Cognitive Consequences of Thalamic, Basal Ganglia, and Deep White Matter Lacunes in Brain Aging and Dementia

Gabriel Gold, MD; Enikö Kövari, MD; François R. Herrmann, MD, MPH; Alessandra Canuto, MD; Patrick R. Hof, MD; Jean-Pierre Michel, MD; Constantin Bouras, MD; Panteleimon Giannakopoulos, MD

Background and Purpose—Most previous studies addressed the cognitive impact of lacunar infarcts using radiologic correlations that are known to correlate poorly with neuropathological data. Moreover, absence of systematic bilateral assessment of vascular lesions and masking effects of Alzheimer disease pathology and macrovascular lesions may explain discrepancies among previous reports. To define the relative contribution of silent lacunes to cognitive decline, we performed a detailed analysis of lacunar and microvascular pathology in both cortical and subcortical areas of 72 elderly individuals without significant neurofibrillary tangle pathology or macrovascular lesions.

Methods—Cognitive status was assessed prospectively using the Clinical Dementia Rating (CDR) scale; neuropathological evaluation included Aβ-protein deposition staging and bilateral assessment of microvascular ischemic pathology and lacunes; statistical analysis included multivariate models controlling for age, amyloid deposits, and microvascular pathology.

Results—Thalamic and basal ganglia lacunes were negatively associated with CDR scores; cortical microinfarcts, periventricular and diffuse white matter demyelination also significantly affected cognition. In a multivariate model, cortical microinfarcts and thalamic and basal ganglia lacunes explained 22% of CDR variability; amyloid deposits and microvascular pathology explained 12%, and the assessment of thalamic and basal ganglia lacunes added an extra 17%. Deep white matter lacunes were not related to cognitive status in univariate and multivariate models.

Conclusions—In agreement with the recently proposed concept of subcortical ischemic vascular dementia, our autopsy series provides important evidence that gray matter lacunes are independent predictors of cognitive decline in elderly individuals without concomitant dementing processes such as Alzheimer disease. (Stroke. 2005;36:1184-1188.)

Key Words: aging ■ brain injuries ■ cognition ■ dementia ■ lacunar infarction ■ vascular diseases

Morphological substrates of cognitive decline associated with cerebrovascular disease are still strongly debated. The traditional view of a close relationship between a volume of cerebral infarcts >100 mL and dementia proposed by Tomlinson has been challenged by neuropathological studies that indicated that small macroinfarcts and even microscopic ischemic lesions can lead to dementia. More recently, focus has shifted to the identification of more homogeneous subtypes of vascular dementia such as subcortical ischemic vascular dementia, characterized clinically by a dysexecutive syndrome and memory deficits and neuropsychologically by lacunes and deep white matter changes. Although the contribution of deep white matter changes to cognitive decline is now well-documented, the clinical significance of lacunes has been difficult to establish.13 In the Cardiovascular Health Study, 23% of individuals older than age 65 had MRI evidence of lacunes; however, 89% were essentially clinically silent from a cognitive point of view. In other studies, the prevalence of silent lacunes ranged from 11% to 24%. In a large neuropathological series, lacunes were present in approximately one-quarter of elderly cases without psychiatric or neurological disease. In contrast, the Nun study demonstrated that cognitive function was markedly influenced by thalamic, basal ganglia, and deep white matter lacunes in individuals with Alzheimer disease (AD) neuropathology. Moreover, a recent study reported intriguing results regarding the cognitive consequences of silent brain infarcts. At baseline, no relationship was found between the presence of silent brain infarcts and impaired cognition, yet cases with new silent brain infarcts during follow-up did have cognitive decline.

Several methodological issues may explain difficulties encountered when attempting to define the role of lacunar

Received November 30, 2004; final revision received February 15, 2005; accepted February 25, 2005.

From the Departments of Psychiatry (A.C., E.K., C.B., P.G.) and Geriatrics (G.G., F.R.H., J.P.M.), HUG Belle-Idée, University of Geneva School of Medicine, Geneva, Switzerland; Service of Old Age Psychiatry (P.G.), University of Lausanne School of Medicine, Lausanne; Fishberg Research Center for Neurobiology and Kastor Neurobiology of Aging Laboratories (P.R.H., C.B.), and the Departments of Geriatrics and Adult Development and Ophthalmology (P.R.H.), Mount Sinai School of Medicine, New York, NY.

G.G. and E.K. contributed equally to this work.

Correspondence to Dr Gabriel Gold, Department of Geriatrics, University of Geneva Hospitals, 1226 Thônex-Geneva, Switzerland. E-mail gabriel.gold@hcuge.ch

© 2005 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000166052.89772.b5

1184
pathology in brain aging. Because lacunes occur diffusely within the brain, a valid evaluation of their repercussion on cognition presupposes their systematic bilateral assessment in regions known to be highly involved in dementia and prone to development of lacunes such as the thalamus, basal ganglia, and deep white matter. Moreover, the concomitant presence of other age-related dementing pathology may mask the cognitive consequences of lacunes. This includes AD pathology such as amyloid deposits and, most importantly, neurofibrillary tangles (NFT), which represent the strongest correlate of neuronal loss and cognition in AD.\textsuperscript{16,17} and also microvascular lesions such as cortical microinfarcts and periventricular and diffuse white matter demyelination, which have been shown to negatively influence cognitive performance in brain aging.\textsuperscript{4}

To address these issues, we report clinicopathological correlations in a series of prospectively investigated elderly individuals with various degrees of cognitive impairment but without significant NFT pathology or macrovascular lesions. To define the cognitive consequences of lacunar pathology, we compared the semi-quantitative assessment of cognitive findings to the semi-quantitative assessment of lacunes in the deep white matter, basal ganglia, and thalamus. The present analysis is based on multivariate models that control for the interaction with age, amyloid deposits, and significant microvascular pathology.

Materials and Methods
We surveyed a 5-year autopsy population of 629 cases from the Geriatric and Psychiatric Hospitals, Geneva University School of Medicine. All patients were from the Geneva area and older than 65 years; there were 270 men (81.0±7.1 years) and 359 women (82.8±7.3 years). In these institutions, all patients older than 65 undergo cognitive screening using the Mini-Mental State Examination\textsuperscript{18} and clock drawing test.\textsuperscript{19} If, as a result, dementia is suspected, neuropsychological evaluation is performed using tests appropriate under cognitive screening with a high inter-rater reliability (κ=0.90 to 0.95).

Maximal likelihood ordered logistic regression with proportional odds was used to evaluate the association between CDR scores (the dependent variable) and neuropathological parameters (Aβ-protein deposition staging, lacune and microvascular pathology scores as the independent variables) in a univariate model. Subsequently, the same variables were included in all cases using the CDR during the 3 months before death (Table). All procedures involving use of postmortem human brain were conducted after written consent of the patients or their family and were approved by the Ethics Committee.

Lacunes were defined as small definitive ischemic necrosis, 1 mm to 1.5 cm, located in white matter, basal ganglia, or thalamus. On histological examination, lacunes consist of cavitations of cerebral tissue with scattered fat-laden macrophages and surrounding gliosis. Younger lesions show mild to severe rarefaction of neurons with reduced number of oligodendrocytes and early signs of cavitation. To visualize lacunes and significant microvascular pathology (ie, cortical microinfarcts, periventricular and diffuse white matter demyelination), tissue blocks from the anterior hippocampus, inferior temporal cortex (area 20), frontal cortex (area 9), and parietal cortex (area 40) bilaterally and basal ganglia and thalamus were cut into 20-μm-thick sections and stained with the Globus silver impregnation technique\textsuperscript{4} (Figure 1). To assess diffuse white matter and periventricular demyelination, coronal slices at the level of the anterior border of the corpus callosum were embedded in paraffin, cut into 20-μm-thick sections, and stained with Luxol-van Gieson.

Lacunes and microvascular pathology assessed semi-quantitatively in 10 sections per area were scored as follows: 0 (absence of such lesions), 1 (<3 lesions per slide), 2 (3 to 5 lesions per slide), and 3 (>5 lesions per slide). A total score was obtained by adding the scores of each area. Severity of diffuse white matter and periventricular demyelination in each hemisphere was estimated in Luxol-van Gieson–stained sections using a semi-quantitative scale: 0=absent, 1=mild, 2=moderate, and 3=severe. Scores for each hemisphere were added to obtain a total score. Thus, 6 scores were determined in each case and used for statistical analysis: a microinfarct score (all microinfarcts regardless of location), 2 demyelination scores (diffuse white matter and periventricular white matter), and 3 lacunar scores according to region of interest (deep white matter, basal ganglia, and thalamus). All neuropathological analyses were performed by 2 independent investigators (E.K. and C.B.), blind to the clinical findings, with a high inter-rater reliability (κ=0.90 to 0.95).

Demographic Data

<table>
<thead>
<tr>
<th>CDR</th>
<th>Mean Age in Years (SD)</th>
<th>No. of Cases (Women/Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>77.9 (9.2)</td>
<td>17 (10/7)</td>
</tr>
<tr>
<td>0.5</td>
<td>84.2 (9.3)</td>
<td>20 (11/9)</td>
</tr>
<tr>
<td>1</td>
<td>88.3 (4.2)</td>
<td>4 (1/3)</td>
</tr>
<tr>
<td>2</td>
<td>86.0 (7.2)</td>
<td>17 (8/9)</td>
</tr>
<tr>
<td>3</td>
<td>84.2 (5.6)</td>
<td>14 (7/7)</td>
</tr>
<tr>
<td>All cases combined</td>
<td>83.4 (8.4)</td>
<td>72 (37/35)</td>
</tr>
</tbody>
</table>

CDR indicates Clinical Dementia Rating; SD, standard deviation.
was entered in the models as 3 dummy variables. Maximum likelihood ordered logistic regression could be used to measure the relationship between an ordinal outcome variable (CDR) and several independent variables. It can also evaluate the amount of variability of the outcome variable (ie, the CDR score) that can be explained by the independent variables (ie, age, Aβ-protein phase, lacune scores, microinfarcts, and demyelination) and thus provide an estimate of the strength of the relationship. Statistical analyses were performed with Stata software package, release 8.2 (College Station, Tex).

Results
The study sample included 17 cases with no dementia (CDR 0), 20 cases with questionable dementia (CDR 0.5), and 35 cases with varying severity of dementia (CDR 1 to 3) (Table). Lacunes were present in 21 cases in the basal ganglia, in 18 cases in deep white matter, and in 9 cases in the thalamus. Cortical microinfarcts were found in 29 cases, periventricular demyelination in 43 cases, and diffuse white matter demyelination in 62 cases. Mild Aβ-protein deposition was present in most cases (45.8% were stage A, 27.8% stage B), but 26% displayed substantial Aβ-protein deposition within the medial temporal lobe (22.2% stage C, 4.2% stage D).

There were 16 cases with lacunes and without cortical microinfarcts: 3 cases with no dementia (CDR=0), 3 cases with questionable dementia, 6 cases with moderate dementia (CDR=2), and 4 cases with severe dementia (CDR=3). The 3 cases with no dementia had small amounts of lacunes (score of ≤1) in both deep white matter and basal ganglia. All but one of these cases also had white matter lesions.

In a univariate model, Aβ-protein deposition staging explained 7% (P=0.002; R²=0.07) and age only 3% (P=0.02; R²=0.03) of the variability in CDR scores. Among the different types of microvascular pathology, cortical microinfarcts (P<0.001), diffuse white matter (P=0.03), and periventricular demyelination (P=0.01) were all significant correlates of cognitive function and explained, respectively, 11% (R²=0.11), 6% (R²=0.06), and 6% (R²=0.06) of the variability in cognitive function as measured by the CDR.

Lacunes in the thalamic and basal ganglia significantly predicted cognitive status (P=0.02) and explained 5% (R²=0.05) and 6% (R²=0.06) of CDR variability, respectively. However, there was no significant relationship between deep white matter lacunes and CDR score (P=0.19).

We performed a multivariate model including the following variables: age, Aβ-protein deposition staging, cortical microinfarcts, and basal ganglia and thalamic lacunes scores were significantly related to CDR. The latter 3 vascular variables were used to develop a combined vascular score ([thalamic score + basal ganglia score + microinfarct score] ÷ 4; the microinfarct score was divided by 4 to ensure that each of the 3 subscores had the same weight). This combined score explained 22% of the CDR variability (Figure 2). Importantly, in a forward stepwise regression model, the best predictors of cognitive status were in order of decreasing strength cortical microinfarcts, basal ganglia lacunes, thalamic lacunes, and Aβ-protein deposition staging. In this model, lacunes explained 17% of the clinical variability.

Discussion
To our knowledge, this is the first study addressing the cognitive impact of silent lacunar infarcts and microvascular changes in an autopsy series of prospectively assessed elderly individuals. Its strengths include the detailed analysis of lacunes and different types of microvascular lesions in cortical areas bilaterally and control for the most important confounding variables (substantial NFT pathology corresponding to limbic and neocortical Braak stages and microinfarcts) and use of multivariate models for statistical analysis, which can estimate the predictive value of each neuropathological measure taking into account the strength of their interaction. As usual, limitations related to the size of
the study population and neuropathological sampling methods must also be taken into account. However, in view of the relative scarcity of cases with pathological changes confined to lacunes, demyelination, and microinfarcts, our series represents an unusually large autopsy cohort. Moreover, although we cannot exclude that additional pathology may have been present mainly in neocortical areas, we have minimized this bias by examining ten sections per area.

Consistent with our previous observations in an autopsy sample including elderly individuals with isolated microvascular pathology, cortical microinfarcts and periventricular and diffuse white matter demyelination were all significant determinants of cognitive decline in this series. Not surprisingly, this association was substantially weaker in the present cohort of cases with mixed vascular pathology compared with our previous results. Most importantly, our neuropathological data suggest that cortical microinfarcts are a strong predictor of cognitive changes in brain aging. The present data also support the strategic importance of location in defining the cognitive impact of lacunes. In univariate and multivariate models, thalamic and basal ganglia but not deep white matter lacunes significantly predicted CDR scores. It has long been considered that cognitive deterioration in patients with lacunes may result from disruption of subcortical–frontal circuits. The present findings are partly consistent with this hypothesis because they indicate that damage in subcortical gray matter may decisively influence cognitive performances. However, they clearly demonstrate that the frequent development of lacunes within deep white matter in brain aging is not sufficient to induce dementia.

It is noteworthy that assessment of vascular pathology in the present series can predict at best 22% of CDR variability. This value is comparable to that previously reported for NFT Braak staging in a large autopsy series, indicating that assessment of microvascular changes and lacunes may represent a valid predictor of cognitive decline, in the absence of substantial NFT pathology, as strong as NFT staging in elderly individuals without vascular pathology. The relative weakness of the relationship between vascular pathology and cognitive status may reflect methodological issues related to semi-quantitative assessment of microvascular changes and lacunes. This possibility is further supported by recent findings showing that rigorous stereological assessment of NFT in vascular pathology-free cases leads to >85% prediction of clinical variability. Alternatively, other neuropathological variables such as neuronal or synaptic loss may decisively contribute to cognitive impairment in this context. The analysis of large autopsy series including various cognitive parameters and stereological assessment of microvascular changes, lacunes, as well as neuronal and synaptic loss is warranted to define precisely the structural background of dementia in cases with predominant vascular pathology.

These new data may be also relevant with respect to current efforts at neuropathological standardization in the dementia field. The current debate regarding the definition of these conditions mostly reflects the difficulty in evaluating the relative clinical impact of the various types of vascular lesions in pure vascular cases and defining the synergistic effect of vascular and AD-type changes in mixed conditions. Our previous work in cases with isolated microscopic ischemic pathology led to the conclusion that cortical microinfarcts are a strong predictor of cognitive changes in brain aging. The present observations complete this first study by providing an estimate of the cognitive consequences of gray matter lacunes in cases without AD neuronal pathology. These findings may be of particular importance for the
definition of neuropathological criteria for vascular and mixed dementia and should serve as a basis for future clinicopathological studies exploring the combined effect of clinically relevant macroscopic and microscopic ischemic vascular and degenerative changes in mixed conditions.

Acknowledgments
Supported by grants AG02219 and AG05138 from the National Institutes of Health, Bethesda, Md (P.R.H.) and by an unrestricted grant from the Jérôme Tissières Foundation (P.G.)

References
Cognitive Consequences of Thalamic, Basal Ganglia, and Deep White Matter Lacunes in Brain Aging and Dementia

Gabriel Gold, Enikö Kövari, François R. Herrmann, Alessandra Canuto, Patrick R. Hof, Jean-Pierre Michel, Constantin Bouras and Panteleimon Giannakopoulos

Stroke. 2005;36:1184-1188; originally published online May 12, 2005;
doi: 10.1161/01.STR.0000166052.89772.b5

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/6/1184

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/