Hippocampal Lesions in Dominantly Inherited Alzheimer's Disease

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Abstract. We compared hippocampal lesions in three pedigrees of Familial Alzheimer's Disease (FAD). In these pedigrees, the disease is inherited as an autosomal dominant disorder and has been linked to DNA markers on chromosome 21. In eight cases of FAD (four from one pedigree and two each from two others) we quantified neurofibrillary tangles (NFT) and senile plaques (SP) in hippocampal subvolumes CA1-4, subiculum, presubiculum, and dentate gyrus. We observed consistent patterns of the distribution of lesions: The highest density of NFT and SP was present in CA1-2; virtually no SP or NFT were present in presubiculum; SP diameter was consistently greater in CA4. We found no overall differences among pedigrees in total densities of NFT and SP, but statistical analyses disclosed that an uncommon type of SP was disproportionately present in two pedigrees. This type of SP was usually restricted to CA4, had a marked amyloid core devoid of argyrophilic neurites. These studies also disclosed inter- and intrafamilial heterogeneity of lesion distribution (including congophilic angiopathy and cerebellar plaques) in these three pedigrees.

Key Words: Alzheimer’s disease, familial; Hippocampus; Neurofibrillary tangles; Senile plaques.

INTRODUCTION

Alzheimer's disease (AD), manifested by progressive memory and cognitive deficits, is characterized neuropathologically by a high density of senile plaques (SP) and, to a lesser extent, neurofibrillary tangles (NFT) in amygdala, hippocampus, and neocortex (1–6). Although the sporadic occurrence of AD is more common, a subset of familial cases, particularly those of early onset, has an autosomal dominant pattern of inheritance (7–12). The chromosomal location of the abnormal gene(s) is not clear. In four pedigrees of early onset familial Alzheimer's disease (FAD) the disease has been linked to a region near the centromere of chromosome 21 (13), although in another study, of a more heterogeneous population, linkage to 21 was not demonstrated (14). Genetic predisposition is further complicated by studies of monozygotic twins discordant for neuropathologically confirmed (15) or clinically suspected AD (16). Hence, it appears that non-genetic factors may play a role in the expression of AD. This study was performed to analyze the variability in the presentation of the neuropathologic lesions of FAD.

We quantified SP and NFT in hippocampus both within and among families in

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Supported by USPHS Grants NIH AG05146 and AG03359.
three autopsy-proven pedigrees of FAD where linkage to chromosome 21 has been reported (13). Distribution and densities of SP and NFT were homogeneous among the three pedigrees. However, one type of lesion, plaques with amyloid cores, was distributed differentially among pedigrees, suggesting that other factors, perhaps genetic, may modify the expression of the pathologic lesions of AD. In addition, SP in the cerebellum and congophilic angiopathy were variably found in these cases of FAD.

MATERIALS AND METHODS

Initially we evaluated slides from fifteen dominantly inherited, autopsy-proven cases of FAD obtained by one of us (RJP). Autopsies were performed between 1966 and 1987. Because medial temporal cortex is severely affected in AD and contains multiple subregions with varying susceptibility to the lesions of AD (1, 17, 18), paraffin-embedded blocks, formalin fixed, wet tissue or unstained slides of this region were selected for quantitative analysis. In addition, as many other possible brain regions as were available were inspected. For inclusion in this study, sections of hippocampus had to be available from at least two members from each pedigree; three separate pedigrees met this criterion. Eight cases were selected for quantitative study. The pedigrees selected corresponded to three of the four families (pedigrees 1, 2, and 4) in which the disease was linked to a marker on chromosome 21 (13); four cases were from a Canadian pedigree (#1), two cases were from a German pedigree (#2), and two cases were from an Italian pedigree (#4). Clinical characteristics of these cases are shown in Table 1. In addition, two more cases (one each from pedigrees #1 and #4) became available for evaluation after the quantitative part of this study was completed. These cases were evaluated but not quantified. Observations from these cases are included.

Histological Stains

In seven cases, paraffin-embedded blocks of hippocampus and other brain regions (see Results) were sectioned (10 μm) and stained with: hematoxylin & eosin (H&E), cresyl violet, Naoumenko-Feigen silver stain (19) combined with periodic acid Schiff (NF-PAS), and Congo red stain for amyloid. In one case, (BRC 309), unstained sections (ca. 15–20 μm thick) of the complete temporal lobe, frontal pole, and cerebellum were available; these sections were stained by NF-PAS and H&E. Six of the eight hippocampi were sampled at the level of the lateral geniculate nucleus (LGN). Case #369 was slightly caudal to the LGN and #370 was rostral to the LGN but caudal to the pes. During the neuropathological analysis and quantitation the individual performing morphometric analysis (RGS) did not have access to information concerning pedigree status.

Nomenclature of Subdivisions of Hippocampus

Based on studies of primate hippocampus (20–24), the following subdivisions of hippocampus were identified: CA1–2, CA3, and CA4; dentate gyrus; subiculum; and presubiculum (Fig. 1). Nissl-stained sections were used to define the boundaries of each subdivision. Although the dentate gyrus and molecular layer are readily delineated, precise divisions between CA3–4, CA2–3, CA1–2, and subiculum–CA1 have been the subject of some controversy. CA4 was defined as that region subjacent to the granule cell layer; the division between CA4 and CA3 was operationally defined as the region where tightly packed pyramidal cells characteristic of CA3 replaced multipolar neurons characteristic of CA4. The CA3 border with CA1–2 was identified as the site where the monolayer of pyramidal cells of CA3 was replaced by a wider arrangement of pyramidal neurons. For analysis, no attempt was made to define a separate CA2 division because of the difficulty of defining its boundaries. The beginning of the subicular region was defined as the region where a deep layer of Nissl-rich neurons appeared. The junction of the subiculum and presubicular region was defined by the presence of a population of small, superficially placed neurons.
TABLE 1
General Information on FAD Members

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at onset (years)</th>
<th>Age at death (years)</th>
<th>Tissue samples*</th>
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<tr>
<td>Canadian (#1)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>299</td>
<td>M</td>
<td>40</td>
<td>53</td>
<td>Paraffin blocks</td>
</tr>
<tr>
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<td>58</td>
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<td>Fixed brain</td>
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<td>Fixed brain</td>
</tr>
<tr>
<td>Mean duration</td>
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<td>German (#2)</td>
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<tr>
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<td>F</td>
<td>44</td>
<td>48</td>
<td>Slides</td>
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<td>369</td>
<td>M</td>
<td>53</td>
<td>61</td>
<td>Fixed brain samples</td>
</tr>
<tr>
<td>Mean duration</td>
<td></td>
<td>6.0 years</td>
<td></td>
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<td>F</td>
<td>40</td>
<td>51</td>
<td>Paraffin blocks</td>
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<tr>
<td>372</td>
<td>M</td>
<td>39</td>
<td>53</td>
<td>Fixed brain samples</td>
</tr>
<tr>
<td>396</td>
<td>M</td>
<td>49</td>
<td>58</td>
<td>Paraffin blocks</td>
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<tr>
<td>Mean duration</td>
<td></td>
<td>11.3 years</td>
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</table>

* Tissue samples available from each case. Fixed brain included either one-half or the complete brain. “Fixed brain samples” included small cortical pieces fixed in 10% formalin. Slides from one case (#309) were unstained coronal sections of temporal lobe at hippocampal and amygdalar level, frontal pole, brainstem at the level of the inferior olives and midbrain at the level of the pons.

NFT and SP

Neurofibrillary tangles (NFT) were easily recognized by argyrophilia and characteristic shape (Fig. 2A). SENile plaques (SP) were easily recognized in the NF-PAS stain by the presence of argyrophilic neurites associated with varying amounts of PAS-stained amyloid. Two subcategories of SP were defined: Type I comprised 94% of SP found in the hippocampal formation and were characterized by an amorphous appearance with PAS-stained amyloid intermixed with neurites (Fig. 2A). In contrast, Type II SP displayed a conspicuous amyloid core devoid of argyrophilic neurites, but usually surrounded by multiple argyrophilic neurites. Within this general category, two types of Type II plaques could be distinguished: those with a PAS-stained amyloid core with a diameter of ca. 20 µm, (Fig. 2B) and those with a star-like core with few neurites (Fig. 2C). Comparison of adjacent Congo red stained sections examined with polarized light displayed the yellow-green birefringence characteristic of amyloid in these cores.

Computer Assisted Analysis of Distribution of NFT and SP

NFT and SP were quantified using a Loats Image Analysis System (Loats Associates Inc., Westminster, MD), an IBM-PC AT-based image analysis system interfaced with a mechanical stepping microscope stage. The initial step in analysis was to delimit subregions of the hippocampus at low power (×10). The boundaries were marked on the Nissl-stained slide coverslip. The marked slide was then apposed to the silver-stained slide and the boundaries copied. Then, using the image analysis system, each separate sub-boundary on each slide was entered (i.e. CA1–4, etc.). We mapped NFT (×400) and SP (×250). Each sub-boundary was divided automatically into windows, smaller than the field of view, preventing double counting of objects. For SP quantitation, window size was 0.097 mm² and for NFT it was 0.041 mm². Following quantitation within a window, the stepping stage moved to the next window. The
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Fig. 1. Normal hippocampus with subdivisions within hippocampus and medial temporal lobe. Arrowheads mark transition zones between subdivisions. Abbreviations: F, fornix; FD, fascia dentata; SUB, subiculum; PSUB, presubiculum. Bar: 1 mm.

The number of fields to completely map a sub-boundary ranged from thirteen (CA3 case #299) to 205 (CA1–2, case #369). For NFT, an operator-selected optical density (OD) was chosen to include the complete NFT. Each NFT was marked with a cursor pad, and automatically the outline, based on the selected OD, was drawn. When necessary, hand editing was used to separate two NFT. Because of the heterogeneous nature of SP (i.e., there was no consistent OD border between SP and neuropil), automated selection could not be used; the outline of each SP was drawn by hand. Only one observer (RGS) performed quantitative analysis.

Statistical Analysis

Repeated-measures analysis of variance (ANOVA) was used with pedigree as the independent measure and hippocampal region as the repeated factor. For SP, density and size within a region were analyzed. The analysis of size was performed initially on data combining both Type I and Type II plaques. This pooling was justified as Type II SP were uncommon, and, in many regions, none were seen, thus making 'missing data' a significant problem. After this initial combined stage, density analysis was performed separately for Type I and Type II SP because statistical analysis suggested they were not correlated ($r = 0.42$; non-significant). For
Fig. 3. Cases #299 (A, B) and #304 (C, D) show variability of neuronal loss within the same pedigree. NF-PAS staining disclose SP and NFT in CA1–2 of both cases (A, C). However, Nissl stains (B, D) of adjacent sections disclose marked neuronal loss in case #299 (B), but less in case #304 (D). Abbreviations: A, alveus; P, pyramidal layer; R, stratum radiatum. Bar: 50 μm for A–D.

NFT, only density is reported; analysis disclosed no statistically significant differences in NFT size among various regions or many pedigrees (data not shown).

RESULTS

Diagnostic Studies

All cases fulfilled the clinical criteria for a diagnosis of probable Alzheimer’s disease (25). In all cases, SP were abundant (>15/mm²), as were NFT, in multiple cortical regions exceeding the guidelines for “definite” AD (26). Two cases (#299, #372) had severe loss of pyramidal neurons in Sommer’s sector; the other cases displayed less neuronal loss in this region (Fig. 3).

Granulovacuolar degeneration was found in all cases but the distribution varied as a function of perikaryal loss. In cases where few or no pyramidal neurons were present in CA1, GVD were found in CA3. Otherwise, they were found in CA1 with few or none in CA3. Clearly identifiable Hirano bodies were found in all cases save those with severe loss of CA1 neurons.

Fig. 2. Different types of senile plaques (SP). Naoumenko-Feigen-PAS (NF-PAS)-stained sections. A. A Type I SP with both argyrophilic elements and pink-stained amyloid (confirmed with Congo red) but a core is not apparent. Several argyrophilic NFT (arrows) are visible (CA1–2 of Case #306). B. Type II SP with marked core, surrounded by argyrophilic neurites (CA4 of Case #309). C. Type II plaque is shown with few neurites but a marked accumulation of amyloid (CA4 of Case #370). Bar: 20 μm for A, B, C.
TABLE 2  
General Neuropathological Features

<table>
<thead>
<tr>
<th>Case</th>
<th>SP*</th>
<th>NFT†</th>
<th>DENSITY‡</th>
<th>Vascular amyloid§</th>
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<td></td>
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<td>II</td>
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<td></td>
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</tr>
<tr>
<td>299</td>
<td>26.9</td>
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</tr>
<tr>
<td>304</td>
<td>9.9</td>
<td>18.5</td>
<td>0.6</td>
<td>0.0</td>
</tr>
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<td>305</td>
<td>12.7</td>
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<td>306</td>
<td>33.1</td>
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<td>2.2</td>
<td>0.6</td>
</tr>
<tr>
<td>593</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
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<td></td>
</tr>
<tr>
<td>309</td>
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<td>2.5</td>
<td>6.0</td>
</tr>
<tr>
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<td>5.2</td>
</tr>
<tr>
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<td>62.9</td>
<td>12.2</td>
<td>2.6</td>
</tr>
<tr>
<td>596</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
</tr>
</tbody>
</table>

* Maximal density (per mm²) of senile plaques; in all cases in the CA1–2 subdivision.
† Maximal density (per mm²) of neurofibrillary tangles (NFT), in all cases in the CA1–2 subdivision.
‡ Density (per mm²) of Type I and Type II SP in CA4.
§ Hippocampal vascular amyloid rated by one author (JCH) as to presence in leptomeningeal vessels (L), and focally (P) or widespread (P+) in parenchymal vessels.
N/A: Sufficient tissue not available for analysis.
N/D: Quantitative analysis of SP and NFT densities not done on these cases obtained late in the study.

Congophilic angiopathy was present in all cases, but no pattern emerged for more severe lesions in one pedigree than in another (Table 2). Spherical cerebellar plaques were present in all members of pedigree #1 with cerebellar tissue available. In contrast, in pedigree #2, case #369 displayed numerous cerebellar SP; #309 had none, in spite of full coronal sections of cerebellum at both the mid-pontine level and at the level of the inferior olives. The distribution and the lack of radiating fibers from the amyloid core in those cases with SP were features against these being Kuru-type SP. While no cerebellar SP were found in pedigree #4, so little tissue was available for evaluation that conclusions were not warranted.

Total hippocampal area ranged from 15.4 to 48.4 mm². Statistical analyses did not disclose any differences among the pedigrees (F = 0.25, df = 2.5; NS) nor was there an interaction between sub-region and pedigree (F = 1.13, df = 10.25; NS). Hence differential hippocampal shrinkage among families was not detected.

Densities of NFT

Among pedigrees no significant differences were found in the total density of hippocampal formation NFT (F = 0.08, df = 2.5; NS). Significant differences in regional distribution of NFT were found (F = 41.46, df = 4.20; p < 0.01); CA1–2 had higher densities than any other region, with densities ranging up to 63 NFT/mm². Other regions did not differ statistically from one another (Figs. 4A, B and 5A). Interaction between pedigree and region was not significant (F = 0.97, df = 8,20; NS). Also, statistical analysis disclosed no size differences in NFT among regions or pedigrees (mean area ranged from 69–169 μ²).
Fig. 4. Distribution of NFT (A, B) and total SP (C, D) in hippocampal formation of two FAD cases (the case is noted on the figure). The absence of apparent pathological change in presubiculum is striking, as is the marked decrease in lesion density in CA3 and CA4. Abbreviations: FD, fascia dentata; SUB, subiculum; PSUB, presubiculum.
Densities of Senile Plaques

The highest density of Type I SP was seen consistently in the CA1-2 region, with a general decreasing density of SP on either side of this region (Figs. 4C, D and 5B). ANOVA disclosed no pedigree differences in the density of SP (F = 0.59, df = 2.5; NS) nor was there a differential regional distribution by pedigree (F = 0.79, df = 10.25; NS). A statistically significant pattern of distribution of SP was found (F = 20.34, df = 5.25; p < 0.01). Post hoc testing (Tukey's HSD test) (27) disclosed that CA1-2 had a higher density of SP than any other region. Subiculum and dentate gyrus had an approximately equal density which was greater than CA3, CA4 or presubiculum. The latter three areas did not statistically differ among themselves.

Analysis of Type II SP densities did disclose pedigree differences (Table 2; Fig. 5C). Pedigrees #2 and #4 had significantly more Type II SP than pedigree #1 (F = 177.83, df = 2.5; p < 0.01). The highest density of Type II SP was found in CA4 (F = 38.57, df = 5.25; p < 0.01). Finally, the interaction term of pedigree by region showed that Type II plaques were primarily found in CA4 (F = 9.64, df = 10.25; p < 0.01) in pedigrees #2 and #4.

The sizes of SP were not different among pedigrees (F = 0.90, df = 2.5; NS), nor did pedigrees differ among themselves as a function of region (F = 0.35, df = 8.20; NS). Senile plaque sizes did vary according to hippocampal regions (F = 5.81, df = 4.20; p < 0.01); post hoc testing disclosed that the average area (ca. 4,000 μm²) of SP in CA4 was larger than that of any other region (Fig. 5D).

DISCUSSION

The current study focused on three well studied pedigrees of AD (11, 12) from which we were able to obtain tissue from multiple members. The goal was to determine which neuropathologic characteristics of FAD were common to all pedigrees, presumably reflecting a genetic abnormality, and which varied within pedigrees, presumably representing determinants not directly associated with the FAD gene. The hippocampus was selected for quantitative analysis because of its putative role in the memory deficits characteristic of AD and for its characteristic regional distribution of lesions.

The distribution and density of NFT was comparable to that previously reported (17, 18, 28) and differences within families were as great as those among families. The higher density of SP in CA1 than in subicular cortex is not congruent with a report suggesting that subicular densities are greater than CA1 (29). The reason for this discrepancy is unclear and may represent differing hippocampal nomenclature, the older age of their cases, or the much higher densities in CA1 that we encountered in these cases. Our average subicular density was comparable to this report, but our CA1 density was much higher (Fig. 5B).

Other neuropathologic markers associated with AD were similar to NFT and total SP populations in that they did not assort by family (30). Severity of perikaryal loss, granulovacuolar degeneration (GVD) and Hirano body formation, congophilic angiopathy and spherical cerebellar SP did not discriminate among the pedigrees, nor could these factors be related to age of onset or duration of disease (Tables 1 and 2).

One relatively uncommon type of SP, our Type II category, did significantly assort by pedigree. Pedigree #1 displayed very few SP with neurite-free cores in CA4 compared to pedigrees #2 and #4. While some SP in pedigree #1 met the operational criteria of a Type II SP (i.e. a neurite-free core), these cores stained much less intensely than those in pedigrees #2 and #4 and were evenly distributed throughout the hip-
Fig. 5. Density of NFT (A), Type I SP (B), Type II SP (C) and distribution of SP diameters (combining type I and II—see text) in D. In A, NFT are principally found in CA1–2 (Sommer's sector). The FD is not shown as no NFT were found there. Type I SP (B) are most common in CA1–2, with SUB and FD displaying a lower density; Type I SP are rare in PSUB. Type II SP (C) are most common in CA4. Each pedigree is charted separately; pedigrees #2 and #4 have significantly more SP than pedigree #1 and preferentially in CA4. The ordinate is expanded in C compared to B. As shown in D, the diameter of all SP was greatest in CA4. In both C and D the PSUB is not plotted as there are no Type II SP there, and in some cases, no SP, making areal estimates inaccurate.

Hippocampal regions sampled. In contrast, pedigrees #2 and #4 both displayed significantly more Type II SP than did pedigree #1, and when present, these SP were almost exclusively found in CA4. This selective distribution was confirmed by inspection of the two cases obtained after the quantitative project was completed; each could be assigned blindly to the appropriate pedigree. Finally, it is worth mentioning that most Type II SP of pedigree #2 and pedigree #4 were slightly different, with the circular core (Fig. 2B) characteristic of #2 and the starburst of #4 (Fig. 2C). However, the small sample size from the two pedigrees restricts further conclusions. In another study of thirty clinically characterized cases of AD, we found that approximately 75% of cases have Type II SP in CA4 (31). Hence, this type of SP is uncommon only by their generally low density in hippocampus.

Factors predisposing to the formation of the Type II SP are unknown. In the present observations, evolution (32, 33) of Type I plaques, with diffuse amyloid, to amyloid-rich Type II SP appears unlikely. Type II SP are significantly present in only two of the three pedigrees, even though total SP density among pedigrees was not different. Further, an evolution from Type I SP to Type II would predict Type II SP to be more common in regions with higher SP densities. This was not the case; the highest density of Type I SP was found in CA1–2 while Type II SP were found in CA4. Finally, the duration of disease (Table 1) and vascular amyloid (Table 2)
do not appear to be related to Type II SP. Therefore, evolution of SP types does not appear to be a correct explanation.

It is unclear why Type II SP were preferentially found in CA4. Gene(s) coding for amyloid, reported to be localized on chromosome 21 (34–36), but separate from the gene associated with AD (34, 35), could show regional specific expression (37). Vascular associations with SP formation are another possibility (38). Bell and Ball (39) reported that the density of hippocampal vasculature is greater in CA1 than in CA4, where we find the majority of amyloid-rich cores. The precise relationship between vascular elements, SP formation and amyloid deposition is unclear (38, 40), but vascular elements and the dynamic of amyloid deposition may interact to determine the final form of the SP. Finally, subtle genetic variation in hippocampal formation afferents are well known in rodents (41, 42), and perhaps such variations in human patients might underlie the pathologic presentation of these cases.

Cases of multigenerational-, neuropathologically-confirmed FAD represent only a small proportion of AD (see 43) but they present a unique opportunity to appreciate the genetic contribution to the clinical and neuropathological expression of the disease. Delineation of characteristic lesions observed in cases of genetic AD may serve as a comparative base for determining factors that lead to the histopathologic lesions used in the diagnosis of AD.

ACKNOWLEDGMENTS

We thank Drs. P. Scott Becker, Michael D. Applegate and Lary C. Walker for helpful discussions. We also thank Dr. Richard H. Meyers of Boston University, Department of Neurology, for obtaining tissue in one case and Molly Lange and Lisbeth Raskin for invaluable assistance.

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(Received July 18, 1989/Accepted May 8, 1990)
MS 89-51