Stable Size Distribution of Amyloid Plaques Over the Course of Alzheimer Disease

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Abstract

Amyloid β plaques are a key pathologic feature of Alzheimer disease (AD), but whether plaque sizes increase or stabilize over the course of AD is unknown. We measured the size distribution of total immunoreactive (10D5-positive) and dense-core (Thioflavin S–positive) plaques in the temporal neocortex of a large group of subjects with AD and age-matched plaque-bearing subjects without dementia to test the hypothesis that amyloid plaques continue to grow along with the progression of the disease. The size of amyloid β (10D5)–positive plaques did not differ between groups, whereas dense-core plaques from the group with AD were slightly larger than those from the group without dementia (~25%–30%, p = 0.01). Within the group with AD, dense-core plaque size did not independently correlate with duration of clinical disease (from 4 to 21 years, p = 0.68), whereas 10D5-positive plaque size correlated negatively with disease duration (p = 0.01). By contrast, an earlier age of symptom onset strongly predicted a larger postmortem plaque size; this effect was independent of disease duration and the presence of the APOEε4 allele (p = 0.0001). We conclude that plaques vary in size among patients, with larger size distributions correlating with an earlier age of onset, but plaques do not substantially increase in size over the clinical course of the disease.

Key Words: Alzheimer disease, Amyloid plaques, APOE genotype, Dense-core plaques, Plaque growth, Plaque size.

INTRODUCTION

Despite the substantial body of evidence supporting its central role in the pathophysiology of Alzheimer disease (AD), the dynamics of the amyloid β (Aβ) peptide deposition in vivo remain largely unknown. Aβ is an amphilic aggregation-prone peptide with 40 or 42 amino acids resulting from the sequential proteolytic cleavage of the amyloid precursor protein (APP) by the enzymes β- and γ-secretases. In vitro studies using synthetic Aβ peptides have established that the formation of Aβ fibrils similar to those present in senile plaques is a nucleation dependent rather than a linear polymerization process. According to this in vitro model, the growth or elongation of Aβ fibrils can only occur above a certain critical concentration of Aβ and is preceded by the formation of nuclei or seeds identified as intermediate soluble oligomeric species or protofibrils. This nucleation or lag phase is rate limiting, with its duration depending on the concentration of the Aβ peptide, but it can be dramatically shortened by the presence of preformed Aβ seeds.

Experiments in vivo have generally confirmed these predictions. Injection of exogenous Aβ “seeds” accelerates plaque deposition in the cortex of APP-overexpressing mice after a lag time of more than 1 month that presumably is necessary for the seeding of endogenous Aβ. Our direct observation of plaque formation in these mouse models by in vivo multiphoton microscopy revealed that plaques form quickly and grow to a mature, stable size within days (8, 9); however, other mouse studies have recently reported that plaques can grow over the course of weeks to months (10–13). Whether amyloid plaques continue to grow, or stabilize, in the course of human AD is critical to understand the dynamics of Aβ in vivo. A number of previous autopsy studies on the progression of amyloid deposition established that the cross-sectional area covered by amyloid immunoreactivity plateaus soon after symptom onset (14–19). Most longitudinal amyloid PET studies conducted at different stages of the disease have supported this conclusion (20–24) (see also Jack et al [25] and the placebo groups in Rinne et al [26] and Ostrowitzki et al [27]). On the basis of these findings, we hypothesized that plaque growth would parallel the saturation of amyloid burden. To test this hypothesis, we examined the plaque size distribution in the temporal associative neocortex of patients with AD with a wide range of disease duration—over 2 decades. We observed that plaque size does not substantially increase over the clinical course of AD and, in fact, is similar in patients with AD and age-matched individuals without dementia with amyloid deposits noted at
postmortem evaluation. The size of the subset of plaques detected with Thioflavin S ([Thio-S], dense-core plaques) also remained stable throughout the clinical progression of AD, but a small increase was observed in the transition between “normal” aging and early symptomatic AD. Taken together, we conclude that plaques reach a stable size distribution and do not substantially grow over decades. Interestingly, however, the absolute average plaque size does vary among individuals and correlates best with age of symptom onset, leading us to speculate that risk factors that predispose to an earlier onset might also predispose to a larger plaque size.

**MATERIALS AND METHODS**

**Subjects**

Ninety-one patients with sporadic AD were selected on a consecutive fashion from the Massachusetts Alzheimer Disease Research Center Brain Bank based on tissue availability and good quality of clinical information. Twelve control subjects without dementia but with sufficient number of amyloid plaques were included in the analyses for comparison purposes. Study subjects were from the Massachusetts General Hospital Memory Disorders Unit. Relevant clinical information such as age of symptom onset and duration of illness was obtained from the clinical records. The Massachusetts General Hospital Institutional Review Board approved the study protocol. Demographic characteristics of the subjects are depicted in Table 1. All patients with AD fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association’s criteria for probable AD (28) and the NIA-Reagan criteria for high likelihood of AD (29). The control group without dementia included 1 subject with a formal diagnosis of mild cognitive impairment shortly before death (30). This subject was annually evaluated over 8 years and scored 0.5 in the Clinical Dementia Rating (CDR) scale in his last 2 visits, with a CDR sum of boxes of 5 in his last evaluation 8 months before death (31). The neuropathologic assessment revealed mild AD changes consisting of sparse to moderate neuritic plaques and a Braak stage II of neurofibrillary tangles, consistent with a NIA-Reagan category of a low likelihood of AD. The remaining control subjects without dementia did not meet the pathologic diagnostic criteria for any neurodegenerative disease. Cases with cerebrovascular disease considered severe enough to contribute to the dementia syndrome or with Lewy body pathologic disease were excluded.

**Brain Specimens and Histological Procedures**

The temporal association cortex (BA 38) was chosen because previous neuropathologic and amyloid PET imaging studies have shown that this is a region of early amyloid deposition, thus enabling the measurement of plaque size in both subjects without dementia and patients with early stages of AD dementia (22–25, 32, 33). Eight-micrometer-thick paraffin-embedded sections were deparaffinized and immunostained for Aβ using the 1D5 mouse monoclonal antibody (Elan Pharmaceuticals, Inc., South San Francisco, CA) and the peroxidase-DAB method, as previously described (19). Nearly adjacent temporal sections from a subset of 40 AD subjects and 9 controls without dementia (including the subject with mild cognitive impairment) were deparaffinized and stained with Thio-S (Sigma, St Louis, MO) 0.05% in 50% ethanol for 8 minutes, and then coverslipped with Vectashield mounting medium containing 4,6-diamidino-2-phenylindole (Vector Laboratories, Burlingame, CA). This AD subset (n = 40) was selected from the original group (n = 91) based on a wide range of clinical disease duration (≤5 years, n = 10; 6–10 years, n = 10; 11–15 years, n = 10; 16–20 years, n = 10), whereas the subset of controls without dementia (n = 9) was selected from the original control group (n = 12) based on the presence of a sufficient number of dense-core plaques. Both subsets were representative of their corresponding groups according to their demographic characteristics (Table 1); the AD subset was also comparable to the entire group with AD with respect to neuropathologic quantitative measures of cortical thickness, amyloid burden, neurofibrillary tangles, and astrocytic and microglial responses (19).

**Analysis of Plaque Size Distribution**

The size distribution of 1D5-positive amyloid plaques was obtained from each of the 91 patients with AD and 12 controls without dementia using the optical threshold application of the BIOQUANT software (version 6.90.10; MBSR, Nashville, TN). This software is coordinated with

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**TABLE 1. Demographic Characteristics of Groups Without and With AD**

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 12)</th>
<th>AD Group (n = 91)</th>
<th>p</th>
<th>Control Subset (n = 9)</th>
<th>AD Subset (n = 40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n female (%)†</td>
<td>7 (58.3)</td>
<td>58 (63.7)</td>
<td>NS</td>
<td>4 (44.4)</td>
<td>26 (65.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Age of death, mean ± SD, y*</td>
<td>78.2 ± 14.0</td>
<td>79.0 ± 7.8</td>
<td>NS</td>
<td>80.3 ± 14.4</td>
<td>77.6 ± 8.6</td>
<td>NS</td>
</tr>
<tr>
<td>Age of onset, mean ± SD, y</td>
<td>NA</td>
<td>68.7 ± 8.8</td>
<td>NA</td>
<td>NA</td>
<td>66.9 ± 10.2</td>
<td>NA</td>
</tr>
<tr>
<td>Disease duration, median (IQR), y</td>
<td>NA</td>
<td>9.6 (6.8–13.6)</td>
<td>NA</td>
<td>NA</td>
<td>9.9 (5.7–15.0)</td>
<td>NA</td>
</tr>
<tr>
<td>APOE genotype†</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>APOE4 carriers, n (%)</td>
<td>4 (33.3)</td>
<td>59 (64.8)</td>
<td>0.0561</td>
<td>3 (33.3)</td>
<td>21 (52.5)</td>
<td>NS</td>
</tr>
<tr>
<td>APOE4 alleles, n (%)</td>
<td>4 (16.7)</td>
<td>72 (39.6)</td>
<td>0.0410</td>
<td>3 (16.7)</td>
<td>25 (31.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Postmortem interval, mean ± SD, h*</td>
<td>16.4 ± 11.0</td>
<td>13.9 ± 9.0</td>
<td>NS</td>
<td>17.4 ± 11.4</td>
<td>14.1 ± 6.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Two-tailed Mann-Whitney U test or Student t-test.
†Two-tailed χ² with Fisher exact test.
AD, Alzheimer disease; IQR, interquartile range; NA, not applicable; NS, not significant.
the motorized stage of an upright Leica DMRB microscope equipped with a CCD camera (Model DC330; DAGE-MTI, Inc, Michigan City, IN). The 10D5-immunostained amyloid deposits were thresholded under the 10× objective after background correction to avoid uneven lighting. The calibration was kept constant at a magnification factor of 1.6158 μm² per pixel. The diffuse deposits often seen in the subpial surface of the cortex in cases with advanced-stage AD were excluded from the analysis.

In addition, the size distribution of dense-core plaques in the subsets of 40 AD cases and 9 controls without dementia was obtained. Thio-S-positive plaques per specimen were randomly selected using CAST stereology software and photographed (20×) using an Olympus BX51 epifluorescence upright microscope equipped with a CCD camera (Model DP70; Olympus, Tokyo, Japan). This stereology software ensures an even and random sampling of all 6 layers of the cortex. The cross-sectional area of these Thio-S-positive plaques was measured by manual outlining of their perimeter with the appropriate tool of the public domain software ImageJ (http://rsbweb.nih.gov/ij/).

To minimize variability in the size measurements, all cases were stained within the same batch and were analyzed by the same person. In addition, size measurements were done blinded to the clinical information to prevent bias.

**APOE Genotyping**

APOE genotype was determined in all the study subjects by restriction fragment length polymorphism analysis as described previously (34).

**Statistics**

Normality of data sets was tested with D'Agostino-Pearson omnibus test. As expected from our previous work, the distribution of plaques size was positively skewed rather than Gaussian, so that the mean is not a representative measure (17). We used the clustered Wilcoxon rank sum test to compare the entire size distributions of subjects with AD and control subjects without dementia and of AD APOEε4 carriers and noncarriers (35). To evaluate the effect of disease duration, age of onset, and APOE genotype on plaque size, we fit mixed-effects regression models using all the plaques for all AD subjects and allowing for correlation within subject. We tested whether the slopes of the regression lines were different from zero at a significance level of p < 0.05 in all statistical analyses. Statistics were performed with SAS (version 9.2; SAS Institute, Cary, NC). Graphs were done with GraphPad Prism (version 4.0; GraphPad Software, Inc, La Jolla, CA).

**RESULTS**

Because immunopositive amyloid deposits and dense-core amyloid plaques may behave differently in size change or growth rate, we addressed the growth of both subtypes of amyloid plaques in the temporal neocortex over the clinical course of AD. The anti-Aβ antibody 10D5 was used to display all plaques (diffuse and compact), and Thio-S was used to display only dense-core plaques. We obtained the size distribution of the 10D5-positive plaques of a large group of patients with AD (n = 91) with a broad range of clinical disease duration (4–21 years, as defined by the survival from the

**FIGURE 1.** Comparison of plaque size distributions between patients with Alzheimer disease (AD) and age-matched subjects without dementia. (A, B) 10D5-positive plaques from patients with AD were not significantly larger that those from individuals without dementia (A, p = 0.6380), whereas dense-core (Thio-S-positive) plaques from patients with AD as a group were slightly but significantly larger than those from subjects without dementia (B, p = 0.0110). Scatter dot plots represent the median values of the plaque size distributions from patients with AD and subjects without dementia, but for statistical analyses, the entire distributions were used.
age of symptom onset), and the size distribution of dense-core (Thio-S-positive) plaques from a representative subset of 40 AD cases. For comparison purposes, a group of 12 individuals without dementia with some 10D5-positive plaques, including a subset of 9 subjects without dementia with sufficient numbers of dense-core plaques to assess, was also analyzed.

**Comparisons of Plaque Size Between Individuals Without Dementia and Patients With AD**

If plaques grow over time, we predicted that patients with AD would have larger plaques than plaque-bearing individuals without dementia, who presumably would be at an earlier stage of the disease when they died. This prediction was clearly rejected because the size of 10D5-positive plaques did not differ significantly between the 2 groups (p = 0.6380; Fig. 1A). By contrast, the subset of dense-core plaques from subjects without dementia were modestly smaller (~25%–30%) than those from patients with AD (p = 0.0110; Fig. 1B), suggesting that a fibrillization process of diffuse amyloid deposits is ongoing during the transition from “normal” aging to AD dementia.

**Age of Symptom Onset Is a Stronger Predictor of the Final Plaque Size Than Duration of the Clinical Disease**

As another test of the hypothesis that plaques continue to grow, we correlated plaque size in the group with AD as a function of duration of clinical illness over a range from 4 to 21 years. We obtained no significant correlations between 10D5-positive plaque size and duration of clinical disease (p = 0.4962; Fig. 2A). By contrast, focusing on the subset of Thio-S-positive dense-core plaques, we observed a trend toward a significant positive correlation of dense-core plaque size with disease duration (p = 0.0675; Fig. 2B), suggesting that dense-core plaques may grow not only before the clinical onset of the disease but also along its clinical course. However,

**FIGURE 2.** Correlations of plaque size with duration of clinical disease and age of symptom onset. (A-D) Measures of 10D5-positive plaque size and Thioflavin S (Thio-S)-positive plaque size did not correlate with the duration of clinical disease (A, B) but showed a strong negative correlation with age of symptom onset (C, D) (Table 2). Graphs represent median values of the size distributions from patients with Alzheimer disease (AD), but for statistical analyses, the entire distributions were used. p values refer to regression Models 1 and 2 in Table 2.
it should be noted that the magnitude of this change was very modest, with an average increase of only ~30% over the 17 years of disease duration assayed (i.e. <2%/y, or 7.7 ± 4.2 μm²/y).

A potential confounder of using disease duration is that subjects are censored at the time of death, raising the possibility that an earlier age of onset (rather than duration of illness) might influence plaque size. In our group with AD, there was, in fact, a significant negative correlation between age of onset and disease duration (r = -0.4544, p < 0.0001). That survival in AD is negatively correlated to age of onset has been previously established by a number of epidemiological studies (36–39). Surprisingly, both 10D5-positive and dense-core plaque size correlated negatively with age of onset (p = 0.0039 and p < 0.0001, respectively; Figs. 2C, D), indicating that amyloid plaques from subjects with younger age of onset actually tend to be larger at death than those from subjects with late-onset cognitive symptoms.

To discern the effects of both duration of clinical disease and age of symptom onset on plaque size, we added both covariates to the regression model. After adjusting for disease duration, the negative correlation between 10D5-positive plaque size and age of onset described above remained highly significant (p = 0.0002), arguing that an earlier age of onset strongly predicts a larger final (postmortem) size of 10D5-positive plaques, independently of disease duration. Interestingly, the nonsignificant negative correlation between 10D5-positive plaque size and disease duration became statistically significant after adjusting for age of onset (p = 0.0162), suggesting that there is, in fact, a reduction in size of 10D5-positive plaques through the clinical course of the disease (Table 2).

Likewise 10D5-positive plaque size, adjusting for disease duration did not change the highly significant negative correlation observed between dense-core plaque size and age of onset (p < 0.0001). However, the trend toward a positive correlation between dense-core plaque size and disease duration described above was completely abolished after adjusting for age of onset (p = 0.6929), indicating that duration of clinical disease is not an independent predictor of dense-core plaque size but depends on the age of symptom onset (Table 2).

### DISCUSSION

Although any longitudinal extrapolation of cross-sectional neuropathologic data should be interpreted with caution, the unbiased stereology-based quantitative analyses performed in a large sample of AD cases with broad ranges of age and disease duration, age of onset, and APOE4 status (e4 carrier vs noncarrier) (Model 4).

### TABLE 2. Summary of the Main Results From This Study

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
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<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>p</td>
<td>Estimate</td>
<td>p</td>
</tr>
<tr>
<td>10D5+ plaques</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>-2.5 ± 3.7</td>
<td>0.4962</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age of onset</td>
<td>—</td>
<td>—</td>
<td>-4.9 ± 1.7</td>
<td>0.0039</td>
</tr>
<tr>
<td>APOE4 status</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dense-core plaques</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>7.7 ± 4.2</td>
<td>0.0675</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age of onset</td>
<td>—</td>
<td>—</td>
<td>-8.0 ± 1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APOE4 status</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</table>

Mixed-effects regression models of plaque size measures (outcome variable) were fit for disease duration (Model 1); age of onset (Model 2); disease duration and age of onset (Model 3); and disease duration, age of onset, and APOE4 status (e4 carrier vs noncarrier) (Model 4).

For Models 3 and 4, each p value represents the effect of each variable.

Estimates (± SD) represent the slopes of the regression lines and p values indicate whether these slopes were significantly different from zero (significance level at p < 0.05).
clinical disease duration and age of onset, as well as in plaque-bearing individuals without dementia, enabled us to examine the hypothesis that amyloid plaques grow during the natural history of the disease. Our conclusions can be summarized as follows: 1) plaques do not substantially grow over decades of clinical progression of AD; 2) a younger age of symptom onset may be associated with larger plaques, pointing possibly to genetic or other risk factors affecting Aβ fibrillization or metabolism; and 3) although the APOE ε4 allele is known to be associated with an earlier clinical onset, the APOE genotype itself influences neither the final plaque size nor the effect of age of onset on plaque size.

Pathophysiologic Implications

Recently, the development of in vivo multiphoton microscopy has enabled researchers to monitor the appearance and growth of individual plaques over time in mouse models of brain β-amyloidosis. Early studies described a rapid appearance of plaques and little, if any, growth of plaques after formation (8, 9); however, more recent studies with longer follow-up have reported a gradual or even a more dramatic growth of newly formed plaques over weeks to months but not of preexisting plaques (10–13). For example, 1 study suggests a dramatic doubling of plaque size over the course of 24 weeks, affecting similarly both newly formed and preexisting plaques (13). The different findings in these animal studies may depend on technical factors involving imaging protocols and/or different transgenes and strains of mice.

Our current study shows no substantial change in plaque size over clinical disease duration of up to 21 years, strongly arguing that plaque size does not continue to increase over time in human AD. The significant although modest increase in the size of dense-core plaques, with unchanged size of 10D5-positive plaques, between controls without dementia and patients with AD may be attributable to an ongoing fibrillization of amyloid plaques in the transition between “normal” aging and AD dementia and suggests that this fibrillization of amyloid plaques may be associated with an earlier age of onset of cognitive decline. Our results clearly indicate that, once cognitive deficits develop, there is no further growth of either total (10D5-positive) or dense-core (Thio-S-positive) plaques. In fact, we observed a significant reduction of the size of 10D5-positive plaques (but not of dense-core plaques) over the clinical course of the disease after controlling for age of onset. Earlier studies already pointed that Aβ fibrillization can be reversible not only in vitro (45–47) but also in vivo (17, 48, 49), and even a regression stage before the disappearance of amyloid plaques has been proposed (50). Along this line, release of Aβ-soluble species from the periphery of dense-core plaques, as suggested by more recent studies, might underlie the differential reduction in the size of 10D5-positive plaques but not dense-core plaques (51–53). Alternatively, preferential phagocytosis and degradation of these more soluble Aβ species by plaque-associated reactive astrocytes and activated microglial cells might explain this finding (50, 54, 55).

Importantly, the negative correlation observed between age of onset and plaque size after controlling for disease duration is also consistent with the idea that plaques reach a maximum size early in the AD pathologic process and do not undergo much change thereafter. We speculate that genetic or other risk factors involved in Aβ metabolism might underlie both an earlier onset of AD symptoms and larger plaques. Our observation that a larger plaque size is associated with an

FIGURE 3. Comparison of plaque size distributions of patients with Alzheimer disease (AD) divided by APOE status (ε4 carriers vs noncarriers). (A, B) No significant differences were observed between both genotypes in the size of either 10D5-positive plaques (A) or Thioflavin S (Thio-S, dense-core) plaques (B). Scatter dot plots represent the median values of the plaque size distributions, but for statistical analyses, the entire distributions were used.
earlier onset is in agreement with prior observations that a number of AD-related neuropathologic phenotypes are more dramatic in patients with earlier-onset AD (56–58). Known genetic factors with these 2 effects include duplication of the APP gene in Down syndrome (42) and the variant AD with spastic paraparesis due to a deletion of exon 9 in the presenilin-1 gene (PSEN1ΔE9), which is characteristic for the finding of large “cotton-wool” plaques (59). The APOEε4 allele is the strongest genetic risk factor to develop sporadic AD; it is also associated with an earlier onset of clinical symptoms (40) and a higher plaque burden (41–44). Our present data are in agreement with the idea that higher numbers of amyloid plaques, rather than an increased size, account for the higher plaque burden observed in patients with AD carrying the APOEε4 allele (42).

A potential limitation of this study is that we measured the size of amyloid plaques but not the intensity of the 10D5 immunostaining or the Thio-S staining, a parameter that would also contribute to reflect the amount of Aβ within the plaque. However, in a previous biochemical study in the temporal cortex of a large sample of AD cases, we found no correlation between either TBS-soluble or formic acid–extractable Aβ and duration of clinical disease, suggesting that there is no further accumulation of soluble or insoluble Aβ species within the plaques once cognitive decline has started (18). It should also be recognized that the stability of plaque size observed in the temporal cortex may not be fully generalizable to other brain regions with later amyloid deposition; according to previously described staging systems (32, 60), the primary cortices, and particularly the cerebellum and subcortical structures (including brainstem nuclei), may indeed exhibit an increase in plaque size during the clinical course of the disease.

Therapeutic Implications

Understanding if plaques grow in a consistent and dramatic fashion in human AD is critical to interpret the beneficial effect of anti-Aβ-directed therapies. For example, we have previously reported that patients with AD who received anti-Aβ active immunization have not only fewer but also smaller 10D5-positive and Thio-S–positive amyloid plaques remaining in their hippocampus, compared with age- and Braak stage–matched nonimmunized patients with AD (61). The limited plaque growth through the clinical course of the disease shown herein suggests that clearance of existing plaques, rather than slowing of the growth of newly formed plaques, underlies the reduction in amyloid load and plaque size observed after anti-Aβ immunization in patients with AD. By contrast, unlike anti-Aβ immunotherapy, in vivo multiphoton microscopy in AD transgenic mouse models has revealed that γ-secretase inhibitors do not reduce the size of existing plaques but can prevent their growth as well as the birth of new plaques (11, 62).

In summary, we have previously shown that the progression of cortical amyloid deposition in the temporal neocortex fits into a saturation model in which, after an initial increase, amyloid burden reaches a plateau early after (or even before) the clinical onset of cognitive symptoms (14, 15). Our present results indicate that this saturation model also applies to the size of plaques. These findings help to understand the dynamics of Aβ deposition in the human AD brain and interpret the effects of anti-Aβ–directed therapies.

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REFERENCES


