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Neuropathology in Controls and Demented Subjects From the Baltimore Longitudinal Study of Aging

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TRONCOSO, J. C., L. J. MARTIN, G. DAL FORNO AND C. H. KAWAS. Neuropathological in controls and demented subjects from the Baltimore Longitudinal Study of Aging. NEUROBIOIL AGING 17(3) 365-371, 1996.—To establish correlations among cognitive states and neuropathology, we have examined 22 subjects (69-97 years of age) from the Baltimore Longitudinal Study of Aging (BLSA), of whom 15 had normal and stable cognitive performances and seven had dementia of variable severity. In the majority of normal subjects, few or no β-amyloid (Aβ) deposits or senile plaques (SP) were present in the neocortex, but neurofibrillary tangles (NFT) were consistently found in CA1 of hippocampus and layer II of entorhinal cortex. In two (15%) normal individuals, the densities of SP were consistent with the diagnosis of possible Alzheimer’s disease (AD). We speculate that these cases with normal cognitive states and abundant neocortical SP may represent preclinical AD. We conclude that the neocortex of a majority of cognitively intact individuals can remain free of Aβ deposits or SP, even into the tenth decade of life.

Aging Alzheimer’s disease β-Amyloid protein Senile plaques

CORRELATIONS among cognitive performances and neurodegenerative abnormalities in the brains of elderly individuals have, over the years, produced conflicting interpretations, in particular, concerning the densities of Aβ deposits and SP in neocortex. Considerable time elapsed since Alzheimer’s original description of degenerative changes (i.e., SP and NFT) in dementia (1) until the demonstration, in the 1960s, of a correlation between the number of SP and the severity of dementia (32). Initially, there was some reluctance to accept a correlation between dementia and degenerative changes because multiple reports described SP and NFT in the brains of older individuals who were allegedly normal (17,33,34). However, in 1968, Tomlinson et al. (40) reported their landmark observations in the brains of nondemented older subjects who underwent prospective neurological and cognitive evaluations shortly before death. In 20 of 28 cases, SP were absent or were present in very small numbers in the neocortex, and NFT occurred frequently but were limited to the hippocampus. Since the reports of Tomlinson et al. (40,41), many studies have examined the neuropathology of older individuals in various types of populations by retrospective and prospective clinical analyses and with different neuropsychological assessment tools. Despite the methodological differences in these studies, it is generally agreed that the brains of cognitively normal elderly individuals show NFT in neurons of the entorhinal cortex and hippocampus, but there is no consensus concerning the deposition of cerebral Aβ and the development of SP in the brains of these same individuals. In some studies, extensive Aβ and SP were observed in the neocortices of normal individuals (11,14,20), whereas, in other studies, the brains of carefully characterized normal subjects were virtually free of Aβ and SP (6).

The resolution of these divergent neuropathological observations could have important implications for understanding the biology of cognitive decline in elderly individuals. In this communication, we report clinical and neuropathological observations in 22 elderly subjects from the BLSA who had undergone prospective longitudinal, neurological, and cognitive evaluations for up to 5 years prior to death. The subjects were evaluated shortly before death. These subjects, 15 of whom were diagnosed as being cognitively intact at the time of death and seven with mild-to-moderate impairment of cognition and diagnosed as having AD, provide an excellent opportunity for understanding the neuropathology of normal aging and early AD.

METHOD

Subjects

Subjects for this study were recruited from the BLSA. The BLSA is a longitudinal study of normal aging in volunteer recruits that began in 1958 and is currently under the auspices of the

1 Requests for reprints should be addressed to Juan C. Troncoso, M.D., Neuropathology Laboratory, The Johns Hopkins University School of Medicine, 558 Ross Research Building, 720 Rutland Avenue, Baltimore, MD 21205-2196.
National Institute on Aging. The study has included > 2,000 participants who return biennially to the Gerontology Research Center for 2.5 days of multidisciplinary evaluations (37). Subject recruitment has largely been by word of mouth, with participants recruiting friends and family. Although enrollment was initially limited to men, the recruitment of women volunteers began in 1978. From the group of all participants, we have recruited a cohort of 228 volunteers 65 years of age or older who have consented to longitudinal neuropsychological evaluations and eventual postmortem examination of the brain. In general, at entry in the cohort, we excluded individuals who had an abnormal neurological examination. Most participants had a Blessed Information-Memory-Concentration (BIMC) score of ≤ 8 at entry. However, we also recruited and followed a few individuals with a BIMC score of 8–12 (consistent with mild dementia). Since the inception of our study, 23 subjects have died, and we have obtained autopsies on 22 cases.

Clinical Evaluation

On enrollment and subsequently every 2 years, all subjects were examined according to BLSA protocols (37), complemented by a comprehensive medical history, a complete standardized neuropsychological examination, and a battery of neuropsychological procedures. This battery included the BIMC (8), Mini-Mental State Examination (MMSE) (15), Immediate and Delayed Cued Recall (16), Boston Naming Test (19), Controlled Verbal Fluency (Fruits, Animals, Vegetables, F.A.S.) (5), Trail Making Tests part A and B (13), Clock Drawing and other constructions (35), Center for Epidemiologic Studies-D Depression Inventory (36), Pfeffer Functional Activities Questionnaire (31), the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) construction (28), the National Adult Reading Test (30), and the Clinical Dementia Rating questionnaire (CDR) for both the subject and an informant (7,18). In the year between clinical evaluations at the Gerontology Research Center, participants were interviewed over the telephone to update the medical history and to administer a telephone BIMC (T-BIMC) (21). Our experience with this instrument shows excellent reliability when compared to in-person observation (21). Subjects who showed a decline of two or more points in the T-BIMC was made independently and blindly to the pathologic diagnosis.

Evaluation of Neuritic Plaque

To define neuritic plaques, we visualized them in silver-stained sections. Criteria for the identification of SP included: extracellular argyrophilic structures (> 10 μm); amorphous or fibrillary; with or without apparent neuritic elements; and adjacent to neurons or vessels or free in the neuropil (42). A subset of these SP had a central dense core. Neuritic plaques were distinguished from diffuse plaques by readily identifiable swollen/axon-dendritic processes.

Post mortem examinations were conducted on 22 individuals. Following a two-week fixation in 10% buffered formaldehyde, brains were examined externally and then cut in 1 cm coronal slabs using an electric rotary slicer. Tissue blocks were consistently dissected for histological examination from the basal ganglia, brainstem, cerebellum, cerebral cortex, entorhinal cortex, and hippocampus. To insure consistency, all specimens were dissected by the same investigators (J. C. Troncoso and/or L. J. Martin). Dissection of cortical regions followed Brodmann’s classification. Following dissection, tissues were embedded in paraffin, cut into 10 μm sections, and stained with hematoxylin & eosin and silver using the Hirano method (44). Selected sections were stained with thioflavin and immunostained with antibodies for Aβ (a gift from Dr. Colin Masters, Melbourne, Australia) (25), tau (Sigma, St. Louis, MO), and A68 (a gift from Dr. Peter Davies, Bronx, NY) (43), using a standard immunoperoxidase procedure (24). Tissues for Aβ immunoreactivity were pretreated with 50% formic acid for six minutes. Tissue samples from well-documented cases of AD were always used as positive controls for all histological and immunocytochemical stains.

Aβ, SP, and NFT were visualized in silver-stained sections from the midfrontal gyrus (area 9), mid and superior temporal gyr (areas 21,22), inferior parietal region (areas 39, 40), occipital region (areas 17, 18, 19), hippocampus, entorhinal cortex, and amygdala (one slide per region). The identification of SP was based on the silver method and immunostaining for Aβ, but quantification was performed on silver-stained sections. Criteria for the identification of SP included: extracellular argyrophilic structures (> 10 μm); amorphous or fibrillary; with or without apparent neuritic elements; and adjacent to neurons or vessels or free in the neuropil (42).

A subset of these SP had a central dense core. Neuritic plaques were distinguished from diffuse plaques by readily identifiable swollen/axon-dendritic processes.

In our experience, the Hirano silver method is more sensitive than Aβ immunocytochemistry for detection of neuritic and diffuse SP and detects intra- and extracellular NFT. Thus, we counted SP and NFT on silver-stained tissue sections. Quantification was performed by two observers (J. C. Troncoso and L. J. Martin), who examined tissue sections together to ascertain that quantification was performed in the same microscopic fields and who arrived to a consensus count of SP and NFT. Both observers were blinded to the clinical states of the subjects. Because the large majority of our control cases had no or few SP or NFT, we counted these abnor-

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>DEMOGRAPHIC INFORMATION AND COGNITIVE EVALUATION OF BLSA SUBJECTS</td>
</tr>
<tr>
<td>Normal Subject</td>
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<tr>
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<tr>
<td>CDR = 0 (n = 15)</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
</tr>
<tr>
<td>Percent males</td>
</tr>
<tr>
<td>Mean years of education (range)</td>
</tr>
<tr>
<td>Mean BIMC score (SD)</td>
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</table>

(SD) standard deviation
malities in locations of the tissue section where they were most abundant. To this end, the slide was scanned at low magnification (20x) to identify the sites showing the greatest number of abnormalities (Fig. 1), and the observers counted SP and NFT at 100x in three separate 2.0 mm² fields. Averages of counts were expressed as SP or NFT per mm² (Tables 2 and 3). In addition and for neuropathological diagnostic purposes, when SP were present, we ranked neuritic SP as sparse, moderate, or frequent, according to recommendations of CERAD (27). The same method for quantification of SP and NFT was applied in all cases independently of cognitive status. In selected cases, we also counted SP and NFT in thioflavin-stained section from the neocortical region that showed the highest number of argyrophilic degenerative changes.

Cases were classified according to the AD histopathological diagnostic criteria of CERAD (27).

RESULTS

Clinical Observations

Of the 22 subjects who had postmortem examinations, 15 had been diagnosed clinically to be cognitively intact at the time of death. These observations were supported by informant interviews. The remaining seven had clinical diagnoses of cognitive impair-

ment: one subject was suspected to have possible early dementia (CDR = 0.5), whereas six subjects met clinical criteria for a diagnosis of mild to moderate dementia (CDR = 1) (Table 3).

Neuropathology

Subjects With Normal Cognitive Status. In the neocortices of subjects with normal cognitive status (Table 2), we classified the severity and distribution of SP into three grades (Fig. 2). In the first grade, the neocortex showed no SP (and no Aβ) in at least three of the four neocortical regions examined. In the second grade, we identified sparse foci of predominantly diffuse SP (Figs. 1, 2A and B), usually < 5 per mm², but most of the neocortex was free of pathology. The third grade included those specimens in which SP were moderate (> 10/mm²) or frequent (> 15/mm²) and widespread throughout the neocortex (Fig. 2C). In these cases, the densities of neuritic SP reached levels of moderate or frequent by CERAD standards and were sufficient to fulfill the histopathological criteria for a diagnosis of AD (23) or possible AD (27). Eight individuals showed no amyloid deposits or SP in the neocortical regions sampled. Five subjects had foci of neocortical SP in more than one cortical region. SP were predominantly of the diffuse type, without a dense core and apparently without neurites detected by light microscopy (Fig. 1). The densities of SP (Table 2) reflect isolated foci of SP, because most of the cortex was spared. The paucity of SP was determined in silver- and thioflavin-stained sections and in sections processed immunocytochemically to reveal Aβ, tau, and Aβ8. Neither NFT nor tau-immunoreactive neurites were present in the neocortex of individuals discussed above, independent of the presence of SP, with one exception, which had few NFT but no SP. Only two individuals (cases Nos. 732, 767) with normal cognitive evaluation had widespread amyloid deposits and SP in neocortex. In these brains, there were variable densities of neocortical SP accompanied by no or minimal NFT. One case (No. 767) showed < 80 SP/mm², many with thickened neurites and/or amyloid cores (frequent neuritic SP by CERAD standard (27)), and a few NFT within multiple neocortical areas. The second case (No. 732) showed < 17 SP/mm² (moderate neuritic SP by CERAD standard), tau threads, and tau-positive neurons but no NFT in neocortex. These two cognitively normal cases met the requirements for a diagnosis of AD by the Khachaturian criteria (23) and possible AD by CERAD criteria (27).

The brains of all individuals with normal cognitive evaluations showed pathologic changes in amygdala, entorhinal cortex, or hippocampus. SP and NFT were observed in entorhinal cortex and hippocampus in all subjects. NFT were frequent in the CA1-subiculum of the hippocampus and were virtually a consistent feature in layer II of the entorhinal cortex. Pathological changes were more variable in the amygdala, with six cases free of SP or NFT. In normal individuals, the basal forebrain appeared normal, and the substantia nigra and locus coeruleus were free of degeneration.

Subjects With Abnormal Cognitive Evaluations. Among seven subjects in this group (Table 3), four cases (Nos. 741, 890, 976, 1101) showed moderate-to-frequent numbers of neocortical SP, many with neurites and cores and Aβ deposits consistent with definite or probable AD by CERAD criteria (27), including scant NFT and tau threads in neocortex. These cases also exhibited degeneration of the amygdala, entorhinal cortex, and hippocampus, characterized by dystrophic nerve fibers, SP, and NFT. Two other cases (Nos. 790, 916) had sparse but widespread neuritic SP in the neocortex and were consistent with a diagnosis of possible AD (23,27). One of these cases (No. 916) showed marked degeneration of the substantia nigra, characterized by neuronal loss, free pigment in the neuropil, and Lewy bodies diagnostic of Parkinson's disease. A single case (No. 1055) had neither SP nor NFT in

FIG. 1. Distribution of silver-stained SP in the occipital cortex of a control subject from the BLSA. (A) Low-magnification photomicrograph illustrating the focal localization of neocortical SP. Scale bar: 860 µm. (B) Higher magnification of boxed area in A shows that these SP are of the diffuse type. Scale bar: 111 µm.
### TABLE 2
**NEUROPATHOLOGY IN BLSA SUBJECTS WITH NORMAL COGNITIVE EVALUATIONS (CDR = 0)**

<table>
<thead>
<tr>
<th>SP or NFT/sq. mm*</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frontal</td>
</tr>
<tr>
<td>n=13¶</td>
<td>&lt;12</td>
</tr>
<tr>
<td>M (n = 11)</td>
<td>0</td>
</tr>
<tr>
<td>F (n = 2)</td>
<td>2</td>
</tr>
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</table>

* Density of all SP (diffuse and neuritic) or NFT (intra- and extracellular) refers to the most affected microscopic fields within anatomical region.
† Interval: months elapsed between death and last clinical evaluation.
‡ Frequency of neuritic SP in most affected neocortical region according to CERAD (27).
§ Neuropathological diagnosis of AD according to CERAD (27); pos., possible.
¶ This row shows mean SP and NFT densities for 13 subjects with normal neuropathological assessments or below threshold for AD.
# Cases 732 and 767 have neuropathological changes consistent with possible AD and are presented individually.

Because of the differences in age between normal and abnormal subjects, we were concerned that differences in plaque counts between the two groups might be caused by age alone. To evaluate this possibility, logistic regression was performed using the presence of dementia vs. no dementia as the outcome measure. When

### TABLE 3
**CLINICAL EVALUATION AND NEUROPATHOLOGY IN BLSA SUBJECTS WITH ABNORMAL COGNITIVE EVALUATIONS (CDR >0.5)**

<table>
<thead>
<tr>
<th>SP or NFT/sq. mm*</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frontal</td>
</tr>
<tr>
<td>Case No.</td>
<td>Interval (Months)†</td>
</tr>
<tr>
<td>890</td>
<td>4</td>
</tr>
<tr>
<td>976</td>
<td>11</td>
</tr>
<tr>
<td>1101</td>
<td>4</td>
</tr>
<tr>
<td>741</td>
<td>7</td>
</tr>
<tr>
<td>790</td>
<td>12</td>
</tr>
<tr>
<td>916</td>
<td>8</td>
</tr>
<tr>
<td>1055</td>
<td>3</td>
</tr>
</tbody>
</table>

n/a = not available.
* Density of all SP (diffuse and neuritic) or NFT (intra- and extracellular) refers to the most affected microscopic fields within anatomical region.
† Interval: months elapsed between death and last cognitive evaluation.
‡ Frequency of neuritic SP in most affected neocortical region according to CERAD (27).
§ Neuropathological diagnosis of AD according to CERAD classification of definite (def.), probable (pr.), or possible (pos.) (27).
¶ Dementia diagnosis utilized criteria from the DSM-III-R (for dementia) and NINCDS-ADRDA (for AD) (26).
PD: Parkinson’s disease.
FIG. 2. Relative abundance of silver-stained SP in the superior temporal gyrus of three different subjects from the BLSA. In grade 1, neocortex is free of SP (not shown). (A) Sparse density of SP (grade 2). Scale bar: 125 μm. (B) Focal/minimal density of SP (grade 2). (C) High density of SP (grade 3).


discussion

Our observations indicate that the majority of elderly BLSA subjects with normal cognitive evaluation (CDR = 0) and no history of cognitive decline do not have Aβ deposits or SP in neocortex. In contrast, subjects with questionable (CDR = 0.5) or mild (CDR = 1.0) dementia had neuropathology that met or approached the histological threshold for a diagnosis of AD (23,27). However, in two brains from individuals with a CDR of 0 (case Nos. 732, 767), we also observed severe neocortical histopathological changes consistent with a diagnosis of AD (23) or possible AD (27). These subjects were last examined 12 months (case No. 732) and 24 months (case No. 767) before death, and it is possible that, within these time intervals, these individuals underwent cognitive decline that was not noted by the informants but might have been detected by an intervening evaluation. This possibility underscores the need for frequent cognitive evaluations in longitudinal studies of aging. These observations are in agreement with previous studies, in particular, those of Tomlinson et al. (40) and Berg et al. (6). In the first study (40), which included 28 nondemented old individuals, significant numbers of SP in neocortex were present only in eight cases. NFT were not found in 11 cases, limited to hippocampus in 14 cases, and visualized in neocortex in 3 cases. Because some subjects whose brains had SP and NFT suffered terminal confusional states, it is possible that subtle changes in cognition were not detected. The second study (6) included five normal individuals with a CDR of 0, >80 years of age, whose brains showed few or no SP or NFT in neocortex. The similarity of our neuropathological observations to those of this latter study (6) is particularly important because subjects in both studies underwent comparable clinical evaluations, and their cognitive status was measured with a common scale (CDR).

However, our observations contrast those of other studies that describe abundant SP in the neocortex of large numbers of nondemented older individuals (2,11,14,20). There are several possible explanations for these different observations. Katzman et al. (20) reported a subgroup of ten individuals (mean age 86.7 years) with preserved mental status and numerous neocortical SP. The mean BIMC score in this cohort was 3.8 (SD 3.3), which is higher than the scores of normal BLSA subjects examined by us. A similar difference in BIMC scores is evident when we compare our BLSA cohort to the 20 nondemented subjects reported by Crystal et al. (12), of which half had >15 SP per 200× field in the frontal neocortex. Thus, we believe that differences in the cognitive status of nondemented subjects may explain the discrepancies in densities of neocortical SP observed in our study vs. those of Katzman et al. (20) and Crystal et al. (12). Dickson et al. (14) reported that examination of the brains of 14 nondemented subjects from the Bronx Aging Study showed abundant SP but no NFT in the neocortex in half of the subjects. This cohort is comparable to our BLSA normal subjects in age, BIMC scores, and interval between the last clinical evaluation and death. However, we believe that a potentially important difference exists in the clinical assessment of these two groups of subjects. The clinical status of the Bronx Aging Study was established on the basis of a battery of neuropsychological testing, whereas our subjects were assessed also using CDR, which includes historical information from a reliable informant. It is possible that this historical information, in addition to formal neuropsychological testing, enhances sensitivity for the detection of subtle cognitive decline.

Studies that have reported significant densities of neocortical SP in nondemented subjects have primarily used thioflavin S staining and Aβ immunocytochemistry, whereas we used primarily the Hirano modification of the Bielschowsky silver method. This staining technique also detects intra- and extracellular NFT (44). In our experience, the Hirano silver method is more sensitive for the detection of SP than thioflavin S or Aβ immunostaining; therefore, false negatives are likely to be ruled out. An additional methodological complication is that, in some studies (11,14), plaque...
counts are expressed as SP per 200x field, whereas, in other reports (ours included), counts are expressed as SP per mm².

All cases diagnosed as being cognitively abnormal revealed a widespread distribution of sparse-to-frequent numbers of neuritic SP, many of which contained amyloid cores that met the histological criteria for the diagnosis of definite or borderline AD, with one exception (case No. 1055), which was diagnosed as hippocampal sclerosis (10). These observations parallel those of Morris et al. (29), who described abundant SP in individuals with a CDR of 0.5 and concluded that, at the time when dementia is minimal, the neuropathology of AD is already firmly established. For example, case No. 890, who had a BIMC score of seven, which falls within the nondemented category in the Bronx Aging Study (12, 20), had high counts for all histopathological lesions characteristic of AD, including NFT in the parietal and occipital cortices. These observations are important, because they may explain previous reports of SP and amyloid deposition in older subjects with allegedly normal or borderline cognitive status.

In the BLSA cohort, we have identified two major categories of neocortical pathology of increasing severity and assigned them tentative clinical correlates: in the first category, the cortex is virtually free of SP and, if present, SP are of the diffuse type and distributed in isolated foci. In this category, individuals (mean age 82.15 years) have low BIMC error scores (< 3) and a CDR of 0. The second category is characterized by widespread diffuse and neuritic SP in neocortex in numbers sufficient to fulfill the neupathological criteria for AD or borderline AD (23,27). In these cases, neuropil has tau-positive threads and in some cases few NFT. This second pathological category includes primarily individuals (mean age 90.5 years) who are demented or in the early stages of dementia (CDR ranging from 0.5 to 3) and, in some cases, cognitively normal subjects (mean age 87.5 years) with stable BIMC error scores of < 3 and a CDR of 0. The number of subjects reported in the present study is relatively small and does not allow us to draw conclusions regarding the potential transition between categories. However, based on the commonality of their lesions (i.e., widespread neuritic SP) and the increase in mean ages, the cognitively intact and mildly demented subjects within the second category may constitute a clinical-neuropathological continuum.

We noted limited, although consistent, neurofibrillary pathology in the entorhinal cortex and hippocampus of all brains examined independently of the degree of neocortical pathological changes. These changes were more severe in individuals with abnormal cognitive evaluations. Less consistently, some degenerative changes were also present in the amygdala. These observations are consistent with previous reports in the literature (9).

In view of the high prevalence of lesions of entorhinal cortex and hippocampus in older subjects with normal scores on the BIMC, it is possible that because of the redundancy and/or plasticity of the neuronal circuitry involved, these lesions may not result in overt cognitive defects (4) but in perturbations that are below the sensitivity of neuropsychological instruments being used. Thus, further research in the detection of subtle neuropsychological deficits in the elderly appears to be warranted.

We conclude that the neocortex of the majority of cognitively normal individuals can remain free of Aβ or SP even into the tenth decade of life. Nevertheless, older individuals also appear to be at high risk for developing degenerative changes of the brain. Although NFT in hippocampus and entorhinal cortex are relatively common in older subjects, independent of cognitive status, significant neocortical neuritic SP and Aβ deposition are uncommon in cognitively intact individuals, and these lesions occurred in only two subjects in our study. Because this percentage falls within the range (~ 15%) of reported prevalences of AD in the population > 85 years of age (3), it is possible that, as proposed by previous studies (11,20), neocortical amyloid deposition in these subjects corresponds to a preclinical stage of AD in individuals who can tolerate a certain degree of neurodegenerative changes without obvious cognitive decline.

ACKNOWLEDGEMENTS

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