trend for the infarcted volume to be greater in DV than UDV and it is possible that had we had the opportunity to examine both cerebral hemispheres, as in the study of Del Ser *et al*,[10] this would have reached significance. Bilaterality of infarcts in relation to dementia could also not be considered directly in our study. Location of infarcts is also thought to be important in promoting dementia, but did not clearly emerge in the present study as of importance, in part because several DV cases did not have macroscopic infarction and the distribution of infarcts in the remainder was highly variable and not significantly different from the UDV cases.

This study supports the view that subcortical vascular damage is a prime substrate for much of the cerebral damage that is relevant in vascular dementia.[14 22 25–27] Although only three of the present cases may be regarded neuropathologically as cases of pure Binswanger's disease, with grade 3 severity of cribriform change and no cortical infarction, the great majority of other DV cases had lesions of similar type, albeit of lesser severity or admixed with cortical infarction. Although the present study contained only six DV cases in which both cerebral hemispheres were available for microscopic examination, we gained the

impression that the microvascular damage of importance in dementia is generally symmetric between the two cerebral hemispheres. This suggests that reliable information on the extent of such change can be obtained from the study of only one hemisphere, as may be necessary in centres where one hemisphere is frozen for neurochemical research. We shall now carry out further studies to examine the relation of the severity of subcortical damage with the severity of cognitive decline in another series of cases with systematic cognitive scoring and examine the interaction of such damage with Alzheimer's disease type pathology.

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