Interhemispheric Distribution of Alzheimer Disease and Vascular Pathology in Brain Aging

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Background and Purpose—Most of the neuropathological studies in brain aging were based on the assumption of a symmetrical right–left hemisphere distribution of both Alzheimer disease and vascular pathology. To explore the impact of asymmetrical lesion formation on cognition, we performed a clinicopathological analysis of 153 cases with mixed pathology except macroinfarcts.

Methods—Cognitive status was assessed prospectively using the Clinical Dementia Rating scale; neuropathological evaluation included assessment of Braak neurofibrillary tangle and Aβ deposition staging, microvascular pathology, and lacunes. The right–left hemisphere differences in neuropathological scores were evaluated using the Wilcoxon signed rank test. The relationship between the interhemispheric distribution of lesions and Clinical Dementia Rating scores was assessed using ordered logistic regression.

Results—Unlike Braak neurofibrillary tangle and Aβ deposition staging, vascular scores were significantly higher in the left hemisphere for all Clinical Dementia Rating scores. A negative relationship was found between Braak neurofibrillary tangle, but not Aβ staging, and vascular scores in cases with moderate to severe dementia. In both hemispheres, Braak neurofibrillary tangle staging was the main determinant of cognitive decline followed by vascular scores and Aβ deposition staging. The concomitant predominance of Alzheimer disease and vascular pathology in the right hemisphere was associated with significantly higher Clinical Dementia Rating scores.

Conclusions—Our data show that the cognitive impact of Alzheimer disease and vascular lesions in mixed cases may be assessed unilaterally without major information loss. However, interhemispheric differences and, in particular, increased vascular and Alzheimer disease burden in the right hemisphere may increase the risk for dementia in this group. (Stroke. 2009;40:983-986.)

Key Words: Alzheimer ▪ cerebral infarct ▪ cognition ▪ white matter disease

Several clinicopathological studies postulated that the presence of cortical microinfarcts or lacunar infarcts significantly increases the risk for dementia among individuals with Alzheimer disease (AD) lesions.1-5 The vascular burden in brain aging may, however, influence the extent of AD pathology without having a significant impact per se.6 We recently reported that cortical microinfarcts and lacunes explained 15% of the presence of dementia in mixed cases without macroinfarcts and with various degrees of AD pathology.7 One main limitation of this latter study was related to the use of a global bilateral microvascular score and assessment of AD pathology limited to the right hemisphere. We assess here the interhemispheric differences in AD and vascular lesion severity, relationships between AD and vascular burden in each hemisphere as well as the possible cognitive impact of asymmetrical lesion distribution in an independent series of prospectively studied patients with mixed pathology.

Patients

The initial autopsy series included 1875 patients who died and were autopsied at the Geriatric and Psychiatric Hospitals of the University of Geneva from 1993 to 2006 (mean death rates, 7.5% and 1%, respectively). All of the patients were referred to the hospital from the Geneva area and were >65 years of age. Permission for autopsy was systematically requested as part of the routine clinical work in both hospitals. Four criteria were used to define our sample. First, cases with other central nervous system disorders (ie, tumors, inflammation, Parkinson disease, Lewy body disease) were excluded from the present study (n=194). Second, all cases with macroscopic infarcts or non-AD-related pathology were also excluded from the present series (n=421). Similarly, cases with a history of psychiatric illnesses were not considered (n=44). From the remaining 1216 cases, the final series included 153 right-handed patients aged 73 to 101 years assessed with the Clinical Dementia Rating Scale (CDR) at most 3 months before death (excluding cases with agonal states)8 (Table).
Tissue Processing

Lacunes in the white matter or basal ganglia and thalamus were identified on macroscopic examination and controlled on Luxol-van Gieson-stained coronal sections. To visualize cortical microinfarcts as well as focal cortical and white matter gliosis, 1-cm thick tissue blocks from the anterior hippocampus, inferior temporal, frontal, and parietal cortex bilaterally were cut into 20-μm thick serial sections and stained with Globus silver impregnation.7 To assess diffuse white matter and periventricular demyelination, 20-μm thick sections at the level of anterior commissure were stained with Luxol-van Gieson. Additional 12-μm thick sections were processed bilaterally with antibodies to the tau and core amyloid ß proteins,7-synuclein, and ubiquitin.7

All cases were classified neuropathologically according to the Braak neurofibrillary tangle (NFT) staging system9 and amyloid nomenclature.10 Lacunes, cortical microinfarcts, and focal cortical gliosis were assessed in 10 sections per area using the following score: 0 (absence of such lesions), 1 (3 lesions per slide), 2 (3 to 5 lesions per slide), or 3 (>5 lesions per slide). Assessment of white matter gliosis, diffuse white matter, and periventricular demyelina-

tion in each hemisphere was made using a similar rating scale: 0 = absent, 1 = mild, 2 = moderate, or 3 = severe. For each of these lesions, a mean score by area was calculated based on the 10 sections. Subsequently, a mean score by hemisphere was obtained for each lesion (sum of the mean scores/number of areas). A total vascular score by hemisphere was calculated by adding the total scores for the 6 lesions considered (with a maximum score of 18 for each case).

Statistical Analysis

The interhemispheric relationships among Braak NFT, Aβ deposition staging, and vascular scores were assessed using the Wilcoxon signed rank test and Spearman correlation coefficients. A possible age effect on the relationships between AD and vascular lesions in demented cases was investigated by linear regression. Maximal likelihood ordered logistic regression models with CDR scores (independent variable), Braak NFT, Aβ deposition staging, vascular scores, and age (dependent variables) were built. Logistic regression analysis with a repeated measure design, including the hemispheric side predominance, was also performed (306 observations for 153 subjects).

Results

There were strong positive relationships among the left and right Braak NFT staging ($r_s = 0.93$, $P < 0.0001$; Figure 1A), Aβ deposition staging ($r_s = 0.89$, $P < 0.0001$; Figure 1B), and vascular scores ($r_s = 0.74$, $P < 0.0001$; Figure 1C). These relationships were present across all CDR scores ($r_s$ values ranging from 0.55 to 0.94, $P < 0.05$ to 0.0001). Unlike Braak NFT and Aβ deposition staging, a marked left predominance was observed for vascular scores (CDR 0: 10 left [L] versus 1 right [R] dominant, $P < 0.01$; CDR 0.5: 24 L versus 3 R dominant, $P < 0.0005$; CDR 1: 6 L versus 2 R dominant, $P < 0.05$; CDR 2: 22 L versus 6 R dominant, $P < 0.001$; CDR 3: 28 L versus 9 R dominant, $P < 0.0005$; Figure 1D).

![Figure 1. Scatterplots illustrating the relationship of Braak NFT staging (A), Aβ deposition staging (B), and vascular scores (C) between the 2 hemispheres (10% random noise was added to discriminate each data couple). Note the strong bilateral correlation between the lesion severity for all 3 neuropathological variables. Representative diagram of left versus right hemispheric predominance for Braak NFT staging, Aβ deposition staging, and vascular scores by CDR group (D). Note the consistent predominance of vascular lesions in the left hemisphere. No significant left–right differences were observed in respect to AD pathology.](http://stroke.ahajournals.org/)

| Table. Demographic Data and CDR Scores in the Entire Sample |
|-----------------|-----------------|-----------------|
| CDR | No. of Cases (W/M) | Mean Age, Years ± SEM |
| 0 | 20 (13/7) | 79.35 ± 2.12 |
| 0.5 | 31 (16/15) | 84.48 ± 1.54 |
| 1 | 14 (7/7) | 86.21 ± 1.48 |
| 2 | 35 (19/16) | 88.31 ± 1.15 |
| 3 | 53 (36/17) | 88.98 ± 0.87 |
| All cases | 153 (91/62) | 86.40 ± 0.64 |

W indicates women; M, men.
0 = no dementia; 0.5 = questionable dementia; 1 = mild dementia; 2 = moderate dementia; 3 = severe dementia.
In both hemispheres, there was a positive association between Braak NFT and Aβ deposition staging in CDR 0.5 to 3 cases ($r_s = 0.47$ to 0.59, $P < 0.01$ to 0.001) but not CDR 0 cases (Figure 2). In contrast, a negative relationship was found between Braak NFT staging and vascular scores only in cases with moderate to severe dementia (CDR 2: $r_s = -0.29$ L, $P < 0.05$, $-0.53$ R, $P < 0.001$; CDR3: $r_s = -0.41$ L, $P < 0.005$, $r_s = -0.57$ R, $P < 0.0001$). These CDR-dependent relationships persisted after controlling for a possible age effect in multivariate models. No significant relationships were found between Aβ deposition staging and vascular scores in either hemisphere (Figure 2).

Braak NFT staging, Aβ deposition staging, and vascular scores were all significantly related to CDR scores in the left hemisphere (12%, 4%, and 4% of the CDR variability, respectively). Quasi-identical percentages were obtained in the right hemisphere. The concomitant predominance of AD and vascular pathology in the right hemisphere was associated with significantly higher CDR scores (OR, 1.41, 95% CI, 1.17 to 1.71; $P < 0.001$).

**Discussion**

In our mixed cases, NFT and Aβ deposition populate the brain symmetrically even in very early stages of neurodegeneration. In contrast, a left predominance of vascular lesions was evident independently of the CDR score. Besides the work of Esiri et al\textsuperscript{11} in 6 demented cases who postulated that the relevant microvascular damage in dementia is generally symmetrical, we are not aware of another neuropathological study addressing the lateralization of vascular lesions in mixed cases. The increased vascular burden in the left hemisphere was observed not only in demented, but also in CDR 0 cases, suggesting that it is mostly related to normal brain aging and has no impact on cognitive deterioration.

The Aβ deposition and Braak NFT staging were unrelated in cognitively intact cases but showed a significant positive correlation not only in cases with clinically overt dementia, but also in CDR 0.5 cases (for review, see Imhof et al\textsuperscript{12}). In the absence of a categorical definition of mild cognitive impairment subgroups, this finding suggests that at least some of them could be very mild AD cases. Unlike Aβ deposition staging, our results partly support a synergistic effect of NFT and vascular lesions in mixed cases in that they reveal a weak yet significant negative relationship between Braak NFT staging and vascular score in both hemispheres in cases with moderate to severe dementia.

The percentage of CDR variability explained by each neuropathological parameter was nearly identical in the 2 hemispheres implying that the assessment of vascular and AD pathology in one hemisphere is sufficient to establish valid clinicopathological correlations in these mixed cases. However, the concomitant occurrence of higher AD pathology staging and vascular scores in the right hemisphere is associated with increased CDR scores. This observation parallels the earlier report of Reed and coworkers\textsuperscript{13} in patients with lacunes. The predominant development of vascular lesions in the left hemisphere may remain cognitively silent because of a functional compensation assumed at least partly by the right hemisphere.\textsuperscript{14} The invasion of the right hemisphere by AD and vascular lesions would disrupt this phenomenon leading to the expression of clinically overt dementia or increased dementia severity.

Several limitations should, however, be considered when interpreting our data. To focus on brain aging, we did not make a categorical distinction between demented and nonde-
mented cases but also consider CDR 0.5 cases. This highly heterogeneous group includes cases with mild cognitive impairment (amnestic or nonamnestic, single domain or multidomain, vascular or degenerative), but also cases with very mild dementia. Moreover, we did not include cases with macroinfarcts that are thought to make a significant contribution, at least in severe cases of mixed dementia. The clinical assessment was based on the CDR score that may not be sensitive enough to the differences in interhemispheric relationships between lesion severity and cognitive deficits. Finally, the neuropathological assessment of microvascular lesions and lacunes remains dependent on the sampling strategy used. Additional studies coupling imaging data with neuropathological and neuropsychological observations in community-based series are needed to further explore the differential interhemispheric vulnerability in patients with mixed pathology.

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Disclosures
None.

References
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