Shift from fibrillar to nonfibrillar Aβ deposits in the neocortex of subjects with Alzheimer disease

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A morphometric study of amyloid-β-positive plaques in the neocortex of eight non-demented people from 68 to 82 years of age and 17 subjects with late-stage Alzheimer disease (GDS stage 7/FAST stages 7a–f) from 73 to 93 years of age shows a shift from prevalence of fibrillar plaques to prevalence of nonfibrillar plaques. In the aged, non-demented subjects, about 4/mm^2 plaques are detectable in the neocortex, and the majority are fibrillar plaques. Specifically, 64% of plaques in the neocortex of the normal aged subjects were found to be classical fibrillar and Thioflavin-S-positive bright primitive plaques. A lower percentage of pale primitive plaques (35%) and diffuse plaques (1%) was observed, reflecting the relatively small proportion of plaques that are poor in thioflavin S-positive fibrils. The numerical density of plaques in the severe stage of AD increases to about 41/mm^2. Severely demented subjects appear to maintain an active process of fibrillar plaque formation. This is reflected in the presence of 3% fibrillar classical and 27% bright primitive plaques. Severely demented subjects also manifest plaque degradation, reflected in the presence of 22% pale primitive and 48% diffuse-like Thioflavin S-negative plaques. Comparable percentages of classical fibrillar plaques in non-demented subjects and in the end stage of disease suggest that once activated, the process of fibrillar plaque formation persists at a somewhat stable rate during the whole course of brain amyloidosis.

Journal of Alzheimer's Disease 3 (2001) 49–57
ISSN 1387-2877 / $8.00

Keywords: Alzheimer disease, diffuse plaques, fibrillar plaques, morphometry

1. Introduction

The deposition of amyloid-β (Aβ), the degeneration of tissue in response to extracellular fibrillar amyloid deposits in the brain parenchyma and in the vascular wall, and amyloid degradation and clearance are central events in the course of Alzheimer disease (AD). Aβ appears in fibrillar Thioflavin-S-positive form in classical and primitive plaques and in the wall of capillaries [37,38], arteries, and veins [39] and in non-fibrillar form in diffuse deposits. This topographic and morphological diversity suggests more than one source of Aβ; however, the origin of the amyloid accumulated in different types of deposits in the brain of people with AD is not clear because numerous types of neuronal and non-neuronal cells express amyloid β-protein precursor (AβPP) and produce and accumulate or secrete Aβ.

Diffuse amorphous nonfibrillar Aβ deposits, also called amorphous plaques [23], pre-plaques [15], or pre-amyloid deposits [26], are considered to be of neuronal origin [1,18–20,30,40,41]. Some studies suggest periterminal neuronal Aβ release [19]). The absence of fibrillar amyloid, dystrophic neurites, activated microglial cells and astrocytes, and chaperone proteins suggests that some diffuse Aβ deposits may correspond to intracellular Aβ accumulation in nerve terminals [30]. Differences between diffuse deposits in the molecular layer of the human cerebellum [24, 31], the molecular layer of human and animal dentate

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gyrus [30], the human parvopyramidal layer of the presubiculum [41], the human caudate nucleus [5,6,12], plaques with N-terminal truncated fragments of Aβ in the internal layers of the entorhinal cortex [27] and neocortex [4], and plaque-like parenchymal deposits of AβPP after ischemia [14] suggest that diffuse deposits are heterogenous and represent several types of Aβ doposits with topographically specific differences in the amount, distribution, and properties of AβPP or nonfibrillar products of AβPP processing.

Diffuse plaques are considered an initial stage of fibrillar neuritic plaque formation [15,26,42,43]. However, the exclusive presence of diffuse plaques in the molecular layer of the cerebellum, the parvopyramidal layer of the presubiculum, and caudate nucleus in moderate and severe stages of AD opposes the hypothesis that diffuse plaques transform into fibrillar plaques.

Because of technical reasons the contribution of electron microscopy to the characterization of diffuse Aβ deposits is very limited. On the other hand, electron microscopy provides surprisingly detailed characteristics of the development of fibrillar plaques and fibrillar vascular deposits and their growth and degradation [33, 39]. Ultrastructural studies also do not support the concept of evolution of diffuse deposits into classical or primitive plaques. In contrast, electron microscopic studies suggest that a large proportion of diffuse-like plaques in the human neocortex is the product of fibrillar plaques degradation [38]. Because of morphological similarities between the products of fibrillar plaques degradation and original diffuse plaques, distinguishing between these two categories of Aβ deposits in the neocortex is impossible with routine methods.

We hypothesized that characterization of the number of different types of plaques and proportions between fibrillar and diffuse plaques in normal aged subjects and subjects with late-stage AD would assist in characterization of the origin of neocortical plaques. If diffuse plaques precede fibrillar plaques, one would also expect that in non-demented people affected by early AD pathology diffuse plaques should prevail, whereas in the late stage of AD, fibrillar plaques should dominate. Accordingly, we characterized the number of classical, primitive, and diffuse plaques in the neocortex of non-demented, but plaque-positive subjects and in subjects with severe AD. We observed the prevalence of fibrillar plaques in the early stage of neocortical amyloidosis and the prevalence of diffuse/diffuse-like plaques in late stages of AD, indicating that the majority of neocortical plaques start as fibrillar Aβ deposits.

2. Material and methods

The cerebral cortices of one hemisphere of eight non-demented people from 68 to 82 years of age and 17 subjects with severe Alzheimer disease from 73 to 93 years of age (Table 1) were examined morphometrically. The level of cognitive and functional decline of subjects with AD was assessed with the Global Deterioration Scale (GDS [21]). At the time of demise, all subjects were in GDS stage 7. At this stage, subjects almost invariably score zero on the mini-mental state examination [3]. The progress of functional deterioration was characterized with the Functional Assessment Staging (FAST) procedure [22]. In accordance with the FAST staging procedure, patients who were deficient in activities of daily life (ADLs), were doubly incontinent, and had incipient averbalism were classified as substages 7a (five patients) and 7b (six patients). Incipient loss of ambulation in addition to the earlier functional deficits was noted in one case (FAST substage 7c). Substage 7d, with progressive immobility and loss of the ability to sit up, was not represented in the examined population. Loss of the capacity to smile in addition to ADL dependence, incontinence, absence of verbalization, and immobility characterized three patients (substage 7e), and further loss of the ability to hold up the head independently, two patients (substage 7f).

Brains fixed for at least six weeks with 10% buffered formalin were divided sagitally. One-half of each brain was cut coronally into 4.8-mm-thick slabs, processed, and embedded in paraffin. Eight-μm-thick sections were stained with cresyl violet, Bielschowsky silver method, and monoclonal antibody (mAb) 4G8 raised against the 17–24 amino acid sequence of Aβ protein [13]. To enhance immunoreactivity with mAb 4G8, sections were treated with concentrated formic acid.

The clinical diagnosis of AD was confirmed histopathologically according to CERAD criteria [17]. Frontal, temporal, parietal, occipital, limbic, and insular cortices were examined. The frontal cortex was divided into superior, middle, inferior, orbital, rectus, precentral, and paracentral gyrus. Superior, middle, inferior, and fusiform gyri were examined in the temporal cortex. In the parietal cortex, superior, postcentral, supramarginal and angular gyrus and the precuneus were distinguished. The occipital cortex was divided into occipital gyri, the lingual gyrus, and the cuneus. The numerical density and the total number of plaques were evaluated morphometrically in all examined neocorti-

Table 1
Clinical data

Group	Case #	FAST stage	Age (y)	Sex	Cause of death
AD	1	7a	73	M	Heart failure
	2	7a	77	F	Sepsis
	3	7a	81	M	Sepsis
	4	7a	84	M	Heart failure
	5	7a	85	F	Sepsis
	6	7b	68	M	Pneumonia
	7	7b	75	M	Heart failure
	8	7b	85	F	Pneumonia
	9	7b	87	F	Sepsis
	10	7b	70	M	Unknown
	11	7b	93	M	Stroke
	12	7c	83	M	Pneumonia
	13	7e	77	M	Unknown
	14	7e	77	F	Heart failure
	15	7e	86	M	Pneumonia
	16	7f	76	F	Unknown
	17	7f	87	F	Sepsis
Non-demented	1	N/A	68	F	Pneumonia
	2	N/A	71	M	Unknown
	3	N/A	71	F	Hepatitis
	4	N/A	75	F	Peritonitis
	5	N/A	77	M	Pneumonia
	6	N/A	79	M	Unknown
	7	N/A	79	F	Pneumonia
	8	N/A	82	M	Pneumonia

cal regions. Specific evaluations included the numerical density and total number of (a) all plaques detectable with mAb 4G8, (b) classic plaques detectable in sections stained with mAb 4G8, (c) primitive plaques with bright fluorescence, and (d) primitive plaques with poor fluorescence (pale plaques) detectable in sections stained with Thioflavin S and examined in UV light. Because of the lack of unquestionable markers of diffuse plaques, the numerical density of diffuse plaques was estimated as the difference between the number of all plaques stained with mAb 4G8 and the sum of the numerical densities of both classical and primitive (bright and pale Thioflavin-S-positive) plaques. Because neither classical plaques nor pale plaques are distinguishable by automatic image analyzer, the manual method of delineation of plaques was applied. Plaque profiles were digitized at 165x magnification by using a digitizer (Numonics) and the Sigma Scan program (Jandel Scientific). An average of 520 test areas were examined in the neocortex in each case. For each neocortical subdivision, differences between the AD and the normal aged control group were evaluated by the Student t test. Correlation between numerical densities of plaques and the duration and stage of AD were evaluated with Pearson's correlation coefficient.

3. Results

Only in two non-demented subjects aged 75 and 82 years at the time of demise were amyloid deposits absent in the neocortex in sections stained with Thioflavin S and examined in fluorescence and in sections immunostained with mAb 4G8. Because intralobular differences in the numerical densities of amyloid deposits in five amyloid-positive, non-demented subjects and the AD subjects were not significant, the measures of amyloid deposits were summarized for frontal, temporal, parietal, limbic, insular, and occipital cortices.

3.1. Numerical density of amyloid deposits

3.1.1. All types of plaques

In the neocortex of non-demented subjects, the mean numerical density of all amyloid deposits detectable with mAb 4G8 varies in range from 2.7/mm^2 in the parietal and occipital cortices to 4.8 and 4.9/mm^2 in the temporal and insular cortices (Table 2, Fig. 1). In the severe-stage AD cohort, the numerical density of neocortical amyloid deposits detectable with mAb 4G8 is from 7 to 15 times more than in the non-demented subjects and varies in range from about 33/mm^2 in the occipital cortex to about 44 to 45/mm^2 in the frontal and temporal cortices. In all neocortical regions examined,

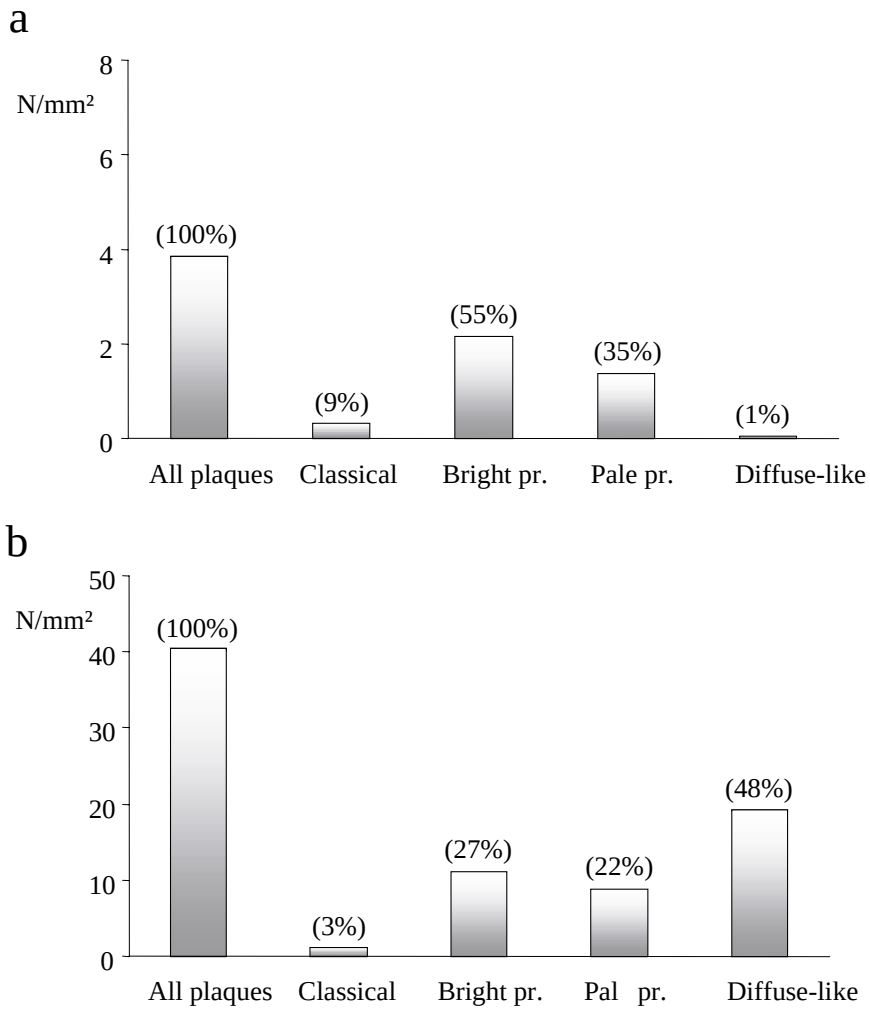

Fig. 1. Numerical density (n/mm^2) of plaques in the neocortex of non-demented (a) and AD (b) subjects. Shift from the prevalence of fibrillar classical (9%) and bright Thioflavin S-positive plaques (55%) in the neocortex in aged non-demented subjects to the prevalence of poorly fibrillized plaques that are pale in fluorescence (22%) and non-fibrillar diffuse-like Thioflavin S-negative Aβ deposits (48%) in the neocortex of subjects with severe AD.

the differences in the densities of amyloid deposits detectable with mAb 4G8 between the non-demented cohort and the dementia subject group were significant ($p < 0.001$; Table 3). The numerical density of 4G8-positive plaques in the AD cohort does not correlate with the age of subjects or the duration and stage of AD.

3.1.2. Classical plaques

The numerical density of classical plaques in the non-demented subject cohort is low and varies in range from 0.5/mm^2 in the frontal and limbic cortices to 0.3/mm^2 in the temporal, parietal, and insular cortices, and only 0.07/mm^2 in the occipital cortex. The contribution of classical plaques to the general plaque population is relatively high: they constitute from 11–13% of all mAb 4G8-positive plaques in the frontal, parietal, and limbic cortices, and about 6–7% in the temporal and insular cortex. In the occipital cortex, classical plaques constitute only 2.6% of all 4G8-positive plaques.

The numerical density of classical plaques in the frontal (1.14/mm^2), temporal (1.07/mm^2), limbic (0.88/mm^2), and insular (0.84/mm^2) cortices in the severely demented AD subjects is higher than in the non-demented subject cohort; however, the differences noted in regional densities of classical plaques between the demented and non-demented subject group are not statistically significant.

Table 2
Numerical density (n/mm^2) of plaques in the neocortex of non-demented subjects

Staining	Type of plaque	Cortical regions						All Neocortex
		Frontal	Temporal	Parietal	Occipital	Limbic	Insular	
mAb 4G8 (fibrillar and non-fibrillar Aβ)	All	4.2 ± 4.0 (100%)	4.8 ± 5.5 (100%)	2.7 ± 2.6 (100%)	2.7 ± 4.8 (100%)	3.8 ± 4.4 (100%)	4.9 ± 5.9 (100%)	3.85 ± 0.98 (100%)
Thioflavin-S (fibrillar Aβ)	0.51 ± 0.81 Classical	0.32 ± 0.44 (12.0 %)	0.30 ± 0.34 (6.6 %)	0.07 ± 0.14 (11.1 %)	0.49 ± 0.85 (2.6 %)	0.31 ± 0.46 (12.9 %)	3.85 ± 0.16 (6.3 %)	(8.6 %)
	Primitive bright	2.9 ± 3.4 (69.0 %)	1.9 ± 2.8 (39.6 %)	2.4 ± 3.5 (88.9 %)	1.9 ± 3.2 (70.3 %)	1.9 ± 2.2 (50.0 %)	1.9 ± 2.8 (38.3 %)	2.15 ± 0.42 (55.84%)
	Primitive pale	0.79 ± 0.94 (19%)	2.58 ± 3.00 (37.8 %)	0 ± 0	0.73 ± 1.31 (27.1 %)	1.41 ± 1.91 (37.1 %)	2.69 ± 3.89 (55.4 %)	1.36 ± 1.08 (35.3%)
mAb 4G8 (non-fibrillar Aβ)	Diffuse-like (estimated)	0 ± 0	0.23 ± 0.29 (4.8%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0.04 ± 0.09 (1.04%)

Data are presented as mean $\pm$ standard deviation and as percentages of all types of plaques present.

Table 3
Numerical density (n/mm^2) of plaques in the neocortex of subjects with severe AD (Global deterioration scale and functional assessment staging, stage 7 subjects)

Staining	Type of plaque	Cortical regions						All Neocortex
		Frontal	Temporal	Parietal	Occipital	Limbic	Insular	
mAb 4G8 (fibrillar and nonfibrillar Aβ)	All	44.3 ± 22.5** (100%)	44.5 ± 17.0** (100%)	41.7 ± 20.5** (100%)	32.6 ± 14.8** (100%)	42.7 ± 19.7** (100%)	37.0 ± 15.8** (100%)	40.5 ± 4.7 (100%)
Thioflavin- S (fibrillar Aβ	Classical	1.14 ± 0.97 (2.6%)	1.07 ± 1.07 (2.4%)	1.46 ± 1.16* (3.5%)	1.38 ± 1.30* (4.2%)	0.88 ± 0.75 (1.9%)	0.84 ± 0.86 (2.3%)	1.13 ± 0.25 (2.8%)
	Primitive	10.29 ± 3.92 (23.2%)	12.32 ± 4.69 (27.7%)	11.59 ± 4.48 (27.8%)	12.27 ± 3.66 (37.6%)	9.16 ± 4.72 (21.4%)	10.63 ± 4.22 (28.7%)	11.04 ± 1.24 (27.3%)
	Pale	8.52 ± 3.63 (19.2%)	10.41 ± 3.94 (23.39%)	8.53 ± 3.68 (20.45%)	8.07 ± 2.66 (8.15%)	8.24 ± 3.14 (19.3%)	9.54 ± 3.67 (25.78%)	8.88 ± 0.9 (21.9%)
mAb 4G8 (non-fibrillar Aβ)	Diffuse-like (estimated)	24.35 ± 13.09 (54.97%)	20.7 ± 10.39 (46.51%)	20.12 ± 10.51 (48.25%)	10.88 ± 13.49 (33.3%)	24.42 ± 13.49 (57.19%)	15.99 ± 8.67 (43.21%)	19.41 ± 5.2 (47.92%)

Data are presented as mean $\pm$ standard deviation and as percentages of all types of plaques present.
$^*p < 0.01$, $^{**}p < 0.001$ (the difference between non-demented and AD group of subjects).

3.1.3. Thioflavin S-positive bright and pale primitive plaques

In the non-demented subject group, the numerical density of primitive Thioflavin-S-positive bright plaques in the cortical regions examined varied in a narrow range from 1.9/mm^2 to 2.9/mm^2. They constitute from about 38–40% of all mAb 4G8-positive plaques in the temporal and insular cortices, to 89% of all plaques in the parietal cortex of the non-demented subjects. The percentage contribution of pale primitive plaques to the total plaque burden in the six brain regions examined varied from zero, in the parietal cortex, to 55% in the insular cortex, in these non-demented subjects.

In the severely demented AD subjects, the numerical density of bright primitive plaques varied in range from 9–12/mm^2 in the neocortical regions examined. The proportions between classical and bright primitive plaques in the neocortex of the severely demented cohort (from $1:8$ to $1:12$) is similar to the proportions that were observed in the non-demented subjects. In the severe AD subjects, the numerical density of pale primitive plaques was approximately the same as that of bright fluorescent plaques (8–10/mm^2).

Classical plaques and Thioflavin-S-positive bright and pale plaques all contain fibrillar Aβ and constitute the fibrillar plaque burden in the neocortex. These fibrillar plaques constitute almost 100% of neocortical plaques in the non-demented cohort, whereas in the severe stage of AD, their contribution decreases to about 40–50% of all 4G8-positive plaques.

3.1.4. Diffuse-like plaques

The numerical density of diffuse-like plaques in non-demented and severely demented people is strikingly different. Diffuse-like plaques are virtually absent in the major part of the neocortex of non-demented subjects. They were noticed to a small extent only in the temporal cortex (0.23/mm^2).

In severely demented AD subjects, Thioflavin-S-negative, diffuse-like Aβ deposits are the most common form of plaques. Their numerical density varies in range from about 20/mm^2–24/mm^2 in the temporal,

parietal, frontal, and limbic cortices and about 11/mm^2 and 16/mm^2 in the occipital and insular cortices, respectively. Diffuse-like plaques constitute from 33% of all plaques in the occipital cortex to 57% in the limbic cortex.

4. Discussion

The presence of mAb 4G8- and Thioflavin-S-positive plaques in five of eight non-demented subjects (62%) from 68 to 82 years of age indicates that β-amyloidosis is a common pathology in non-demented elderly people. The detection of 3.8–4.8/mm^2 immunopositive plaques in the frontal, temporal, limbic, and insular cortices, and 2.7/mm^2 plaques in the parietal and occipital cortices, suggests that amyloid-positive subjects are affected by incipient AD pathology. The prevalence of this Alzheimer type pathology observed in this postmortem study in the normal control cohort is higher than would be anticipated from the percentage of persons diagnosed clinically as having probable AD -18.7% of subjects from 75 to 85 years of age and 47.2% of those 85 years old [2]. The higher percentage of AD pathology in the brains of the elderly control cohort we studied indicates that neocortical amyloidosis may precede by many years the onset of dementia. The relatively high number of Aβ deposits found in this study is the effect of using sensitive and extensive detection procedures. These include immunocytochemistry, which is more sensitive in detecting Aβ deposits than are histological methods; application of mAb 4G8, which reacts with the 17–24 amino acid residues of Aβ [13] and shows all major species of Aβ peptide; examination of 19 cortical gyri representing six major subdivisions of the neocortex; and evaluation of a large number of test areas (an average of 520 per case), comprising the whole thickness of the cortex.

4.1. Shift from fibrillar to nonfibrillar plaques

Characteristics of plaques in the neocortex of non-demented and severely demented subjects show striking differences in proportions between the amount of classical, bright, and pale primitive plaques and so-called diffuse plaques. Neocortical amyloidosis in non-demented subjects is characterized by a high percentage of classical (8.6%) and bright primitive (55.84%) plaques, which together constitute 64.4% of all plaques. Pale plaques, which are probably the product of degradation of bright fibrillar plaques, constitute about 35.3% of all plaques. The proportion of both bright classical and bright primitive plaques relative to pale primitive plaques ($1.8:1$) suggests the prevalence of fibrillar plaque formation over fibrillar plaque degradation in the early stage of neocortical amyloidosis. In contrast to expectations, diffuse plaques are absent or are present in very small quantities in the neocortex in non-demented subjects. Formation of original diffuse deposits in neocortex is not excluded; however, in the examined late stages of AD, this admixture of original diffuse deposits is indistinguishable from products of fibrillar plaque degradation.

The prevalence of fibrillar plaques in the neocortex of non-demented people indicates that in the neocortex, the majority of cortical plaques start as fibrillar classical and fibrillar, Thioflavin-S-positive, bright primitive plaques. In the early stage of neocortical amyloidosis, fibrillar plaque formation, reflected in the presence of almost 64.4% classical and bright primitive plaques, predominate plaque degradation, reflected in the presence of 35.3% pale primitive and only 1% diffuse plaques. The proportions of different types of plaques noted in severely demented persons appear to indicate a continuation of the very active process of plaque formation which is reflected in the presence of 30% classical and bright primitive plaques, combined with plaque degradation, reflected in the presence of 70% pale primitive and diffuse plaques. Similar trends in the majority of examined cortical regions suggest a rather uniform pattern of amyloid plaque formation and degradation in the neocortex.

The proportion between the total number of classical plaques and all types of plaques in the non-demented population is about $1:11$, whereas in the late stages of AD, it is $1:39$. Surprisingly, the difference in the numerical density and in the total number of classical plaques in non-demented and severely demented subjects is not significant in the majority of cortical regions examined. This suggests that the rate of classical plaque formation is similar in early and late stages of neocortical amyloidosis.

4.2. Fibrillar plaque development and degradation

Ultrastructural studies show that classical plaques consist of microglial cells, fibrillar Aβ, degenerated neuronal processes and synapses, and activated astrocytes [28,35]. The changes in the amount, morphology, and spatial arrangement of these components allow one to distinguish among early classical plaques,

with the dominance of Aβ deposition in the amyloid core; mature classical plaques, with the dominance of neuronal degeneration; and late classical plaques, with amyloid deposit dispersion and degradation. The product of degradation of classical plaque is indistinguishable from that of primitive plaque. Further degradation turns primitive plaque into diffuse-like plaque, with hardly detectable residues of fibrillar Aβ, a few dystrophic neurites that might be overlooked in light microscopy examination, and a variable amount of astrocytic processes [38].

The proportion between classical plaques and all types of plaques observed in the neocortex of nondemented persons appears to be consistent with an early stage of Alzheimer type neuropathology, with numerous new classical and primitive plaques and relatively few old, degraded plaques. The status seen in the late stage of disease appears to be the result of a somewhat stable rate of production of new classical and primitive plaques during both non-symptomatic and symptomatic AD combined with accumulation of the products of degradation of these plaques to diffuse-like plaques. The lack of correlation between the numerical density of plaques and the stage or duration of AD in the neocortex of subjects studied suggests a dynamic balance between plaque formation and degradation by the time of the advent of severe AD [8]. Ultrastructural studies indicate that astrocytes disperse, degrade, and remove fibrillar amyloid in classical and primitive plaques [36,34]. The pattern of amyloid deposition and degradation appears to be brain region-specific. Regression analysis of changes in the amygdala of persons with Down syndrome indicates that in 2.2 years after plaque formation stops, all amyloid will be removed [32].

4.3. Diffuse plaques – a neuronal pathway of Aβ deposition

Development of only diffuse Aβ-positive plaques in the molecular layer of the cerebellum [11,16,31], the parvocellular layer of the presubiculum [41], and the caudate nucleus/putamen [5,6,10,25], which persist in diffuse form to the end stage of AD, suggests that these diffuse plaques represent a separate pathological process. Diffuse plaques are the only plaques detectable in the brain of aged dogs. They develop in brains of all dogs older than 13 years [29], and in unmodified form are found in the brains of dogs that survive up to 24 years of age. The presence of only diffuse plaques in the brain of fennec, lemur, and panther [30] indicates also that diffuse parenchymal Aβ deposits, which does not transform into other types of plaque, are a common form of age-related brain amyloidosis in animals.

The concept that diffuse deposits do not evolve into fibrillar plaques because the survival of affected animals is too short for this evolution is in conflict with early fibrillar plaque formation in the brain of transgenic mice. Transgenic mice carrying the double Swedish mutation in AβPP produce fibrillar plaques at the age of 11–13 months [9], whereas transgenic mice carrying both mutant amyloid precursor protein and presenilin transgenes develop fibrillar plaques at the age of 4 months [7]. Ultrastructural studies of the first plaques in young transgenic mice reveal that they are fibrillar [33]. Our data characterizing the predominance of the fibrillar pathway of plaque formation in human neocortex and our and others' studies of diffuse deposits in the cerebellum, caudate nucleus, and presubiculum support topographic differences in plaque formation [5,6,10,11,16,25,31,41]. These observations suggest a spatial and temporal separation of the nonfibrillar and fibrillar pathways of Aβ deposition in many brain structures. However, because of the topographic overlap of both pathologic processes in other brain regions, these two pathologies become inseparable in routine examination. Species- and region-specific factors appear to determine fibrillar or non-fibrillar Aβ deposition, or activation of both pathways of Aβ accumulation.

Acknowledgments

The authors thank Ms. Maureen Stoddard Marlow for copy editing; Dr. Judy Shek, Ms. Mary Lee, and Ms. Cathy Wang for histology; and Ms. Jadwiga Wegiel for immunocytochemistry. This work was supported in part by funds from the New York State Office of Mental Retardation and Developmental Disabilities and grants from The National Institutes of Health, National Institute of Aging Nos. PO1-HD35897, AG03051, and AG08051.

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