2

Neuropathology of Alzheimer's Disease

Christian Schultz, Kelly Del Tredici, and Heiko Braak

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative and dementing disorder that can be detected clinically only in its end phase. AD is the most widespread type of dementia and affects about 10% of individuals older than 65 years and about 40% of individuals older than 80 years of age *(1,2)*. The earliest sign of AD is a subtle decline in memory functions in a state of clear consciousness. Mental capabilities gradually worsen and personality changes appear, followed by deterioration of language functions, impairment of visuospatial tasks, and, in the disease's final stages, dysfunction of the motor system in the form of a hypokinetic-hypertonic syndrome.

A definitive diagnosis of AD based on clinical observations is impossible and requires confirmation by postmortem examination. One of the neuropathological hallmarks of AD is comprised of extracellular precipitations of the β-amyloid peptide *(3,4)*, which is derived from the amyloid precursor protein (APP) by proteolytic cleavage.

The second acknowledged neuropathological hallmark of AD is the presence of neurofibrillary inclusions composed of an abnormally phosphorylated and aggregated microtubule-associated tau protein *(5–7)*. The lesions develop in the form of neurofibrillary tangles (NFTs, first described and depicted by Aloys Alzheimer) and neuropil threads (NTs). Such neurofibrillary pathology is not unique to AD, but is also seen in other diseases that are collectively designated as "tauopathies." These other disorders that make up this group are distinct from AD in that different brain areas are affected and abundant tau-positive inclusions in glial cells are present *(8,9)*. A heterogeneous group of hereditary tauopathies, referred to as "frontotemporal dementia" and "parkinsonism linked to chromosome 17 (FTDP-17)," is caused by dominant mutations in the tau gene *(10)*. This genetic link underscores the significance of tau dysfunction as a pathogenic factor that can cause neurodegeneration and dementia in humans. AD-related neurofibrillary changes are closely associated with neuronal cell loss and correlate well with the severity of clinical symptoms *(11–13)*. The destructive process that underlies the neurofibrillary pathology in AD commences in a few susceptible types of nerve cells in predisposed cortical induction sites and subsequently invades other portions of the cerebral cortex and specific sets of subcortical nuclei. The pathological changes evolve according to a predictable topographic sequence with little variation among individuals *(6,14–18)*.

ANATOMICAL CONSIDERATIONS

Understanding of the significance of Alzheimer-related lesions can be facilitated by using schematic diagrams of the major cortical pathways that become involved (Fig. 1). The human cerebral cortex is not a uniform entity; rather, it is composed of two divisions: an extensive neocortex and a small allocortex. The allocortex includes limbic system centers, such as the hippocampal formation and the entorhinal region, both of which are interconnected with the subcortical nuclear complex of the amyg-

From: *Current Clinical Neurology,*
Alzheimer's Disease: A Physician's Guide to Practical Management
Edited by: R. W. Richter and B. Zoeller Richter © Humana Press Inc., Totowa, NJo

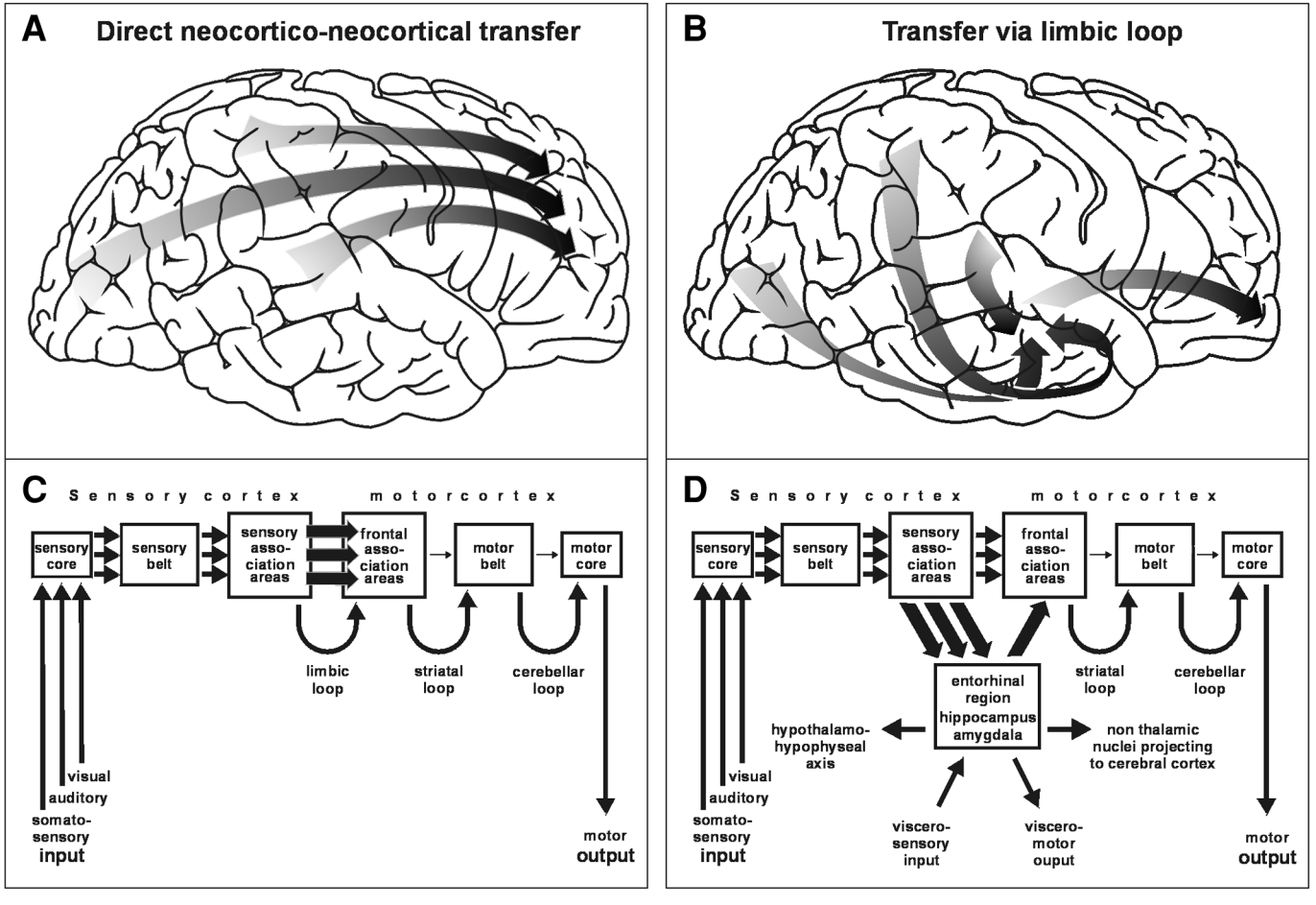


Fig. 1. Two pathways for transfer of somatosensory, visual, and auditory information to the prefrontal cortex are shown schematically in **(A)** and **(B)**, and as block diagrams, including subsequent data flow through motor areas, in **(C)** and **(D)**. The bulk of the sensory data is transferred directly via long cortico-cortical pathways, as depicted in **(A)** and **(C)**, but data entering the prefrontal cortex following processing in the limbic loop in **(B)** and **(D)** are essential for endowing the sensory information with significance as well as vital for processes involving memory, motivation, and emotion. In both cases, data are transferred through primary and secondary areas of the neocortex to a variety of related association areas. From the prefrontal cortex, data flow to the secondary and primary motor fields occurs primarily by way of the striatal and cerebellar loops.

dala. The parietal, occipital, and temporal territories of the neocortex are each comprised of a primary area, a belt of secondary fields, and related higher-order association areas *(19,20)*. Visual, auditory, and somatosensory information proceeds through the respective primary and secondary fields to a variety of related association areas and is then conveyed by long cortico-cortical pathways to the prefrontal cortex (Fig. 1A,C). These data are then transferred through the premotor areas to the primary motor field. The major pathways for this continual data flow are the striatal and the cerebellar loops, which integrate the basal ganglia, many nuclei of the lower brainstem, and the cerebellum into the regulation of cortical output. Some of the exteroceptive data that flow from the sensory association areas to the prefrontal neocortex converge on the entorhinal region and amygdala by way of multiple cortical relay stations. These connections comprise the afferent trunk of the limbic loop, thereby making the neocortex the chief source of input to the human limbic system. The data are subsequently processed by the entorhinal region, amygdala, and hippocampal formation, which represent the principal governing entities within the limbic system. Projections from all components of the limbic loop supply the efferent trunk, which exerts important influence on the prefrontal cortex (Fig. 1B,D). The limbic loop centers play significant roles in memory functions as well as in the maintenance of emotional equilibrium. Notably, these centers are the sites that are most prone to develop Alzheimer-related neurofibrillary lesions.

INTRANEURONAL AGGREGATION OF ABNORMALLY PHOSPHORYLATED TAU PROTEIN

AD-related cytoskeletal alterations result from the formation of an abnormally phosphorylated and aggregated tau protein within a few susceptible classes of neurons. In healthy nerve cells, the tau protein stabilizes microtubular components of the neuronal cytoskeleton that are involved in transporting substances between cellular compartments. Destabilization of the microtubules and obstruction of axonal transport owing to the formation of abnormal tau protein probably result in inappropriate protein metabolism, synaptic malfunction, and impaired signaling by retrograde neurotrophic factors. Decline in these functions may contribute significantly to neuronal death *(21–23)*. The initial product of the pathological phosphorylation is a soluble nonargyrophilic tau protein. In this state, the protein is evenly distributed throughout the cytoplasm of the afflicted nerve cells (group 1 in Fig. 2), which do not yet exhibit any obvious morphological alterations *(24,25)*. Such neurons in the "pretangle" phase appear initially in the transentorhinal region, the site of the earliest cortical AD-related lesions. The later stages of tangle formation are characterized by an aggregation of the abnormal tau protein and the appearance of insoluble argyrophilic precipitates (groups 2 and 3 in Fig. 2). The distal dendritic segments of involved cells become abnormally curved, dilated, and probably detached from the proximal stem. Gracile NTs appear within the twisted dendrites and NFT formation begins in the soma. The argyrophilic fibrillary material accumulates gradually, fills large portions of the cytoplasm, and occasionally extends into the proximal dendrites. After deterioration of the parent cell, the pathological material remains visible in the tissue as an extraneuronal tangle ("ghost tangle"; groups 4 and 5 in Fig. 2).

STAGES IN THE DEVELOPMENT OF NEUROFIBRILLARY TANGLES AND NEUROPIL THREADS

Pathoarchitectonic analyses demonstrate that the destructive process begins in predisposed cortical induction sites, then infiltrates other portions of the cerebral cortex and specific subcortical nuclei in a consistent, predictable topographic sequence *(6,15,26)*. Specific projection cells of the transentorhinal region are the first cortical neurons to become involved in the pathological process. The lesions advance from the transentorhinal region and gradually appear in the entorhinal region proper, the hippocampal formation, amygdala, in higher-order multimodal association areas of the neocortex, and eventually in the primary motor area as well as primary sensory fields. This topographic sequence is remarkably consistent across cases. Through postmortem examination of the distribution pattern and

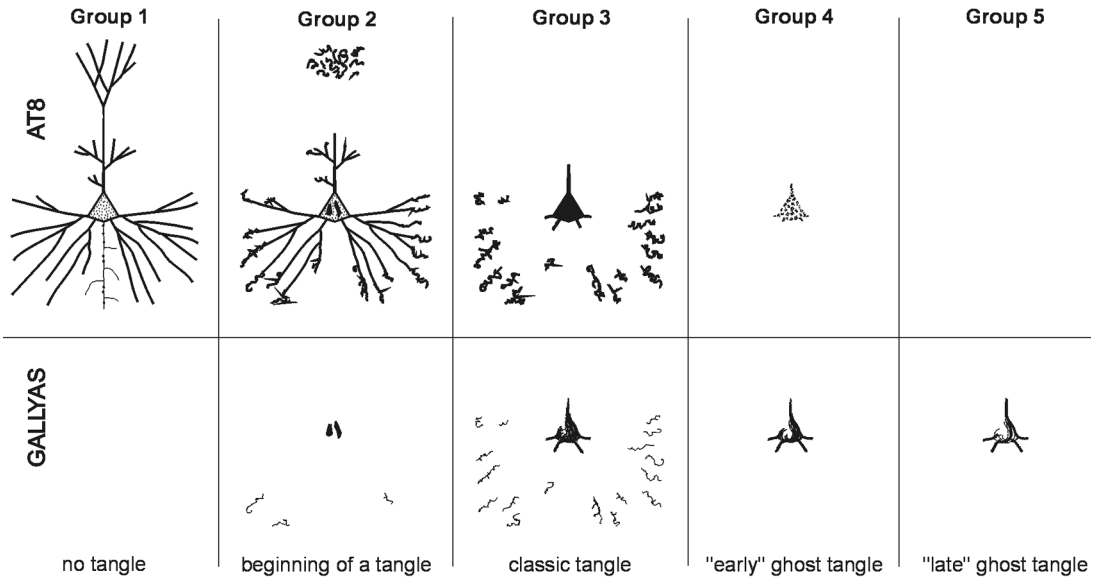


Fig. 2. Schematic drawing that summarizes AT8 immunostaining for abnormally phosphorylated tau protein with the corresponding Gallyas silver staining. The progression of pathological alterations of the neuronal cytoskeleton is shown from group 1 neuron to group 5 structure. Fine dots indicate granular AT8 immunostaining, whereas large dots represent degenerating terminals attached to the disintegrated cell body. Ghost tangles gradually lose anti-tau immunoreactivity (groups 4 and 5). Reprinted with permission from Heidelberg *(25)*.

severity of the cytoskeletal pathology, six stages in the evolution of the neurofibrillary changes have been differentiated *(6,27)*. Since 1997, these stages have been integrated into the consensus recommendations for the postmortem diagnosis of AD by the National Institutes on Aging and by the Reagan Institute Working Group *(28,29)*. In a biochemical study, the predictable sequence of AD-related neurofibrillary lesions was reproduced using Western blot detection of the abnormally phosphorylated and aggregated tau protein *(30)*.

Transentorhinal Stages I and II

The transentorhinal region, normally hidden in the depths of the rhinal sulcus, is the first cortical region to exhibit neurofibrillary changes. This region represents the portal for neocortical information that enters the limbic loop *(20)*. In stage I, the lesions are confined to a few projection cells at this site (Fig. 3A). Increased transentorhinal involvement, together with modest participation of the entorhinal region proper and the first Ammon's horn sector, are seen in stage II (Fig. 3B,C). This limited destruction does not yet manifest itself in the form of clinical symptoms. Accordingly, stages I and II represent the silent, preclinical phase of the disease *(31)*.

Limbic Stages III and IV

Severe affection of the transentorhinal and entorhinal regions is the central feature of stage III (Fig. 3D). Moderate alterations occur in the hippocampal formation, in temporal and insular proneocortical areas, and in a few subcortical nuclei. The mature neocortex remains virtually free of neurofibrillary changes. In stage IV, the destructive process progresses from the entorhinal territory into adjoining higher-order association areas of the neocortex (Fig. 3E,F). The lesions that typify both of these stages are capable of producing the first clinically detectable functional deficits, because they hamper the data exchange between the sensory association fields, the higher-order components of the

limbic system, and the prefrontal cortex. Connections between components of the limbic loop are interrupted at multiple sites, and the influence of the limbic system on the prefrontal cortex becomes markedly reduced. Many patients with stage III or IV pathology exhibit mental deterioration and subtle personality aberrations, whereas in others, the appearance of symptoms still may be obscured by individual reserve capacities *(13)*. Because of the common occurrence of initial clinical symptoms and characteristic brain lesions, stage III or IV is regarded as representing the morphological counterpart of incipient AD *(11,32–35)*.

The Neocortical Stages V and VI

At present, the initial diagnosis of AD by physicians is usually made when patients are in the final phase of the illness, corresponding to stages V and VI (Fig. 3G–I). The hallmark of stage V is the widespread devastation of the neocortex (Fig. 3G). From inferior temporal areas, the lesions spread superolaterally, and large numbers of NFTs/NTs gradually infest the extended multimodal association areas of the neocortex. Only the acoustic system, the primary motor field, primary sensory areas, and unimodal secondary fields remain uninvolved or sustain only mild damage. In stage VI, the pathological process even penetrates into these fields. The end stages of AD are accompanied by a macroscopically detectable cortical atrophy, ventricular widening, and a notable loss in brain weight. With the degeneration of the neocortex, patients become severely demented *(13)*, and major autonomic dysfunctions reflect the far-reaching devastation of the limbic loop centers.

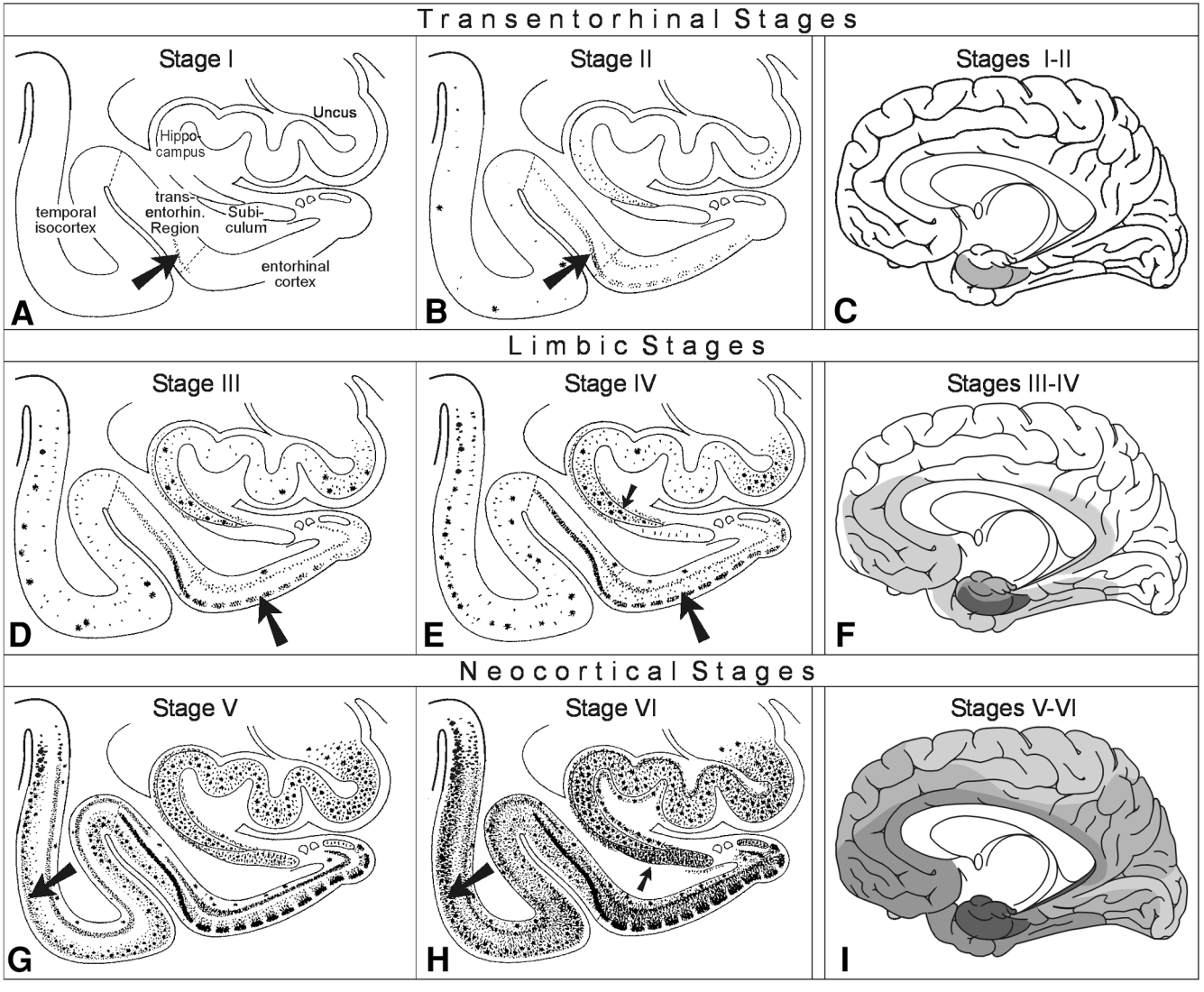
PREVALENCE OF AD-RELATED NEUROFIBRILLARY CHANGES IN NONSELECTED AUTOPSY BRAINS

Age continues to be acknowledged as the single most important risk factor for AD. The relationship between age and AD-related neurofibrillary changes was studied in a large number of nonselected brains at autopsy (n = 2661) *(27)*. By extending this previously published sample, the diagram in Fig. 4 summarizes the NFT stages of 5089 nonselected brains collected postmortally between 1986 and 2002. The columns show the percentage of cases in transentorhinal, limbic, or isocortical stages for the respective age groups. The diagram illustrates a continuum of lesions, beginning with the first NFT at stage I and going on to include the massive destruction seen in fully developed AD at stage VI. The fact that NFTs/NTs occur in a very large proportion of the aging population does not detract from their insidious nature, nor should it mislead us to view them as normal concomitants of aging *(10,28)*. There are considerable interindividual differences regarding the point at which the first "pretangle"-phase neurons begin to develop. The preclinical stages occasionally can be detected at a surprisingly young age. Approximately 23% of individuals in the age group from 30 to 39 years exhibit abnormal changes corresponding to stage I or II. The earliest lesions occur in young, otherwise healthy brains. Several decades elapse between the onset of histologically verifiable lesions and those phases of the illness in which the damage is extensive enough for clinical symptoms to become apparent *(36)*.

SELECTIVE VULNERABILITY IN ALZHEIMER'S DISEASE

The destructive process that underlies AD not only affects specific areas, layers, and subcortical nuclei but also targets only a few of the many types of nerve cells in the human brain *(26)*. It still is not known why some kinds of neurons tend to develop NFTs/NTs, whereas others do not do so until the last stages of the disease.

It has been postulated that neurofibrillary changes are a secondary phemomenon induced by the toxic influence of extracellular β-amyloid deposits designated as "plaques" (review in ref. *4*). Nonetheless, this hypothesis is fraught with inconsistencies. The brain regions, for example, that are most susceptible to the neurofibrillary changes are the ones that are relatively resistant to β-amyloid deposition. For instance, as detailed above, the entorhinal cortex and hippocampal formation are affected by neurofibrillary pathology in the early stages of AD. By contrast, these same regions


Transentorhinal Stages
Stage I
Uncus
Hippo-campus
trans-entorhin. Region
Subi-culum
temporal isocortex
entorhinal cortex
A
Stage II
B
Stages I-II
C
Limbic Stages
Stage III
D
Stage IV
E
Stages III-IV
F
Neocortical Stages
Stage V
G
Stage VI
H
Stages V-VI
I

develop amyloid plaques only in advanced stages of β-amyloid deposition *(37)*. In comparison to neurofibrillary changes the initial β-amyloid deposits evolve in a rather widespread, unpredictable manner and are capable of appearing in nearly any neocortial region *(31,38)*.

During the search for other putative pathogenic factors in AD, it was observed that most of the neuronal types with a propensity for succumbing to the neurofibrillary changes mature late during ontogenesis of the human brain *(39)*. In the cerebral cortex, all NFT-bearing nerve cells belong to the class of pyramidal neurons, and those with long ipsilateral cortico-cortical connections are particularly prone to become involved. In subcortical nuclei, most of the vulnerable cells are also characterized by a conspicuously lengthy axon *(40)*. Late-myelinating cortical areas and layers develop NFTs and NTs earlier and at higher densities than those that commence myelination early. As such, the pathological changes in AD develop in the inverse sequence of cortical myelination during early development of the brain *(39)*.

ANIMAL MODELS OF ALZHEIMER-RELATED NEUROPATHOLOGY

Because of the limitations imposed on experimental studies of the human brain, the question of whether AD-related changes can be investigated in experimental animals is of considerable importance. Amyloid plaques can be induced in transgenic mice that express APP mutations causing autosomal dominant forms of AD in humans (review in ref. *41*). These transgenic mice have provided insights into the pathogenesis and possible treatment of β-amyloid deposition *(41)*. Recent studies have succeeded in generating authentic NFTs in transgenic mice that express human FTDP-17-associated mutations *(42)*. The severity of neurofibrillary changes in FTDP-17 mice is augmented by cortical injections of fibrillar β-amyloid *(43)*. Likewise, the density of NFTs is increased in mice which are carriers of both FTDP-17 and AD-related APP mutations *(44)*. These murine models serve as a means for elucidating possible modulating effects of β-amyloid on the expression of NFTs.

All of the transgenic models are inherently limited by the large phylogenetic gap that exists between the murine brain and that of humans. Nonhuman primate models could help to narrow this gap. In this context, it is of interest to note that a conspicuous pattern of tau pathology was recently revealed in baboons *(45–47)*. The tau pathology in these nonhuman primates preferentially affects neurons and glial cells in the medial temporal lobe. In some of the older animals, a specific pattern of tau pathology was noted in the entorhinal cortex, resembling an early stage of AD-related pathology (Fig. 5A–C). Filamentous tau-positive inclusions accumulated in the dentate granule cells of a 30-year-old animal (Fig. 5D–G).

The aged baboon thus provides a potentially valuable nonhuman primate model for studies of the pathogenesis of selective neuronal tau pathology as it is characteristic of all human tauopathies, including AD. Experiments on both transgenic mice and nonhuman primates may complement one another, thereby helping to pinpoint pathogenic factors that underlie the neurofibrillary pathology in the aging human brain.

SUMMARY

The neuropathological hallmarks of AD are comprised of extracellular and intracellular precipitations of insoluble protein aggregates. Extracellular aggregates consist of the β-amyloid peptide, which is derived from amyloid precursor protein. Intracellular neurofibrillary inclusions are composed of abnormally phosphorylated and aggregated microtubule-associated tau protein. The intracellular lesions develop in the form of neurofibrillary tangles and neuropil threads. The overall amount of these

---

Fig. 3. *(see opposite page)* Distribution pattern of neurofibrillary changes in the course of AD. On the left and in the middle, typical lesions observed in cross sections of the hippocampus, entorhinal region, and temporal neocortex are shown schematically as they appear in appropriately stained sections for each of the six stages in the development of neurofibrillary tangles and neuropil threads. Arrows designate key features discussed in the text. On the right, locations and density of lesions are indicated by shading on medial views of a right hemisphere.

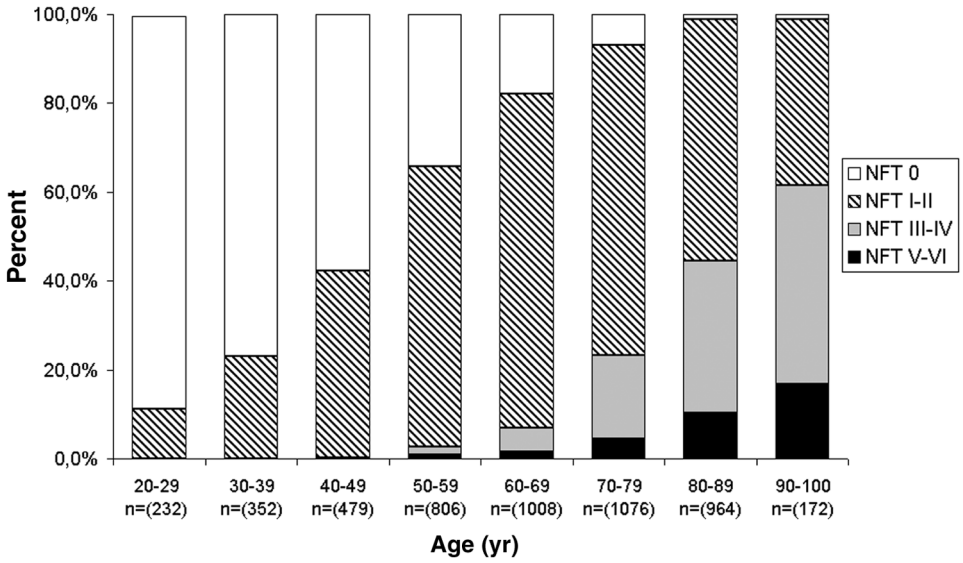


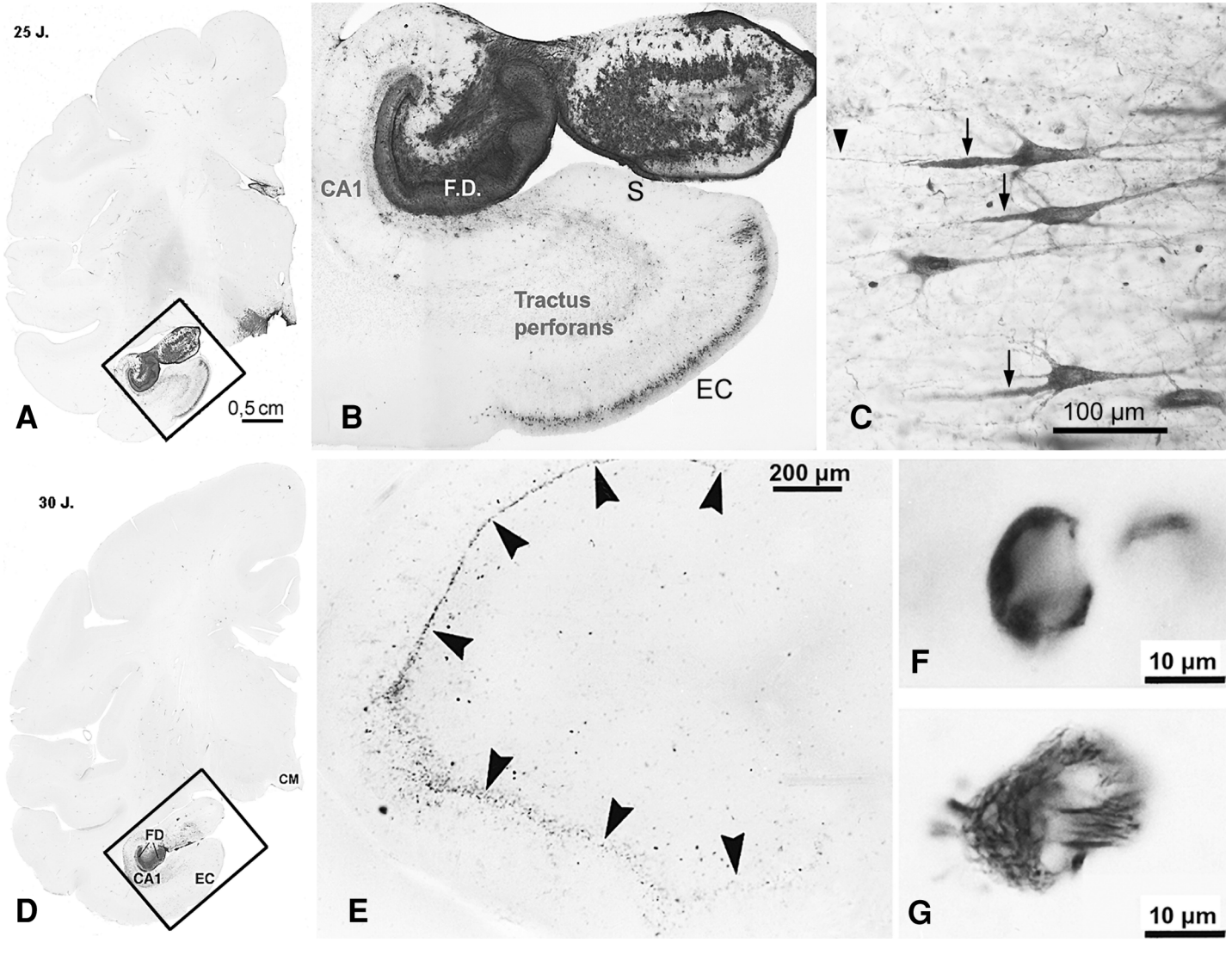
Fig. 4. Procentual frequency of the six stages in the development of AD-related neurofibrillary changes in 5089 nonselected autopsy cases (shown by 10-year age groups). Frequency and severity of the lesions increase with age. The early transentorhinal stages I/II are very common, whereas the symptomatic end stages V and VI are confined largely to elderly age groups. NFT, neurofibrillary tangles.

neurofibrillary changes correlates well with the severity of neuronal cell loss and clinical symptoms. Specific neuronal subsets of the limbic system are most prone to neurofibrillary changes. The lesions advance in a predictable manner from the transentorhinal region and gradually appear in the entorhinal region proper, the hippocampal formation, amygdala, and finally in higher-order association areas of the neocortex. Through postmortem examination, six stages in the evolution of neurofibrillary changes can be differentiated. Several decades elapse between the onset of histologically verifiable lesions and those stages of the illness in which the damage is extensive enough for clinical symptoms to become apparent. The causes underlying the selective vulnerability in AD are still undetermined. The recent identification of authentic tau pathology in transgenic mice and nonhuman primates may lead to experimental studies increasing our knowledge of these enigmatic changes.

ACKNOWLEDGMENTS

This study was supported by Deutsche Forschungsgemeinschaft, Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie, and Degussa of Hanau. The skillful assistance of Miss I. Szász (drawings) is gratefully acknowledged.

Fig. 5. *(see facing page)* Tau pathology in baboons as detected by AT8-immunostaining **(A–D)** and by Gallyas silver staining **(E–G)** (100-µm-thick sections). **(A–C)** Tau pathology in a 25-year-old baboon. **(A)** Low-power view demonstrating AT8-ir changes in the basal medial temporal lobe (framed box). **(B)** The changes preferentially affect the fascia dentata (FD) and the projections neurons in the lamina II of the entorhinal cortex (EC). The subiculum (S) remains virtually untouched; mild involvement is seen in the first Ammon's horn sector (CA1). **(C)** Multipolar projection neurons of entorhinal layer II (Pre-α) with aberrant somatodendritic localization of abnormal tau protein. **(D–G)** Neurofibrillary changes in a 30-year-old male baboon. **(D)** A dense accumulation of AT8-positive cytoskeletal changes is noted in the hippocampal formation (framed). **(E)** Layer-specific accumulation of Gallyas-positive neurofibrillary tangles in the granule cell layer (traced out by arrowheads). **(F)** Typical crescent-shaped NFT located in the granule cell layer. **(G)** Large NFT in the hilus (arrow). Scale bar in **(A)** also applies for **(D)**. (**A–C** reproduced with permission from *[46]* with permission from Elsevier Science, © 2000; **D–G** reproduced with permission from the *Journal of Neuropathology and Experimental Neurology [45]*.)


25 J.
0,5 cm
A
CA1
F.D.
S
Tractus
perforans
EC
B
100 µm
C
30 J.
CM
FD
CA1
EC
D
200 µm
E
10 µm
F
10 µm
G

REFERENCES

1. Evans, D.A. et al.: Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA 1989; 262: 2551–2556.
2. McKhann, G. et al.: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939–944.
3. Beyreuther, K.; Masters, C.L.: Amyloid precursor protein (APP) and beta amyloid-4 amyloid in the etiology of Alzheimer's disease: precursor product relationships in the derangement of neuronal function. Brain Pathol 1991; 1: 241–252.
4. Selkoe, D.J.: Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 2001; 81: 741–766.
5. Arriagada, P.V. et al.: Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 1992; 42: 631–639.
6. Braak, H.; Braak, E.: Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991; 82: 239–259.
7. Esiri, M.M. et al.: Aging and dementia. In: Graham, D.L.; Lantos, P.I. (eds.): Greenfield's neuropathology. Arnold, London, 1997: 153–234.
8. Feany, M.B., et al.: Neurodegenerative disorders with extensive tau pathology: a comparative study and review. Ann Neurol 1996; 40: 139–148.
9. Ikeda, K. et al.: Glial tau pathology in neurodegenerative diseases: their nature and comparison with neuronal tangles. Neurobiol Aging 1998; 19: S85–S91.
10. Hutton, M. et al.: Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393: 702–705.
11. Bancher, C. et al.: Neuropathological staging of Alzheimer lesions and intellectual status in Alzheimer's and Parkinson's disease. Neurosci Lett 1993; 162: 179–182.
12. Price, J.L.; Morris, J.C.: Tangles and plaques in non-demented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999; 45: 358–368.
13. Riley, K.P. et al.: Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. Ann Neurol 2002; 51: 567–577.
14. Kemper, T.L.: Senile dementia: a focal disease in the temporal lobe. In: Nandy, E. (ed.): Senile dementia: a biomedical approach. Elsevier, Amsterdam, 1978: 105–113.
15. Hyman, B.T. et al.: Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 1984; 225: 1168–1170.
16. Hyman, B.T. et al.: Memory-related neural systems in Alzheimer's disease: An anatomic study. Neurology 1990; 40: 1721–1730.
17. van Hoesen, G.W.; Hyman, B.T.: Hippocampal formation: anatomy and the patterns of pathology in Alzheimer's disease. Progr Brain Res 1990; 83: 445–457.
18. van Hoesen, G.W. et al.: Entorhinal cortex pathology in Alzheimer's disease. Hippocampus 1991; 1: 1–8.
19. Braak, H.; Braak, E.: Architectonics as seen by lipofuscin stains. In: Peters, A.; Jones, E.G. (eds.): Cerebral cortex. Vol. 1: Cellular organization of the cerebral cortex. Plenum Press, New York, 1984: 59–104.
20. Braak, H.; Braak, E.: Temporal sequence of Alzheimer's disease-related pathology. In: Peters, A.; Morrison, J.H. (eds.): Cerebral cortex. Vol. 14, Neurodegenerative and age-related changes in structure and function of the cerebral cortex. KluwerPlenum, New York, 1999: 475–512.
21. Goedert, M.: Tau protein and the neurofibrillary pathology of Alzheimer's disease. Trends Neurosci 1993; 16: 460–465.
22. Iqbal, K. et al.: Mechanism of neurofibrillary degeneration in Alzheimer's disease. Molec Neurobiol 1994; 9: 119–123.
23. Mandelkow, E.; Mandelkow, E.M.: Microtubules and microtubule-associated proteins. Curr Opin Cell Biol 1995; 7: 72–81.
24. Bancher, C. et al.: Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. Brain Res 1989; 477: 90–99.
25. Braak, E. et al.: A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. Acta Neuropathol 1994; 87: 554–567.
26. Hyman, B.T.; Gomez-Isla, T.: Alzheimer's disease is a laminar, regional, and neural system specific disease, not a global brain disease. Neurobiol Aging 1994; 15: 353–354.
27. Braak, H.; Braak, E.: Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997; 18: 351–357.
28. Hyman, B.T.; Trojanowski, J.Q.: Editorial on consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institutes of Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol 1997; 56: 1095–1097.
29. Hyman, B.T.: New neuropathological criteria for Alzheimer's disease. Arch Neurol 1998; 55: 1174–1176.
30. Delacourte, A. et al.: The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 2000; 52: 1158–1165.
31. Delacourte, A. et al.: Non-overlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease. Neurology 2002; 59: 398–407.

32. Jellinger, K., et al.: Alzheimer lesions in the entorhinal region and isocortex in Parkinson's and Alzheimer's diseases. Ann NY Acad Sci 1991; 640: 203–209.
33. Duyckaerts, C. et al.: Diagnosis and staging of Alzheimer's disease in a prospective study involving aged individuals. Neurobiol Aging 1994 (suppl. 1); 15: 140–141.
34. Dickson, D.W. et al.: Identification of normal and pathological aging in prospectively studied non-demented elderly humans. Neurobiol Aging 1991; 13: 179–189.
35. Hulette, C.M. et al.: Neuropathological and neuropsychological changes in "normal" aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. J Neuropathol Exp Neurol 1998; 57: 1168–1174.
36. Ohm, T.G. et al.: Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. Neuroscience 1995; 64: 209–217.
37. Thal, D.R. et al.: Sequence of A beta-protein deposition in the human medial temporal lobe. J Neuropathol Exp Neurol 2000; 59: 733–748.
38. Thal, D.R. et al.: Phases of A beta-deposition in the human brain and its relevance for the Development of AD. Neurology 2002; 58: 1791–1800.
39. Braak, H.; Braak, E.: Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. Acta Neuropathol 1996; 92: 197–201.
40. Braak, H.; Braak, E.: Pathology of Alzheimer's disease. In: Calne, D.B. (ed.): Neurodegenerative diseases. Saunders, Philadelphia, 1994: 585–613.
41. Hock, B.J.; Lamb, B.T.: Transgenic mouse models of Alzheimer's disease. Trends Genet 2001; 17: S7–S12.
42. Ishihara, T. et al.: Age-dependent induction of congophilic neurofibrillary tau inclusions in tau transgenic mice. Am J Pathol 2001; 158: 555–562.
43. Götz, J. et al.: Formation of neurofibrillary tangles in P3011 tau transgenic mice induced by Abeta 42 fibrils. Science 2001; 293: 1491–1495.
44. Lewis, J. et al.: Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science (2001); 293: 1487–1491.
45. Schultz, C. et al.: Filamentous tau pathology in nerve cells, astrocytes, and oligodendrocytes of aged baboons. J Neuropathol Exp Neurol 2000; 59: 39–52.
46. Schultz, C. et al.: Age-related progression of tau pathology in brains of baboons. Neurobiol Aging 2000; 21: 905–912.
47. Schultz, C. et al.: The brain of the aging baboon: a non-human primate model for neuronal and glial tau pathology. In: Erwin, J.M.; Hof, P.R. (eds.): Aging in non-human primates. Interdiscipl Top Gerontol, Vol. 31. Karger, Basel, 2002: 118–129.

http://www.springer.com/978-0-89603-891-2

Alzheimer's Disease
A Physician's Guide to Practical Management
Richter, R.W.; Zoeller Richter, B. (Eds.)
2004, XIV, 479 p. 39 illus., Hardcover
ISBN: 978-0-89603-891-2
A product of Humana Press