Regional Distribution of Neuritic Plaques in the Nondemented Elderly and Subjects With Very Mild Alzheimer Disease

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Background: Identification of the neuropathological lesions that are most closely associated with the earliest symptoms of Alzheimer disease (AD) is crucial to the understanding of the disease process and the development of treatment strategies to affect its progress. Do the classical neuropathological lesions of AD precede, follow, or occur in synchrony with the earliest signs of cognitive deterioration?

Design and Outcome Measures: We examined the extent of neuritic plaque (NP) formation in 5 neocortical regions and the hippocampus, entorhinal cortex, and amygdala in 66 elderly subjects with no dementia, questionable dementia, or mild dementia as assessed using the Clinical Dementia Rating Scale (CDR).

Setting and Patients: Postmortem study of nursing home residents.

Results: Even questionable dementia (CDR, 0.5) was associated with a significant (P = .04) increase in neocortical NP density. The density of NPs increased further with increasing dementia severity in all brain regions examined. However, subjects with questionable dementia or definite but mild dementia did not differ significantly from each other. Density of NPs was nearly maximal in subjects with moderate dementia (CDR = 2.0), suggesting that other neuropathological changes may be responsible for cognitive deficits beyond this level. Dementia severity correlated significantly with the density of NPs in all brain regions examined (r range, 0.47-0.56; P < .001), even when subjects with a CDR of 0 were excluded.

Conclusions: These findings are consistent with the hypothesis that NPs are among the earliest neuropathological lesions in AD. Even very mild or questionable dementia is associated with increased density of neocortical NPs that do not distinguish between clinically questionable vs definite dementia.

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A critical question in understanding the classic neuropathological features of Alzheimer disease (AD), ie, neuritic plaques (NPs) and neurofibrillary tangles (NFTs), is whether they precede, follow, or occur in synchrony with the earliest and mildest signs of cognitive deterioration. Although formal neuropathological diagnostic criteria for AD rely almost exclusively on the density of neocortical NPs, and although the neuropathological and molecular biological features of NPs are under intense study, the relationship of NPs to the earliest cognitive impairments in AD has remained largely unexplored. The development of appropriate research and therapeutic strategies for AD depends on the identification of the earliest neuropathological and clinical manifestations of the disease. A small number of studies have investigated the association between NPs and psychometric measures of cognition. Only a few reports have studied NPs in the very mild stages of dementia and determined whether their accumulation in the brain is related to the emergence of cognitive symptoms of the disease.

The study of the relationship between measures of cognitive function and classic AD-related neuropathological lesions conducted by Blessed et al is among the most widely cited examinations of this nature. This study found a robust correlation between NP counts, averaged across 12 cortical regions, and scores on a comprehensive neuropsychological dementia scale. The average density of cortical NPs increased as a function of increasing severity of dementia. Although subjects with a broad spectrum of cognitive deficits were included, the question of the earliest neuropathological manifestations of cognitive deterioration was not ad-

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SUBJECTS AND METHODS

SUBJECTS

Sixty-six subjects were included in this postmortem study as the principal cohort. The subjects were selected from a large group of 278 residents of the Jewish Home and Hospital for Aged (JHHA) in Manhattan, NY, and Bronx, NY. The JHHA is academically affiliated with The Mount Sinai School of Medicine, New York, NY. Because our aim was to identify the relationship of NPs to early and mild dementia, only those subjects with CDR scores of 0 to 2.0 were included. The cohort included in our analysis was obtained as part of a larger clinical and epidemiological study of early AD. All assessments were approved by the JHHA and The Mount Sinai School of Medicine institutional review boards. Autopsies were performed after receiving consent from each subject’s legal next of kin. As part of that study, all consenting residents and new admissions to the JHHA are given mental status screening tests, and more detailed clinical evaluations are performed for patients who are not demented or who have mild cognitive impairment. The JHHA staff routinely request permission for autopsy on all residents who die, irrespective of whether they have undergone psychological testing. Consequently, many of the subjects included in this series died without receiving neuropsychological testing. However, detailed clinical records are available on all residents, and research staff conducted detailed interviews with staff and family caregivers to obtain information about the antemortem functional and cognitive status of the patients. All neuropathological evaluations were performed before the selection of our study cohort, and all neuropathological variables were assessed without knowledge of the subject’s cognitive status. The subject’s age at death, cognitive status, and other relevant clinical information were used to arrive at a final neuropathological diagnosis after the objective variables had been assessed. The subject selection criteria were based on neuropathological and cognitive measures. Initially, all subjects with non–AD-related neuropathological lesions or AD-related neuropathological lesions complicated by other neuropathological lesions of sufficient magnitude to contribute to cognitive dysfunction were excluded from consideration. These neuropathological lesions included, but were not limited to, Pick disease, diffuse Lewy body disease, Parkinson disease, stroke, multi-infarct dementia, and severe cerebrovascular disease. Subjects with mild cerebrovascular disease judged to be insufficient in severity to affect cognitive function were not excluded.

A multistep approach was applied to the assignment of CDR scores based on cognitive and functional status during the last 6 months of life. Initially, a CDR score was obtained following a careful review of all information contained within each patient’s medical chart, including admitting diagnoses, nurses’ notes, social work records, results of psychiatric and neurological consultations, medication histories, results of mental status testing, and all other medical records and laboratory studies. These same records were then reviewed by a second reviewer who was unaware of the initial CDR score and who was experienced in neuropsychological assessment of living elderly patients, and a second independent CDR score was assigned. Subsequently, the second reviewer or another member of the cognitive assessment team conducted telephone interviews with at least 1 family member or caregiver for each subject and assigned a third CDR score. The interrater reliability for 40 subjects undergoing consecutive assessment was high (interclass correlation, 0.88). All 3 CDR scores and all pertinent chart information were subsequently presented to a senior clinician (D.M.), and a consensus CDR score was derived. A subset of the subjects, albeit small, had undergone neuropsychological assessment during life and had participated in longitudinal studies of cognitive function with instruments such as the Mini–Mental State Examination (MMSE) and the Alzheimer’s Disease Assessment Scale. When available, the results of neuropsychological assessments were also considered in deriving the final consensus CDR score. Twenty-two of the 66 subjects had undergone antemortem assessment using the MMSE. The correlation between the consensus CDR score assigned and the MMSE score was −0.48 (P = .03). If only those subjects who had received an MMSE score within 1 year of death were considered (n = 14), then the correlation between the consensus CDR and the last MMSE rose to 0.73 (P = .003).

NEUROPATHOLOGICAL ASSESSMENT

After the subject’s death, consent for autopsy was obtained from the next of kin. A member of the AD brain bank team extracted each brain and extensively photographed the specimen. Any gross abnormalities were noted, and the brain was divided in the midsagittal plane. The right hemisphere was then suspended from the basilar artery in 4% cold (4°C) buffered paraformaldehyde. The left hemisphere was further dissected and snap-frozen. All neuropathological studies were performed on the right hemisphere by 2 of us (D.P.P. and D.P.P.). In some subjects, the left hemisphere was also included for neuropathological study because of gross lesions or suspected neuropathological lesions due to the clinical presentation of specific subjects, but these subjects were excluded from consideration for the studies described herein. Neuropathological assessments were performed after 4 to 6 weeks of fixation. The neuropathological assessment consisted of examining representative blocks from superior and midfrontal gyrus, orbital cortex, basal ganglia with basal forebrain, as well as the principal cortical areas of the cerebral cortex, including the entorhinal cortex, especially within layers II and IV. A small group of subjects with mild dementia. Subjects with even mild dementia (Clinical Dementia Rating [CDR]14,15 range, 0.5–1.0) were found to have profound cell loss in the entorhinal cortex, especially within layers II and IV. An unusual feature of this study cohort was the extensive NP and NFT accumulations that were also
dressed. The results of other studies have not been uniform with regard to the relationship of NPs and cognitive deficits. Some studies have suggested that the density of diffuse plaques is increased in mildly demented subjects,10,12,13 whereas others have failed to observe a relationship between NP accumulation and cognitive impairment.5–11 Recently, Gomez-Isla et al13 reported on stereological neuronal counts of the entorhinal cortex of a small group of subjects with mild dementia. Subjects with even mild dementia (Clinical Dementia Rating [CDR]14,15 range, 0.5–1.0) were found to have profound cell loss in the entorhinal cortex, especially within layers II and IV. An unusual feature of this study cohort was the extensive NP and NFT accumulations that were also
amygda, hippocampus (rostral and caudal levels with adjacent parahippocampal and inferior temporal cortex), superior temporal gyrus, parietal cortex (angular gyrus), calcarine cortex, hypothalamus with mamillary bodies, thalamus, midbrain, pons, medulla, cerebellar vermis, and lateral cerebellar hemisphere. Sections from paraffin-embedded blocks were stained using hematoxylin-eosin, modified Bielschowsky, modified thioflavine S, anti-β-amyloid (4G8 [gift of N. Robakiss, PhD, Mount Sinai School of Medicine]), and anti-tau (AD2 [gift of A. Delacourte, PhD, Unite INSERM 422, Lille, France]). Any subject showing evidence of Lewy body formation in the substantia nigra or locus ceruleus underwent antiubiquitin (Dakka Corporation, Carpinteria, Calif) staining of representative cerebral cortical sections for the identification of cortical Lewy bodies. Immunohistochemical procedures used an avidin-biotin staining procedure with diaminobenzidine detection. All neuropathological data regarding the extent and distribution of neuropathological lesions were collected by neuropathologists unaware of any of the clinical and psychometric data. After all of these data regarding the extent and distribution of relevant neuropathological lesions were collected and entered into the research databases, individual subjects underwent diagnostic neuropathological evaluation. For this process, all clinical, neuropsychological, and laboratory data were evaluated, and a final neuropathological diagnosis was assigned to each subject. Every subject underwent evaluation for the extent of neuropathological lesions using the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropathological battery.

Although the full CERAD neuropathological battery was performed for each subject, only data from examination of the NPs in the hippocampus (CA1), entorhinal cortex, amygdala, midfrontal gyrus, superior and middle temporal gyrus, inferior parietal lobule, and occipital calcarine cortex are presented herein. Multiple high-power fields (5 in general) were examined in each slide, and the density of NPs with and without amyloid cores were rated on a 4-point scale of absent, sparse, moderate, or severe according to the scoring criteria established by CERAD. In addition, quantitative data regarding the density of NPs in the midfrontal gyrus (Brodmann area 9), orbital frontal cortex (Brodmann area 45-47), superior temporal gyrus (Brodmann area 21-22), inferior parietal cortex (Brodmann area 39), and calcarine cortex (Brodmann area 17) were also collected. For these quantitative measures of plaque density, 5 representative high-power fields (0.5 mm²) were examined in each cortical region, and an average density score was calculated for each region and expressed as mean plaque density per square millimeter. Only NPs (with and without cores) were included in the NP counts reported herein. When plaques were unevenly distributed in each slide, plaques in the region with the highest density were counted.

The dependent variables consisted of counts of NPs in the 5 cortical regions described above and CERAD ratings of NP density in the hippocampus, entorhinal cortex, amygdala, midfrontal gyrus, superior temporal gyrus, inferior parietal lobule, and occipital primary visual cortex. Repeated-measures analyses of variance (ANOVA) were used to analyze the NP counts across cortical regions. Newman-Keuls tests were used for between-group comparisons. Because the measures based on CERAD ratings were ordinal in nature, CERAD rating scores were analyzed using Kruskal-Wallis ANOVA for each region. For individual group comparisons, Mann-Whitney U tests were performed when significant overall differences were revealed using the Kruskal-Wallis tests. To determine the correlation between CERAD scores and NP density, Pearson product moment correlations were used for the quantitative NP counts, and Spearman rank order correlations were used for the CERAD rating scores.

final selection

After the completion of the neuropathological studies and assignment of consensus CDR scores, a final consensus conference was held with the participation of most of us (V.H., D.P.P., D.P.P., D.M., K.L.D., and R.C.M.) and the ante-mortem and postmortem assessment team for the selection of subjects for inclusion in our study. Four groups were formed, consisting of subjects with CDR scores of 0 (cognitively intact), 0.5 (questionable dementia), 1.0 (mildly impaired), and 2.0 (moderately impaired). A fifth group was formed from a cohort with CDR scores of 4.0 and 5.0 (severely demented) to provide an extreme comparison group; inclusion and exclusion criteria for this cohort were identical to those described above. The demographic characteristics of the final study cohort are presented in Table 1. Because the focus of the study was on the association of NPs with cognitive deficits, these groups were formed based purely on their CDR scores, without regard to the extent of NP formation. Groups formed based on CDR scores did not differ significantly with respect to age ($F_{3,62} \approx 1.8; P = .15$). Although there were significantly ($P = .006$) more women ($n = 52$) than men ($n = 14$) in the study cohort, the proportion of men and women in the different CDR groups did not differ significantly ($\chi^2 = 0.8; P = .82$).

The principal study cohort consisted of the subjects with CDR scores of 0, 0.5, 1.0, and 2.0). These 4 CDR categories were used as the independent variable for subsequent analyses. Because the aim of our study was to examine the neuropathological features of early AD or mild dementia, data from the extreme comparison group (CDR, 4.0 and 5.0) were not used in any of the statistical tests, but their data are presented in the Table and in Figure 1 and Figure 2 for illustrative purposes.

The dependent variables consisted of counts of NPs in the 5 cortical regions described above and CERAD ratings of NP density in the hippocampus, entorhinal cortex, amygdala, midfrontal gyrus, superior temporal gyrus, inferior parietal lobule, and occipital primary visual cortex. Repeated-measures analyses of variance (ANOVA) were used to analyze the NP counts across cortical regions. Newman-Keuls tests were used for between-group comparisons. Because the measures based on CERAD ratings were ordinal in nature, CERAD rating scores were analyzed using Kruskal-Wallis ANOVA for each region. For individual group comparisons, Mann-Whitney U tests were performed when significant overall differences were revealed using the Kruskal-Wallis tests. To determine the correlation between CDR scores and NP density, Pearson product moment correlations were used for the quantitative NP counts, and Spearman rank order correlations were used for the CERAD rating scores.

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neuropathological features. The range of cognitive deficits was limited to subjects with no dementia or questionable dementia, and not all laboratories would agree with the use of the diffuse plaque measures employed to assign a diagnosis of AD. Nevertheless, subjects classified as cognitively intact had significantly fewer diffuse plaques than those classified as mildly demented. A similar conclusion was reached in an earlier study of a similar cohort of subjects.12

Clearly, there is considerable uncertainty regarding the relationship of NPs to the earliest stages of cognitive impairment and dementia. There is very little information available on the extent and regional distribution of the classic neuropathological index of AD in large cohorts of very mildly demented subjects. Our purpose was to determine the extent and regional distribution of NPs in a group of very elderly nursing home residents who died with cognitive and functional status characteristic of very early or mild AD. The relationship of the density of NPs in various cerebral cortical regions, the hippocampus (cornu ammonis 1), entorhinal cortex, and amygdala as a function of dementia severity. CDR indicates Clinical Dementia Rating Scale.

RESULTS

The NP counts in the 5 cortical regions studied are shown in Figure 1. Analysis of variance revealed that NP density varied significantly as a function of CDR score (F3,61 = 8.7; P<.001) and neocortical region (F4,244 = 2.6; P=.04). Newman-Keuls tests of differences between groups showed that NP density was significantly (P=.04) lower in the group with CDR of 0 compared with each of the other CDR groups in each neocortical region. The occipital cortex was the only region where NP density was not significantly elevated in the group with CDR of 0.5 relative to the group with CDR of 0. More detailed Newman-Keuls analyses showed that the group with CDR of 0.5 did not differ significantly (P=.29) from the group with CDR of 1.0 in any neocortical region, but significant differences existed between the groups with CDRs of 0.5 and 1.0 vs that with 2.0 in all neocortical regions assessed. Nearly identical results were obtained when CERAD rating scores for neocortical NPs were compared using regional Kruskal-Wallis ANOVA, where significant differences existed between CDR groups were observed for each neocortical region (H=13.5 [range, 13.6-19.2]; P<.004 [range, .004 to <.001]). (H indicates the
The results of this study show that the density of neocortical NPs increases significantly when the very first signs of dementia become detectable. With the exception of the primary visual cortex, the density of neocortical NPs was significantly increased, compared with control subjects, even in the very mildly or questionably impaired subjects. This increase in neocortical NP density continued systematically with increasing severity of dementia in all of the brain regions examined. Similarly, the density of NPs in the hippocampus, entorhinal cortex, and amygdala was increased significantly in subjects with CDR ratings consistent with mild dementia relative to subjects who were cognitively intact. This general pattern of results indicates that NPs are present in many brain regions, even in mildly or questionably demented subjects, and that the density of NPs increases in all of the brain regions examined as a function of increasing dementia severity.

With the exception of the occipital cortex, the density of NPs in different neocortical regions was similar at each level of dementia severity. Although the density of NPs increased as a function of increasing CDR score, NP density was similar in the frontal, temporal, and parietal lobe regions examined at each CDR stage. The increase in the density of NPs in the occipital cortex lagged behind the increase in the other cortical regions. Occipital cortex NP density was similar in subjects receiving CDR scores of 0 and 0.5, and became apparent first in those subjects who received a CDR score of 1.0. The similarity of NP density in the different neocortical regions at each CDR stage argues against a clear focus of initial neocortical abnormalities, with subsequent recruitment of other regions as a function of increasing dementia severity. It is possible that such a focus may have existed in a brain region that we did not examine, but this possibility is relatively unlikely. As part of the CERAD neuropathological battery and the general neuropathological evaluation, the Meynert nucleus, substantia nigra, dorsal raphe nucleus, locus ceruleus, lateral cerebellum, cerebellar vermis, thalamus, hypothalamus, and mammillary bodies were all examined. In these regions, NPs were identified in only a few subjects (6 of 37), and all had received CDR scores of 1.0 or 2.0. In these 6 subjects, NPs were identified in the Meynert nucleus only, and NP density was rated as greater than sparse in only 1 subject who had received a CDR score of 1.0. Thus, unlike the results reported by Braak and Braak for the distribution of NPs and NFTs at different stages of neuropathological severity, no neocortical regional variations in NP density as a function of dementia severity could be identified. It is unlikely that neocortical region-specific differences emerge as dementia severity increases beyond that characterized by a CDR rating of 2.0, since perusal of the results presented in Figure 1 fails to reveal such a relationship in the comparison group with CDRs of 4.0 and 5.0.

In general, the densities of NPs in all 8 brain regions examined were highly correlated with the severity of dementia. However, this relationship did not hold for some individuals and is perhaps quite revealing. Five
More robust correlations (Spearman rank order correlation coefficients) show that these discrepancies could be identified even in the groups with CDR scores of 1.0 and 2.0 (3 of 22 and 1 of 15, respectively). One of the subjects with no neocortical plaques and a CDR score of 1.0 had undergone cognitive assessment 6 months before death and had received a score of 18 (of 30) on the MMSE. It is unlikely that the cognitive impairments in these subjects with no neocortical plaques were due to NP accumulation in the hippocampus, entorhinal cortex, or amygdala, since NPs were not identified in any of these regions. Detailed examination of the CERAD neuropathological findings in these subjects failed to reveal any NPs in any of the brain regions examined, including the Meynert nucleus. Of the subjects with CDR scores of 0, 1 subject in particular had an average neocortical density of 12.3 NPs per square millimeter, which was above the average of the subjects receiving a CDR score of 1.0. Clinical and postmortem informant interview records revealed no indication of impaired cognition in this 91-year-old woman who had received an MMSE score of 25 with a 3/3 recall sub-score only 2 months before death. This score places her above average for non-demented community-dwelling persons of similar age and education. This pattern of results suggests that neither neocortical NPs nor mild cognitive deficits necessarily predict each other. On the other hand, the relatively high NP density by CDR score correlation coefficients shows that these discrepancies are not the rule and that, in general, even mild and questionable cognitive deficits are associated with some neocortical NP accumulation.

Severity of dementia and age at death were not related to each other (r = 0.06; P = .53). In the neocortical regions, a slight correlation between increasing NP density in the midfrontal gyrus and age at death was found (r = 0.28; P = .02), but this correlation was weak and was not detected in any of the other 4 neocortical regions. More robust correlations (Spearman rank order correlations) were present between age at death and NP density ratings in the hippocampus (r = 0.39; P = .002), entorhinal cortex (r = 0.37; P = .003), and amygdala (r = 0.27; P = .03). Multiple regression analysis showed that the contribution of age to NP density was greater in the hippocampus and entorhinal cortex than in the amygdala, where the partial correlation with age, after accounting for CDR, was not statistically significant (β = .16; P = .15). In all 3 regions, CDR scores were better predictors of NP density than age at death (partial correlation β range for CDR, .34-.41; β range for age at death, .16-.25). This pattern of results shows that, although the density of NPs may increase as a function of age, this relationship with age is not uniform across brain regions and contributes to NP density less robustly than the severity of dementia.

The results of the correlational analyses of dementia severity and NP density are in general agreement with the findings of Blessed et al., Price et al., and Price, but at variance with some of the other results reported in the literature. The relatively large sample sizes, the focus on subjects with mild dementia, and the rigid criteria used for subject selection are likely to have been instrumental in revealing the relationship between NP density and severity of dementia reported herein. That the correlations between neocortical NP density and cognitive status were even more robust in subjects for whom antemortem MMSE scores were available argues in favor of the relationship between NP density and cognitive function and gives further credence to the results obtained with the CDR scores.

The selection of subjects based on their cognitive status without regard to whether they met neuropathological criteria for AD contributed to our findings. It is clear from Figure 1 that, for most neocortical regions, only minor differences existed in the densities of neocortical NPs of subjects receiving a CDR score of 2.0 and those receiving CDR scores of 4.0 and 5.0 (F1,28 = 1.5; P = .22). In fact, with the exception of the inferior parietal cortex (r = 0.39; P = .38), this impression is confirmed by exploratory post hoc correlational analysis. The correlation between NP density in the various neocortical regions and CDR score for subjects receiving CDR scores of 2.0 and higher were small and not statistically significant (r < 0.26; P = .18). As Figure 1 indicates, the density of NPs in the group with CDR of 2.0 was near the ceiling defined by those with CDRs of 4.0 and 5.0, precluding the possibility of observing significant correlations between both variables. Thus, our results suggest that the density of NPs significantly influences the severity of dementia early in the course of AD, but that other factors must contribute to the progression of dementia beyond that observed in moderately demented subjects. This observation raises the possibility that the failure of some studies to observe robust relationships between NP density and cognitive status may have been due to the relatively advanced state of NP accumulation in their study subjects. Clearly, loss of synapses and pyramidal neurons, neurochemical deficits, and NFT accumulation are likely to contribute to dementia severity in the late and perhaps the early stages of the disease process.

Given that the average age of the subjects studied in the different CDR groups ranged from 83 to 89 years, in general, only those subjects with CDR scores of 2.0 would have meet Khachaturian criteria for AD. A similar argument could be made for the CERAD neuropathological criteria. Only those subjects with CDR scores of 2.0 or higher would meet CERAD criteria for definite AD, whereas subjects with CDR scores of 1.0 would only meet criteria for probable AD. Subjects receiving CDR scores of 0.5 would be classified as healthy with no history of dementia or healthy with a history of dementia, depending on how a CDR score of 0.5 was interpreted. These observations suggest that the conventionally applied cri-
Criteria for AD may be too restrictive, particularly with regard to early disease, and may exclude subjects with adequate NP accumulation to account for their cognitive impairments. These findings raise the possibility that even a moderate density of NPs in the neocortex (more than 5 per square millimeter) is adequate to account for cognitive impairment and that subjects with NP densities in this range may be considered to be in the early stages of AD.

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