Title: Interhemispheric distribution of Alzheimer disease and vascular pathology in brain aging.
Authors: Giannakopoulos P, Kövari E, Herrmann FR, Hof PR, Bouras C
Journal: Stroke; a journal of cerebral circulation
Year: 2009 Mar
Volume: 40
Issue: 3
Pages: 983-6
DOI: 10.1161/STROKEAHA.108.530337

Published in final edited form as:
Stroke. 2009 March ; 40(3): 983–986. doi:10.1161/STROKEAHA.108.530337.

Interhemispheric distribution of Alzheimer disease and vascular pathology in brain aging

Panteleimon Giannakopoulos[*], **Enikö Kövari**[*], **François R Herrmann**, **Patrick R Hof**, and **Constantin Bouras**

Departments of Psychiatry (EK, CB, PG) and Geriatrics (GG, FRH), University of Geneva Faculty of Medicine, Geneva, Switzerland; Division of Old Age Psychiatry (PG), University of Lausanne School of Medicine, Lausanne; and the Department of Neuroscience, Mount Sinai School of Medicine, New York, NY, USA (PRH)

Abstract

Background and purpose—Most of the neuropathological studies in brain aging were based on the assumption of a symmetric right-left hemisphere distribution of both Alzheimer's disease (AD) and vascular pathology. To explore the impact of asymmetric 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 (CDR) scale; neuropathological evaluation included assessment of Braak neurofibrillary tangle (NFT) and Aß-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 CDR scores was assessed using ordered logistic regression.

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

Conclusions—Our data show that the cognitive impact of AD and vascular lesions in mixed cases may be assessed unilaterally without major information loss. However, interhemispheric differences and, in particular, increased vascular and AD burden in the right hemisphere may increase the risk for dementia in this group.

Keywords

Alzheimer; cerebral infarct; cognition; white matter disease

Introduction

Several clinicopathological studies postulated that the presence of cortical microinfarcts or lacunar infarcts significantly increase the risk for dementia among individuals with AD lesions[1-5]. The vascular burden in brain aging may, however, influence the extent of AD

Correspondence to Dr. Enikö Kövari, Department of Psychiatry, Division of Neuropsychiatry, University of Geneva Hospitals, 1225 Chêne-Bourg, Switzerland, tel: 0041-22-3055361, fax:0041-22-3055350, e-mail: E-mail: eniko.kovari@hcuge.ch.
[*]Equally first authors

pathology without having a cognitive 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 possible cognitive impact of asymmetric lesion distribution in an independent series of prospectively studied patients with mixed pathology.

Materials and Methods

Patients

The initial autopsy series included 1875 patients who died and were autopsied at the Geriatric and Psychiatric Hospitals of the University of Geneva during the period 1993-2006 (mean death rates: 7.5% and 1% respectively). All of the patients were referred to the hospital from the Geneva area and were older than 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 (i.e., tumors, inflammation, Parkinson's 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 past 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 three months prior to death (excluding cases with agonal states)[8].(Table 1).

Tissue processing

Lacunes in the white matter or basal ganglia and thalamus, were identified on macroscopic examination and controlled on Luxol-van Gieson (LVG) 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 LVG. Additional 12-μm-thick sections were processed bilaterally with antibodies to the tau and core amyloid ß proteins, α-synuclein and ubiquitin[7].

All cases were classified neuropathologically according to the Braak NFT staging system[9]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 (3-5 lesions per slide), 3 (> 5 lesions per slide). Assessment of white matter gliosis, diffuse white matter and periventricular demyelination in each hemisphere was made using a similar rating scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. For each of these lesions, a mean score by area was calculated based on the ten 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 six lesions considered (with a maximum score of 18 for each case).

Statistical analysis

The interhemispheric relationships between Braak NFT, Aß 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), and Braak NFT, Aß deposition

staging, vascular scores, age (dependent variables) were built. Logistic regression analysis with repeated measure design including the hemispheric side predominance was also performed (306 observations for 153 subjects).

Results

There were strong positive relationships between the left and right Braak NFT staging (r_s = 0.93, $p < 0.0001$; Fig. 1A), Aß deposition staging (r_s= 0.89, $p < 0.0001$; Fig. 1B) and vascular scores (r_s= 0.74, $p < 0.0001$, Fig. 1C). These relationships were present across all CDR scores (r_s values ranging from 0.55 to 0.94, $p < 0.05$-0.0001). Unlike Braak NFT and Aß deposition staging, a marked left predominance was observed for vascular scores (CDR 0: 10 L (left) vs 1 R (right) dominant; $p < 0.01$; CDR 0.5: 24 L vs 3 R dominant, $p < 0.0005$; CDR 1: 6 L vs 2 R dominant, $p < 0.05$; CDR 2: 22 L vs 6 R dominant, $p < 0.001$; CDR3: 28 L vs 9 R dominant, $p < 0.0005$; Fig. 1D).

In both hemispheres, there was a positive association between Braak NFT and Aß deposition staging in CDR 0.5 to 3 cases (r_s= 0.47 to 0.59, $p < 0.01$-0.001) but not CDR 0 cases (Fig. 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 Aß deposition staging and vascular scores in either hemisphere (Fig. 2).

Braak NFT staging, Aß 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 (odds ratio: 1.41, 95% confidence interval: {1.17, 1.71}, $p < 0.001$).

Discussion

In our mixed cases, NFT and Aß 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. [11] in 6 demented cases who postulated that the relevant microvascular damage in dementia is generally symmetric, 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 Aß 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 [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 Aß deposition staging, our results partly support a synergistic effect of NFT and 9 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 two 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 [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[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. In order to focus on brain aging, we did not made a categorical distinction between demented and non-demented cases but also consider CDR 0.5 cases. This highly heterogeneous group includes cases with mild cognitive impairment (amnestic or non amnestic, 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[15]. The clinical assessment was based on the CDR score that may not be sensitive enough to the differences in interhemispheric relationships between lesions' 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.

Acknowlegments and Funding

Supported by grants AG02219 and AG05138 from the National Institutes of Health, Bethesda, Md (PRH)

References

1. Del Ser T, Hachinski V, Merskey H, Munoz DG. Alzheimer's disease with and without cerebral infarcts. J Neurol Sci 2005;231:3–11. [PubMed: 15792814]
2. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. Lancet 1999;354:919–920. [PubMed: 10489957]
3. Kövari E, Gold G, Herrmann FR, Canuto A, Hof PR, Bouras C, Giannakopoulos P. Cortical microinfarcts and demyelination affect cognition in cases at high risk for dementia. Neurology 2007;68:927–931. [PubMed: 17372128]
4. Launer LJ, Petrovitch H, Ross GW, Markesbery W, White LR. AD brain pathology: Vascular origins? Results from the haas autopsy study. Neurobiol Aging. 2007
5. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun study. JAMA 1997;277:813–817. [PubMed: 9052711]
6. Kalback W, Esh C, Castano EM, Rahman A, Kokjohn T, Luehrs DC, Sue L, Cisneros R, Gerber F, Richardson C, Bohrmann B, Walker DG, Beach TG, Roher AE. Atherosclerosis, vascular amyloidosis and brain hypoperfusion in the pathogenesis of sporadic Alzheimer's disease. Neurol Res 2004;26:525–539. [PubMed: 15265270]
7. Gold G, Giannakopoulos P, Herrmann FR, Bouras C, Kövari E. Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain 2007;130:2830–2836. [PubMed: 17878206]
8. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Brit J Psychiat 1982;140:566–572.
9. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–259. [PubMed: 1759558]
10. Thal DR, Rüb U, Schultz C, Sassin I, Ghebremedhin E, Del Tredici K, Braak E, Braak H. Sequence of Abeta-protein deposition in the human medial temporal lobe. J Neuropathol Exp Neurol 2000;59:733–748. [PubMed: 10952063]

11. Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. J Neurol Neurosurg Psychiatry 1997;63:749–753. [PubMed: 9416809]
12. Imhof A, Kövari E, von Gunten A, Gold G, Rivara CB, Herrmann FR, Hof PR, Bouras C, Giannakopoulos P. Morphological substrates of cognitive decline in nonagenarians and centenarians: A new paradigm? J Neurol Sci 2007;257:72–79. [PubMed: 17303173]
13. Reed BR, Eberling JL, Mungas D, Weiner M, Jagust WJ. Frontal lobe hypometabolism predicts cognitive decline in patients with lacunar infarcts. Arch Neurol 2001;58:493–497. [PubMed: 11255455]
14. Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, Koeppe RA. Age differences in the frontal lateralization of verbal and spatial working memory revealed by pet. J Cogn Neurosci 2000;12:174–187. [PubMed: 10769314]
15. Jellinger KA, Attems J. Neuropathological evaluation of mixed dementia. J Neurol Sci 2007;257:80–87. [PubMed: 17324442]

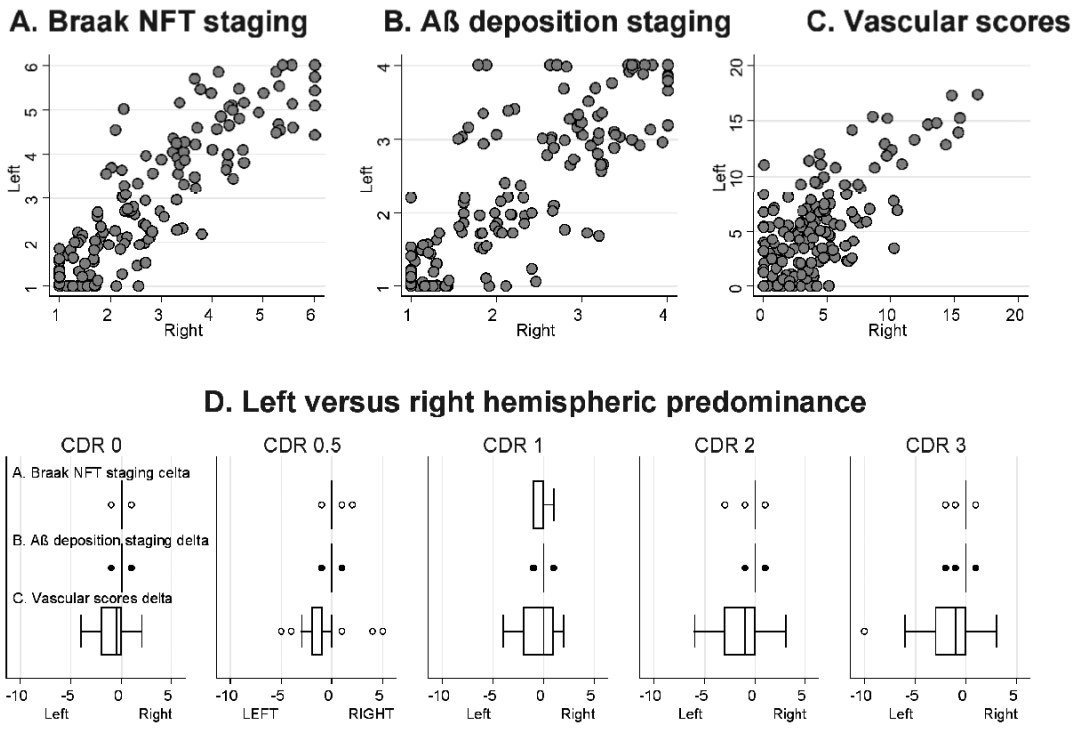

Fig.1.

Scatterplots illustrating the relationship of Braak NFT staging (A), Aß deposition staging (B) and vascular scores (C) between the two hemispheres (10% random noise was added to discriminate each data couple). Note the strong bilateral correlation between the lesion severity for all three neuropathological variables. Representative diagram of left versus right hemispheric predominance for Braak NFT staging, Aß deposition staging and vascular scores by CDR group (D). Note the consistent predominance of vascular lesions in left hemisphere. No significant left-right differences were observed in respect to AD pathology.

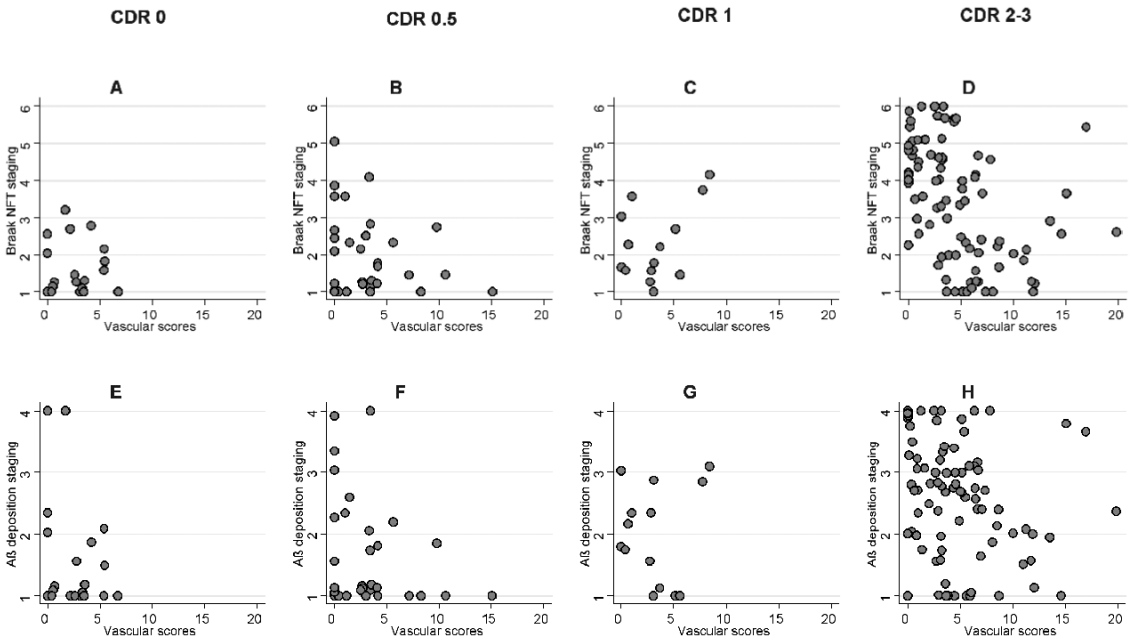

Fig. 2.

Scatterplots illustrating the relationship between Braak NFT staging (A-D), Aß deposition staging (E-H) and vascular scores in the right hemisphere as a function of the CDR group (0, 0.5, 1, 2-3). Note the negative relationship between Braak NFT staging and vascular scores observed in the CDR 2-3 group. See text for details.

Table 1

Demographic data and CDR scores in the entire sample.

CDR	Number 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, women; M, men. CDR, Clinical Dementia Rating score (0: no dementia, 0.5, questionable dementia, 1: mild dementia, 2: moderate dementia, 3: severe dementia).