The Relative Frequency of “Dementia of Unknown Etiology” Increases With Age and Is Nearly 50% in Nonagenarians

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Context: With the recent change in pathological criteria for Alzheimer disease (AD), a group of patients has emerged who do not meet pathological criteria for any well-characterized degenerative dementias. Whether these unclassified patients have vascular dementia or some other form of dementia is not known.

Objective: To determine the clinical characteristics, pathological substrate, and relative frequency of dementia not caused by well-characterized degenerative dementias.

Design/Setting: Clinicopathological study of a prospectively observed sample of elderly nondemented and demented subjects recruited from our urban community.

Methods: In our series of 128 subjects with prospective neuropsychological evaluations as well as neuropathology, we identified 35 clinically nondemented subjects and 20 demented patients who did not meet pathological criteria for well-characterized degenerative dementias such as AD or dementia with Lewy bodies. The 20 demented patients were grouped together under the term dementia of unknown etiology (DUE). We compared clinical, genetic, neuropsychological, pathological, and neurochemical characteristics of the nondemented group, patients with DUE, and 28 patients with AD and no other pathological abnormality.

Results: Mean age at death for patients with DUE was 89.1 ± 5.8 years compared with 79.9 ± 11.4 years for AD (P < .001). Patients with AD and DUE did not differ in sex, risk factors, apolipoprotein E genotype, neuropsychological features, or neurological features. Hippocampal sclerosis (in 11 patients with dementia and no controls) and leukoencephalopathy (in 7 patients with dementia and 1 control) were associated with cognitive impairment; other vascular markers were not. Dementia of unknown etiology accounted for 5% of all cases of dementia among patients dying in their 70s, 21% for patients dying in their 80s, and 48% for patients dying in their 90s.

Conclusions: A significant percentage of demented patients older than 80 years do not meet pathological criteria for AD or dementia with Lewy bodies. Hippocampal sclerosis and leukoencephalopathy are common in these patients but rare in clinically nondemented subjects.
SUBJECTS AND METHODS

SUBJECT RECRUITMENT

Subjects were members of the Bronx Aging Study or the Albert Einstein College of Medicine Teaching Nursing Home study, now combined as the Einstein Aging Study. Methods of recruitment, subject examination, and determination of cognitive status and dementia have been described previously. The present study includes subjects who died between January 1, 1980, and December 31, 1995, had quantitative neuropathological findings, and had at least 2 neurological and neuropsychological evaluations. The institutional review board of Albert Einstein College of Medicine, Bronx, NY, approved all research protocols and consent forms. Informed consent was obtained from nondemented and mildly demented subjects. Assent was obtained from moderately demented patients, and informed consent was obtained from the next of kin of all demented patients.

NEUROPSYCHOLOGICAL AND NEUROLOGICAL EVALUATIONS

Subjects in the Bronx Aging Study were tested on the Wechsler Adult Intelligence Scale (WAIS), and those in the Teaching Nursing Home study were tested on the Wechsler Adult Intelligence Scale–Revised (WAIS-R). To combine scores from the 2 tests, for each subject we computed the z scores for subtests from their raw scores on either the WAIS or WAIS-R. The normal means and SDs for the WAIS were derived from the baseline scores of 180 subjects from the Bronx Aging Study who had follow-up for 5 years without developing dementia. Means and SDs on the WAIS-R were derived from a comparable group of 48 subjects from the Teaching Nursing Home study who followed up for 5 years without developing dementia.

Rate of change on the Blessed information, memory, and concentration test (BIMC) was computed by dividing the difference between the baseline and final BIMC scores by the number of years between the 2 tests. Clinical features were rated according to methods described previously. Gait in the Bronx Aging Study was rated on a dichotomous scale (“normal neurologically” or “not normal neurologically”); gait in the Teaching Nursing Home study was rated on a 5-point scale. In the combined data set, the 5-point scale was collapsed to a 2-point scale.

Diagnoses were made by consensus at a conference attended by a geriatric neurologist (H.A.C.), neuropsychologist (D.M. or E.G.), and usually a geriatric nurse clinician or social worker. The subjects analyzed in this report died between 1983 and 1995. Clinical diagnosis of “dementia” vs “no dementia” followed Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), and, after 1986, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R), criteria. From 1984 onward, the clinical diagnosis of AD followed National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria. Before 1984, the clinical diagnosis of AD followed DSM-III criteria. The clinical diagnoses of vascular dementia and “mixed dementia” followed DSM-III and DSM-III-R criteria. Diagnoses of “dementia, unable to determine type” were made when clinical features were atypical, when multiple causes were present, or when essential clinical data were missing.

PATHOLOGICAL EXAMINATION

Methods of brain removal, dissection, and tissue preparation have been described previously. We used Reagan Institute–NIA pathological criteria for AD and Newcastle criteria for DLB. Pathological criteria for hippocampal sclerosis, leukencephalopathy, microinfarcts, amyloid angiopathy, and cribriform change were described previously.

RESULTS

Demographic characteristics of the 3 subject groups—ND, DUE, and AD—are shown in Table 1. Women comprised the majority of subjects in each group. Ninety-three percent of the subjects were white, and 7% were African American. All 3 groups had comparable levels of education. The most striking difference between the patients in the AD and DUE groups was the very large difference in their mean age at death: patients with AD were about a decade younger than those with DUE. Patients with DUE were less demented when first examined and less demented before death than the patients with AD. The BIMC scores declined twice as fast for patients with AD as for those with DUE, although the difference did not reach statistical significance (P<.09).
CRITERIA FOR PATHOLOGICAL GROUPS

Control subjects and patients with DUE and AD were selected from the 128 subjects who had the requisite neurological and neuropathological examinations. All 35 clinically nondemented (ND) subjects were included as control subjects. None of these 35 subjects met pathological criteria for AD, DLB, or frontotemporal dementia. Fifty-six demented subjects met pathological criteria for AD; the 28 of these subjects who were free of concomitant pathology comprised the “pure” AD group. The 28 patients with AD and other concomitant dementias included 17 with vascular lesions, 9 with D LB, 1 with argyrophilic grain dementia, and 1 with mamillary body changes of unknown etiology. The following vascular markers excluded subjects from the pure AD groups: hippocampal sclerosis, leukoencephalopathy, multiple lacunar infarcts, infarctions caused by occlusions of medium- or large-caliber arteries, cribriform changes, microinfarcts, and evidence of old intracerebral hemorrhage. Amyloid angiopathy did not exclude subjects from the pure AD group.

Nine subjects with D LB without concomitant AD were also excluded. Eight additional subjects with non-AD dementias for whom the pathological substrates for dementia were known included 2 with argyrophilic grain dementia, 2 with corticobasal degeneration, 2 with frontotemporal dementia including Pick disease, 1 with amyotrophic lateral sclerosis–dementia, and 1 with progressive supranuclear palsy; these subjects were also excluded from the analysis (dementia, other). The remaining 20 demented subjects comprised our group of DUE.

We calculated the relative frequency of dementia subtype by using the total number of dementia cases from all causes as the denominator, and the number from each specific subtype as the numerator.

The sensitivity of clinical diagnosis of AD was 79%; its specificity was 70%. As shown in Table 1, only 30% (6/20) of patients with DUE were given a clinical diagnosis of AD, compared with 79% (22/28) of patients with AD. Thirty percent (6/20) of patients with DUE, but only 11% (3/28) of patients with AD, were given a diagnosis of “dementia, unable to specify type.”

Subjects with moderate or severe dementia were unable to complete the WAIS neuropsychological tests. Because many of the patients with AD were first examined when they had moderate or severe dementia, complete neuropsychological data could be obtained on less than half of these patients. The mean BIMC score of patients with AD capable of completing these subtests was 8.6 ± 7.8, reflecting the relatively mild degree of dementia in these patients. Scores on the WAIS subtests (digit symbol, digit span, information, and vocabulary) did not differ between the patients with DUE and testable patients with AD even after controlling for age and severity of dementia as measured by the BIMC score. The AD and DUE groups also did not differ in their scores on the Fuld Object Memory Test, a test of recent memory.32 On every measure, ND subjects were significantly different from both the DUE and AD groups (P < .001).

Apolipoprotein E genotyping was performed on 9 ND subjects, 8 patients with DUE, and 18 patients with AD in the laboratory of John Hardy, PhD, according to previously described methods.30 Apolipoprotein E genotyping on patients who died before 1990 was performed only if blocks of frozen tissue were still available.

NEUROCHEMICAL ANALYSIS

TG3 is a murine monoclonal antibody to paired helical filaments. It recognizes a phosphatedependent epitope on paired helical filament proteins and also τ protein (serine 231). Assay methods have been described previously.31

STATISTICS

Because pathological variables were not normally distributed, we computed medians and quartiles. Median values were compared with the Kruskal-Wallis test. When significant differences were found, pairwise comparisons with the Mann-Whitney test were performed. When differences were less than .05, the significance level was noted. Demographic variables were first compared with 1-factor analyses of variance. Significant differences were followed with pairwise comparisons by means of the t test for independent variables.

Differences among the pathological groups in concentrations of pathological markers could be caused by differences in severity of dementia. To examine this possibility, we statistically controlled for dementia severity by covarying scores from the BIMC.20 Because many of the pathological markers were counts (eg, number of plaques, number of tangles), we used Poisson regression to test for difference between the AD and DUE groups after adjusting for covariates (age and dementia severity). Similar analyses were conducted on the neuropsychological test scores by ordinary-least-squares analysis of covariance.

RISK FACTORS, CLINICAL FEATURES, AND GENETICS

We examined the association between medical history and pathological group. There were no significant differences in the frequency of patient reports of a history of hypertension, angina, myocardial infarction, arrhythmias, diabetes, angina, congestive heart failure, chronic obstructive pulmonary disease, depression, hip fracture, strokes, and cancer among the 3 groups.

Seizures and urinary incontinence were more common in patients with AD than in the ND group (P < .04 for both measures). The frequency of falls was similar among the 3 groups. Sixty percent (12/20) of patients with DUE had gait impairment at some time during the study, compared with 29% (10/35) of ND subjects (P < .05). Forty-six percent (13/28) of AD subjects had gait impairment at some time during follow-up. This frequency was not statistically different from that of the ND subjects or of the patients with DUE.

Thirteen percent (1/8) of patients with DUE had at least 1 apolipoprotein E ε4 allele, compared with 28% (5/18) of patients with AD (difference not significant).
AD, Alzheimer disease; BRWT, brain weight; NBM, estimate of cell loss in the nucleus basalis of Meynert (ranges from 0 [no cell loss; normal] to 2 [marked cell loss]); NBMNFT, neurofibrillary tangles (NFTs) in the nucleus basalis of Meynert below the threshold of the Reagan Institute–NIA criteria for AD; AD, Alzheimer disease; MXD, mixed dementia; VaD, vascular dementia; UDT, unable to determine dementia subtype; and BIMC, Blessed test of information, memory, and concentration. Unless noted, differences between the ND and DUE groups were not significant. DUE and AD (as well as ND and AD) differed on every measure at P < .001.

Counts of senile plaques and neurofibrillary tangles were significantly higher in every brain region in AD than in DUE. Poisson regression was used to model differences in senile plaque count and neurofibrillary tangle count in regions other than neocortex after controlling for dementia severity (the BIMC) and for age. Likelihood ratio tests indicated that the effect of group on both neurofibrillary tangle and senile plaque counts was highly significant (P < .01 in all cases), with the patients with AD having higher counts for both types of pathological markers, even after adjusting for covariates. Among ND patients, minimal TG3 activity was found in the entorhinal cortex, but in no other brain region. Whereas all patients with AD had substantial levels of neocortical TG3, 7 of 9 ND patients had no measurable neocortical TG3 immunoreactivity (data available on request).

OTHER MARKERS

Table 4 lists the association of hippocampal sclerosis, leukoencephalopathy, and 5 markers of vascular dementia in patients with DUE and ND subjects. Eleven subjects had hippocampal sclerosis; all were demented. Seven patients with DUE and 1 control subject had leukoencephalopathy. Four of 11 subjects with hippocampal sclerosis had concomitant leukoencephalopathy. Although each of the 5 markers of vascular dementia was more common in DUE than in ND, these associations were not statistically significant.

On the basis of the data from Table 4, we divided the patients with DUE into the following 4 groups: hippocampal sclerosis, leukoencephalopathy, multi-infarct dementia, and other. Figure 1 shows that there was substantial overlap between these subgroups. We then compared the clinical, pathological, and neurochemical features of the subgroups (Table 5). Because the number

Table 1. Demographic Characteristics of Study Patients*

<table>
<thead>
<tr>
<th>ND (n = 35)</th>
<th>DUE (n = 20)</th>
<th>AD (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, y</td>
<td>86.9 ± 6.1†</td>
<td>89.1 ± 5.8</td>
</tr>
<tr>
<td>Sex, N/F ( % F)</td>
<td>22.0 (71)</td>
<td>11.9 (55)</td>
</tr>
<tr>
<td>Education, y</td>
<td>11.6 ± 4.1</td>
<td>10.6 ± 4.2</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>ND 6 AD, 22 AD, 3 MXD, 2 MXD, 5 VaD, 1 VaD, 6 UDT, 3 UDT</td>
<td>ND 6 AD, 22 AD, 3 MXD, 2 MXD, 5 VaD, 1 VaD, 6 UDT, 3 UDT</td>
</tr>
<tr>
<td>BIMC at entry</td>
<td>2.2 ± 2.3</td>
<td>2.2 ± 2.3</td>
</tr>
<tr>
<td>BIMC before death</td>
<td>3.3 ± 3.1</td>
<td>16.5 ± 7.9§</td>
</tr>
<tr>
<td>Rate of change</td>
<td>0.4 ± 1.7</td>
<td>1.0 ± 1.5</td>
</tr>
<tr>
<td>on BIMC, points/y (n = 32)</td>
<td>(n = 32)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Interval between last evaluation and death, y</td>
<td>1.5 ± 1.3</td>
<td>1.4 ± 1.5</td>
</tr>
<tr>
<td>Interval between first and last observation, y</td>
<td>6.3 ± 3.7</td>
<td>6.2 ± 4.1</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD. ND indicates not demented; DUE, dementia of unknown etiology; AD, Alzheimer disease; MXD, mixed dementia; VaD, vascular dementia; UDT, unable to determine dementia subtype; and BIMC, Blessed test of information, memory, and concentration. Unless noted, differences between the ND and DUE groups and between the DUE and AD groups were not significant.

†P < .003 vs AD.
‡P < .002 vs DUE.
§P < .001 vs ND.
‖P < .03 vs DUE.

Table 2. Neurofibrillary Markers of AD*

<table>
<thead>
<tr>
<th>ND (n = 35)</th>
<th>DUE (n = 18-20)</th>
<th>AD (n = 27-28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRWT (1090-1300)</td>
<td>1135 (1050-1207)</td>
<td>1045 (952-1129)</td>
</tr>
<tr>
<td>Braak score</td>
<td>2 (1-3)</td>
<td>2.5 (1-2.5)</td>
</tr>
<tr>
<td>NBM cell loss</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>NBMNFT</td>
<td>1 (0-1)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>HPMNFT</td>
<td>1 (0-3.2)</td>
<td>1.5 (0-3.7)</td>
</tr>
<tr>
<td>PHPNFT</td>
<td>3.5 (0-10.5)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>PNFT</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>TNFT</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>FNFT</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
</tbody>
</table>

*ND indicates not demented; DUE, dementia of unknown etiology; AD, Alzheimer disease; HPP, hippocampal senile plaques; PHPSP, parahippocampal senile plaques; OSP, occipital lobe senile plaques; FSP, frontal lobe senile plaques. Plaque counts were performed as described previously and, unless otherwise specified, represent the total number of neuritic and nonneuritic plaques. Values represent counts in a 2-mm² area. The first number in each cell is the median. Numbers in parentheses represent the 25th and 75th percentiles. Except for the frontal lobe, plaque counts were arbitrarily truncated at 50 when they were numerous. There were no significant differences between ND and DUE on any measure. DUE and AD (as well as ND and AD) differed on every measure at P < .001.

AD MARKERS

Part of our definition of DUE is that subjects not meet pathological criteria for AD. Nonetheless, many of our subjects had some pathological features of AD, but were below the threshold of the Reagan Institute–NIA criteria for AD. Table 2 and Table 3 compare numbers of AD markers among the 3 subject groups. On 16 of 17 measures, no significant differences between DUE and ND were noted. In particular, Braak scores, degree of cell loss in the nucleus basalis of Meynert, brain weight, and senile plaque counts did not differ between ND and DUE.

Counts of senile plaques and neurofibrillary tangles were significantly higher in every brain region in AD than in DUE. Poisson regression was used to model differences in senile plaque count and neurofibrillary tangle count in regions other than neocortex after controlling for dementia severity (the BIMC) and for age. Likelihood ratio tests indicated that the effect of group on both neurofibrillary tangle and senile plaque counts was highly significant (P < .01 in all cases), with the patients with AD having higher counts for both types of pathological markers, even after adjusting for covariates. Among ND patients, minimal TG3 activity was found in the entorhinal cortex, but in no other brain region. Whereas all patients with AD had substantial levels of neocortical TG3, 7 of 9 ND patients had no measurable neocortical TG3 immunoreactivity (data available on request).
of subjects in each subgroup was small, most differences among the groups were not statistically significant. However, a few trends are worth emphasizing.

1. The leukoencephalopathy group had a lower brain weight than the group without leukoencephalopathy ($P<.02$).

2. The hippocampal sclerosis group was more demented than the group without hippocampal sclerosis on entry and at last evaluation ($P<.01$).

3. Gait impairment occurred in almost all patients in the leukoencephalopathy group and about half of the patients in the other groups (difference not significant).

4. Neocortical TG3 immunoreactivity was present in 2 of 3 subjects with hippocampal sclerosis but in none of the other (non-AD) groups (difference not significant).

5. Detailed clinical histories available in 4 of the 5 patients with multi-infarct dementia showed that 1 of the 4 had been hospitalized for an acute stroke. Brain imaging showed previous strokes in 3 patients; atrophy was the only finding in the fourth. All 4 had focal findings on neurological examinations. Poor balance, falls, and impaired gait were present in all 4.

6. Patients with hippocampal sclerosis had gradual progression of cognitive impairment and had impairment in other cognitive domains as well as memory. Four of the patients with hippocampal sclerosis came from a study of originally nondemented subjects. Two of those 4 had clearly normal memory scores at time of entry, and the other 2 had borderline scores. One subject with hippocampal sclerosis had a history of seizures (compared with 1 patient with leukoencephalopathy, 4 with AD, and no ND patients).

INFLUENCE OF AGE AND BASELINE MENTAL STATUS TEST SCORE ON DEMENTIA SUBTYPE

Figure 2 shows the percentage of cases of AD, AD with concomitant vascular markers or with concomitant DBL, and DUE of all cases of dementia as a function of age at death. The relative percentage of DUE cases of all dementia cases increased steadily from 5% among subjects dying in their 70s, to 21% in the 80s, to 48% in the 90s ($P<.02$).

To our knowledge, this is the first clinicopathological study to demonstrate the influence of age on the relative frequency of dementia not caused by AD, DLB, or other well-characterized degenerative dementias. We found that the percentage of these patients increases with age and is nearly 50% among those dying in their 90s. Furthermore, AD was the cause of dementia in only 22% of subjects who had had normal results of mental status examinations between the ages of 75 and 85 years.

Ninety percent of the DUE group fit into at least 1 of 3 clinicopathological groups—hippocampal sclerosis, leukoencephalopathy, or multi-infarct dementia. Clinical features unusual in AD, including early onset of gait impairment or focal findings on neurological examinations, characterized the leukoencephalopathy and multi-infarct groups. Clinical features in the hippocampal sclerosis group were similar to those in AD. The sensitivities of the clinical diagnoses of AD and of non-AD dementias were nearly comparable (78% vs 70%) with the use of pathological findings as the criterion standard.

In other pathological studies, the relative frequency of dementia not caused by AD, DLB, or other well-characterized degenerative dementias (ie, equivalent to DUE in our study) ranges from 2% to 65%, but most studies from the United States find a frequency of less than 25%. We believe there are 3 reasons why we find relatively numerous cases of DUE. First, Reagan Institute–NIA pathological criteria for AD are more restrictive than earlier criteria, such as the Khachaturian9 or Consortium to Establish a Registry for Alzheimer’s Disease33 criteria. If Khachaturian criteria were used in our study, at least 9 (45%) of 20 patients with DUE would have been diagnosed as having AD. Second, our subjects were substantially older than those in most other postmortem studies. Dementia of unknown etiology appears to become more frequent in the ninth decade. Studies where most subjects die in the eighth decade are unlikely to find many cases of DUE. Third, our method of classification precluded calling DUE “AD with vascular disease” or “mixed dementia.” When subjects are classified as having “mixed dementia,” the invariable tendency is to lump pure and mixed cases together to determine the “total number of AD cases.” This method of classification may overestimate the contribution of AD to dementia.

The cause of dementia in subjects with DUE depends on the clinicopathological subgroup. In multi-infarct dementia, it is loss of discrete “crucial” information processing centers and/or their connections. In leu-
As defined in this article, DUE is a pathological diagnosis of exclusion; consequently, the DUE group is heterogeneous. When the true pathological substrates for DUE are clarified, criteria for inclusion and exclusion will be developed to define clinically and pathologically homogeneous subgroups.

Were the relatively minimal AD findings in subjects with DUE sufficient to account for cognitive impairment? Individuals with large “cognitive” reserves may be better able to tolerate AD changes than subjects with fewer brain reserves. If subjects in the ND group had large brain reserves, perhaps they might tolerate more AD abnormality without developing dementia than subjects in the DUE group. This seems unlikely for several reasons. First, education levels between the ND and DUE groups were equivalent. In addition, baseline WAIS vocabulary scores were comparable in the ND and DUE groups, suggesting that the level of schooling, whether formal or otherwise, was comparable between the groups. Finally, several other studies have demonstrated that modest AD changes are not associated with dementia, and this finding was part of the reason why more restrictive pathological criteria for AD were proposed.

The amount of AD findings in half of the patients with DUE was comparable with that in ND subjects described by Price and Morris with Clinical Dementia Rating scores of 0, who are unlikely to even have preclinical AD. We acknowledge that some of the patients with DUE, as well as about half of the ND subjects, may have had preclinical AD. However, as Price and Morris as well as Hulette et al demonstrated, the amount of AD change is insufficient to cause dementia. We conclude that some other process in addition to AD must account for dementia in these patients.

Even though many patients with dementia lacking distinct histological features have hippocampal sclerosis,
we believe that most, if not all, of the subjects with DUE would not meet criteria for dementia lacking distinctive histological features or some form of frontotemporal dementia. Patients with dementia lacking distinctive histological features have cell loss in the medial thalamus, frontal cortex, and substantia nigra, which was not found in our patients with DUE. Unlike patients with DUE, most subjects with frontotemporal dementia develop symptoms before age 80 years.

Our study suggests that, among the very elderly, dementia not caused by AD, DLB, or frontotemporal dementia is common and can be grouped into specific clinicopathological syndromes of hippocampal sclerosis, leukencephalopathy, and multi-infarct dementia. Studies with much larger numbers of cases will be needed to better define these 3 syndromes. If these findings are replicated and extended, they will have several implications.

1. The contribution of AD to dementia in patients older than 85 years may have been overestimated. Further study in representative postmortem series is warranted.

2. Patients who become demented after they had normal performance on a screening mental status test at age 75 years are unlikely to have AD as the cause of their dementia.

3. The clinical syndromes consisting of cases of leukencephalopathy and multi-infarct dementia are relatively easy to distinguish from AD on clinical grounds. The third syndrome, hippocampal sclerosis, is more difficult to distinguish.

Accepted for publication November 3, 1999.

This study was supported by grant AG03949-15 from the National Institute on Aging, National Institutes of Health, Bethesda, Md.

We acknowledge Robert Katzman, MD; Robert Terry, MD; Miriam Aronson, EdD; Joseph Masdeu, MD; and Leslie Wolfson, MD, for their role in creating and running the Bronx Aging Study and the Teaching Nursing Home study. We thank Martin Slivinski, PhD, and the statistical core for their assistance. We thank Mindy Katz, MS; Gail Kuslan, PhD; and the staff of the Einstein Aging Study clinical core for their help with data collection. We thank Herman Buschke, MD, and Joe Verghese, MD, for helpful discussions. We thank Charlotte Magnotta for clerical assistance.

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