Neuropathology of Alzheimer's Disease

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OUTLINE

ABSTRACT

Alois Alzheimer first pointed out that the disease which would later bear his name has a distinct and recognizable neuropathological substrate. Since then, much has been added to our understanding of the pathological lesions associated with the condition. The 2 primary cardinal lesions associated with Alzheimer's disease are the neurofibrillary tangle and the senile plaque. The neurofibrillary tangle consists of abnormal accumulations of abnormally phosphorylated tau within the perikaryal cytoplasm of certain neurons. The senile plaque consists of a central core of beta-amyloid, a 4-kD peptide, surrounded by abnormally configured neuronal processes or neurites. Other neuropathological lesions are encountered in cases of Alzheimer's disease, but the disease is defined and recognized by these 2 cardinal lesions. Other lesions include poorly understood changes such as granulovacuolar degeneration and eosinophilic rodlike bodies (Hirano bodies). The loss of synaptic components is a change that clearly has a significant impact on cognitive function and represents another important morphological alteration. It is important to recognize that distinguishing between Alzheimer's disease, especially in its early stages, and normal aging may be very difficult, particularly if one is examining the brains of patients who died at an advanced old age. It is also noted that instances of pure forms of Alzheimer's disease, in the absence of other coexistent brain disease processes, such as infarctions or Parkinson's disease–related lesions, are relatively uncommon, and this must be taken into account by researchers who employ postmortem brain tissues for research. ***Mt Sinai J Med 77:32–42, 2010.*** *© 2010 Mount Sinai School of Medicine*

Key Words: Alzheimer's disease, beta-amyloid, neurofibrillary tangle, neuropathology, senile plaque.

Since the original description by Alois Alzheimer of the disease that bears his name, the autopsy continues to represent the means by which the definitive diagnosis is made. In the absence of a valid biological marker, this situation continues. Furthermore, in the absence of a truly complete animal model, Alzheimer's disease remains a disorder of humans, and studies of actual patients with the condition and their brain tissues represent a critical route by which the condition can truly be characterized and understood. It is not likely that this situation will change in the near future, and thus the work of numerous neuropathologists and other neuroscientists who study human autopsy–derived specimens will remain vital to further scientific progress on this most important age-related condition. Here we describe the neuropathological features of the disease and some of the associated issues that arise for individuals who plan research on the disorder.

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GROSSLY VISIBLE LESIONS

At the autopsy table, the brain of a patient with Alzheimer's disease does not show any grossly

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apparent alteration that can be considered to be diagnostic. By and large, any changes that are encountered are considered to be entirely nonspecific in nature and show extensive overlap with findings that are also noted in brain specimens derived from elderly individuals who had displayed normal cognitive function during life. Brain specimens obtained

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from most cases of Alzheimer's disease show a modest degree of cerebral cortical atrophy primarily but not exclusively involving the frontotemporal association cortex. In particular, this atrophy tends to spare primary motor, sensory, and visual areas. However, among elderly subjects, especially those of advanced age, there is considerable overlap between brain weight as well as measures of cerebral cortical thickness between age-matched individuals with normal cognitive function and those with Alzheimer's disease.[1] Accordingly, it becomes difficult, if not impossible, to take the brain weight or cerebral cortical thickness of any individual specimen derived from an elderly individual and, by that value alone, determine whether the person had Alzheimer's disease or not. However, when one is examining cases of Alzheimer's disease that are of presenile onset (arbitrarily set by most as an onset before 65 years of age), comparisons of the brain weight or the degree of cerebral cortical atrophy with those of age-matched controls usually reveal a clear and obvious difference upon gross inspection of the brain.

In cases of Alzheimer's disease, there is an associated loss of brain tissue that generally leads to a symmetrical dilation of the lateral ventricles (hydrocephalus ex vacuo). Again, by examining the lateral ventricles of advanced elderly individuals, one is not able to distinguish with certainty age-matched normals from cases with Alzheimer's disease. However, significant atrophy of the hippocampus, with an associated selective dilatation of the adjacent temporal horn of the lateral ventricle, represents a reasonably reliable clue upon dissection of the brain, suggesting to the neuropathologist that the case will ultimately show microscopic evidence of Alzheimer's disease. In a similar fashion, the absence of this finding is strongly suggestive that other explanations for the underlying cause of dementia will need to be sought.

MICROSCOPIC CHANGES

It is upon the histological examination of the brain specimen that a definitive diagnosis of Alzheimer's disease can be made. This diagnosis is based on the identification of a series of morphological abnormalities that are distributed in a rather stereotyped pattern. It is important to realize that virtually any

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of the alterations upon which the neuropathological diagnosis of Alzheimer's disease is made may also be seen, to some degree, in the brains of elderly individuals who during life had shown normal cognitive function. Often it requires the recognition of the extent of involvement in certain areas of the brain by such lesions for the neuropathologist to be able to declare that Alzheimer's disease was the cause of a patient's cognitive impairment. At times, this may involve subtle distinctions that require considerable experience and expertise, and at other times, the honest neuropathologist may be required to state that this diagnosis can or cannot be rendered with only a degree of probability and not certainty. This is particularly true when one is examining the brains of subjects dying within the oldest-old age range. In individuals dying at an extremely old age, the overlap of neuropathological changes between those found with severe dementia and those with intact cognitive function is extensive, and such distinctions may be very difficult. Indeed, correlations between the extent and distribution of such lesions are currently undergoing detailed scientific study using brain specimens derived from individuals in large cohorts of advanced elderly subjects who underwent rigorous longitudinal neuropsychological studies.[2]

Neurofibrillary Tangles

In his pioneering article,[3] Alois Alzheimer, describing a single case of the disease that would eventually bear his name, noted the presence of abnormal fibrous inclusions within the perikaryal cytoplasm of pyramidal neurons. These inclusions are called Alzheimer neurofibrillary tangles and to this day are considered a cardinal microscopic lesion associated with the

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disease and a requirement for making the pathological diagnosis. Neurofibrillary tangles are very difficult to see with the traditional morphological stain used by pathologists, hematoxylin and eosin. By and large, one of a variety of silver impregnation staining techniques, such as the modified Bielschowski or Gallyas technique, or the fluorochrome dye thioflavin S is typically employed to visualize neurofibrillary tangles (Figures 1 and 2). Additionally, there are a number of immunohistochemical approaches used to visualize neurofibrillary tangles. These have mostly employed antibodies directed against abnormally phosphorylated *tau* (discussed later)[4–6] (Figure 3). Because these techniques require either specialized equipment (the thioflavin S stain requires the use of a fluorescence microscope with specialized excitatory and barrier filters) or experienced histotechnologists (in the case of silver impregnation stains), most anatomic pathologists in general practice lack the capability to properly evaluate brain specimens submitted for the diagnosis of Alzheimer's disease. Such specimens are best referred to specialized neuropathology laboratories where the necessary experience and facilities are in place.

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With these special stains, within neurons with a pyramidal shape to the perikaryon, such as those of the cornu ammonis 1 (CA1) sector of the hippocampus and the layer V neurons in areas of the association cortex, the neurofibrillary tangles appear as parallel, thickened fibrils that surround the nucleus and extend toward the apical dendrite (Figure 4). When the neurofibrillary tangle occurs within a neuron with a more rounded configuration (eg, neurons within the substantia nigra and locus ceruleus), the inclusion appears as interweaving swirls of fibers, and here it is called a globoid neurofibrillary tangle.

The nature of neurofibrillary tangles has been extensively studied over the past several decades, and much has been learned about its structural components. Ultrastructurally, the neurofibrillary tangle is composed of abnormal fibrils measuring 10 nm in diameter that occur in pairs and are wound in a helical fashion with a regular periodicity of 80 nm.[7,8] On the basis of these observations, such structures are generally called paired helical filaments. The primary constituent of the neurofibrillary tangle is the microtubule-associated protein *tau*. The *tau* within neurofibrillary tangles is abnormally phosphorylated with phosphate groups attached to very specific sites

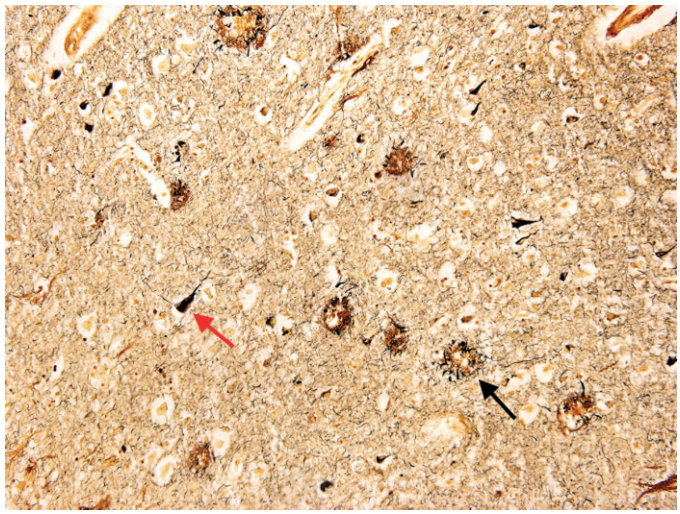

Fig 1. Photomicrograph of the temporal cortex of a patient with Alzheimer's disease (modified Bielschowski stain; original magnification, 40×). Numerous senile (neuritic) plaques (black arrow) and neurofibrillary tangles (red arrow) are shown.

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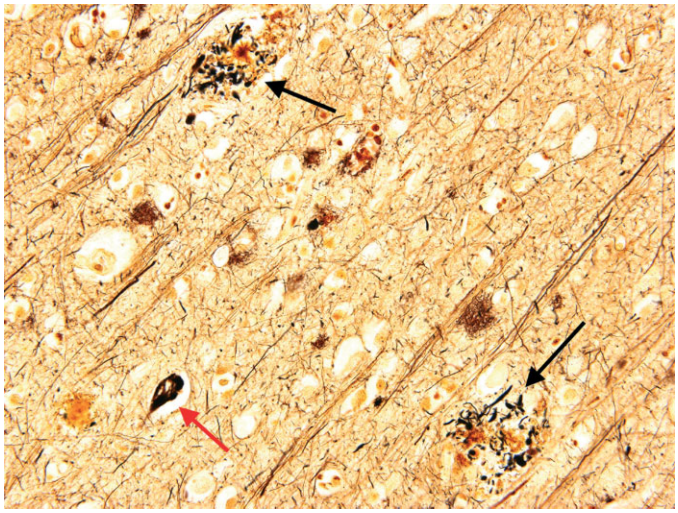

Fig 2. Photomicrograph of the temporal cortex of a patient with Alzheimer's disease (modified Bielschowski stain; original magnification, 100×). Numerous senile (neuritic) plaques (black arrows) and neurofibrillary tangles (red arrow) are shown.

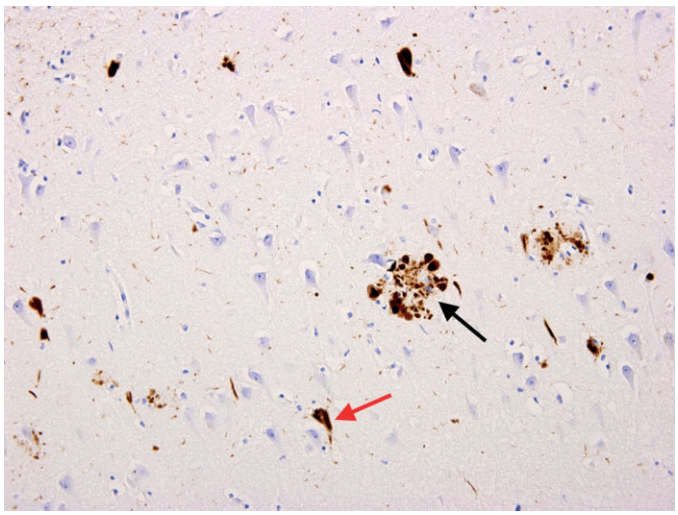

Fig 3. Temporal cortex of a patient with Alzheimer's disease (immunohistochemical stain; original magnification, 100×): the microscopic appearance of an immunohistochemical preparation using an antibody directed against abnormally phosphorylated tau (TG-3; a gift from Dr. P. Davies). This antibody prominently decorates neurofibrillary tangles (red arrow) and swollen dystrophic neurites (neuronal processes) that form the outer rim of the senile (neuritic) plaques (black arrow).

on the molecule.[9] There are a number of other protein constituents associated with the neurofibrillary tangle, such as ubiquitin,[10,11] cholinesterases,[12] and beta-amyloid 4 (βA4; discussed later),[13] but *tau* is considered to be the critical constituent of most of these structures.

The pattern of distribution of neurofibrillary tangles present in cases of Alzheimer's disease is, for the most part, rather stereotyped and predictable. Severe involvement is seen in the layer II neurons of the entorhinal cortex, the CA1 and subicular regions of the hippocampus, the amygdala, and the deeper layers (layers III, V, and superficial VI) of the neocortex.[14] Studies have shown that the extent and distribution of neurofibrillary tangles in cases of Alzheimer's disease correlate with both the degree of dementia and the duration of illness,[15,16] and this suggests that these abnormalities

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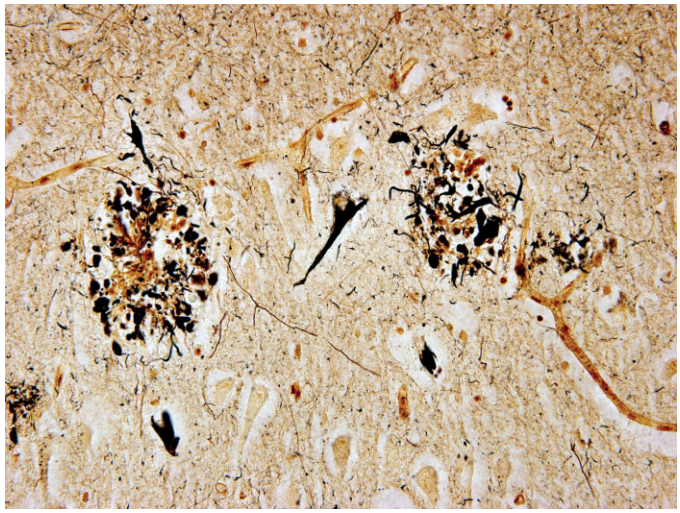

Fig 4. Photomicrograph of the temporal cortex of a patient with Alzheimer's disease (modified Bielschowski stain; original magnification, 400×). Two senile (neuritic) plaques with a neurofibrillary tangle between them are shown.

do have some direct impact on the functioning capacity of the brain. However, it is also clear that other factors contribute to the production of the clinical features of the disease. Although the neurofibrillary tangle is considered a cardinal histopathological feature of Alzheimer's disease, it should be kept in mind that this neuropathological lesion may also be encountered in association with many other disease states.[17] These include disorders such as postencephalitic parkinsonism, posttraumatic dementia or dementia pugalistica, type C Niemann-Pick disease, and amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam. It remains unclear why diseases with such a wide range of underlying etiological mechanisms should all show this one particular neuropathological abnormality.

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Senile Plaques

The other cardinal pathological lesion encountered in patients suffering from Alzheimer's disease is the senile or neuritic plaque. Senile plaques are complex structures that are defined by the presence of a central core accumulation of a 4-kD protein with a beta-pleated sheet configuration called βA4.[18–20] The predominant beta-pleated sheet configuration of this protein confers its ability to bind the planar dye Congo red and produce birefringence when illuminated by polarized light; it thus conforms to the physical definition of an amyloid.

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The brains of aged individuals and cases of Alzheimer's disease may also contain several forms of βA4-containing plaques, and at times, the nomenclature employed for these lesions in the literature can be confusing. The senile or neuritic plaque has a central core of βA4 protein arranged in a radial fashion and is surrounded by a corona of abnormally formed neurites (or neuronal processes, either dendrites or axons). These abnormal or dystrophic neurites stain strongly with the same silver impregnation stains used to identify the neurofibrillary tangles (Figures 2 and 5), and ultrastructurally, these structures contain dense bodies, membranous profiles, and packets of paired helical filaments. In the periphery of the neuritic plaque, one commonly encounters 1 to several microglial cells and, less frequently, reactive astrocytes. Whether these microglial cells are actively involved in a neuroinflammatory pathogenetic cascade or are reacting to the presence

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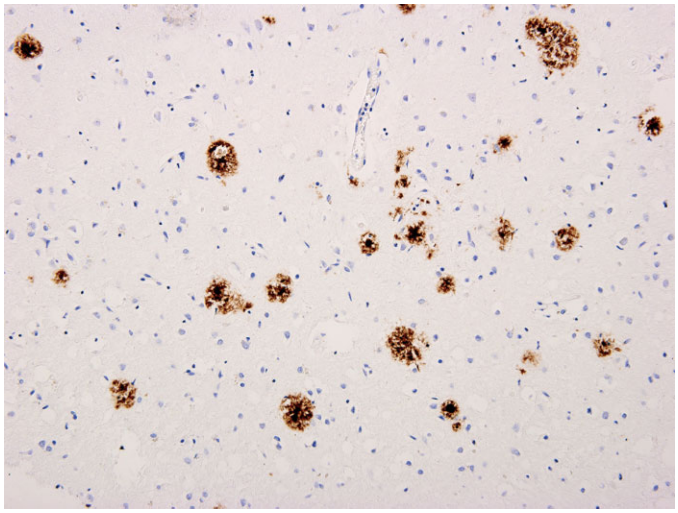

Fig 5. Temporal cortex of a patient with Alzheimer's disease (immunohistochemical stain; original magnification, 100×): the microscopic appearance of an immunohistochemical preparation using an antibody directed against the components of beta-amyloid (4G8; a gift from Dr. Robakis). This antibody selectively decorates the numerous senile plaques present in this case of advanced Alzheimer's disease and demonstrates the extent of amyloid accumulation that one may encounter in the terminal phases of the disease.

of constituents within these lesions remains a matter of intense debate.

Through the use of immunohistochemical techniques with antibodies raised against portions of the βA4 molecule, it has been recognized that focal diffuse deposits of this amyloid protein may occur in the cerebral cortex in the absence of accompanying dystrophic neurites.[21] Such deposits of βA4 will also stain with the aforementioned silver-based stains and especially with enhanced silver stains such as those of the Hedreen, Tago, and Campbell-Switzer methods, and they are called diffuse plaques. Diffuse plaques are very commonly encountered in the brains of elderly individuals and can be seen in relatively large numbers in the absence of any associated evidence of cognitive impairment.[22–24]

A third form of plaque, consisting of a dense core of βA4 that does not show any accompanying dystrophic neurites, has also been identified. Such plaques have been called burned-out plaques and end-stage plaques and are considered to be the remnants of what were once neuritic plaques.[25] Because neuropathological observations of such lesions are, by their very nature, cross-sectional, these interpretations should be best thought of as speculation.

The βA4 protein is derived from a larger amyloid precursor protein, a highly conserved transmembrane glycoprotein.[20] The βA4 portion of the precursor protein is formed through the action of 2 secretases, which split the amino and carboxyl terminals of the 4-kD segment, which is then released and accumulates within brain tissues.[26–28] The carboxyl end cleavage is ragged, with longer forms (having a total of 42 or 43 amino acids) tending to be deposited within senile plaques and a shorter form (containing 40 amino acids) tending to accumulate within the leptomeningeal and cerebral cortical and cerebellar blood vessels (congophilic angiopathy; discussed later).[29] The central cores of senile plaques have been shown to contain several other proteins, such as heparan sulfate glycoproteins,[30–32] apolipoprotein E,[33–35] complement proteins,[36–38] and alpha-1-antichymotrypsin.[39]

Vascular Amyloid Deposition (Congophilic Angiopathy)

In addition to βA4 accumulating in the central core of neuritic plaques, this protein also tends to deposit in the walls of the cerebral cortical blood vessels. The protein accumulates in the walls of small arteries and arterioles of the leptomeninges and within the gray matter of the cerebral cortex. This lesion is often called congophilic angiopathy, which reflects the ability of the Congo red dye to attach to the lesion. These accumulations of βA4 within the vessel walls do not appear to clog the vascular lumina or otherwise interfere with the function of these vessels.

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However, when the degree of vascular involvement is severe, there is a tendency for spontaneous vascular rupture leading to a focal accumulation of blood in the brain tissues. Such hemorrhages are generally not encountered in and around the lenticular nuclei and thalamus, such as is seen as a result of uncontrolled systemic hypertension. These hemorrhages tend to occur in the white matter of the frontal and/or occipital poles, are often small and multiple, and may be microscopic in size. When they are large (this is a relatively rare situation), they may be multiple and are commonly called lobar hemorrhages. Although rare, such lobar hemorrhages represent one of the few fatal intracerebral complications of Alzheimer's disease.

Granulovacuolar Degeneration

Simchowitz[40] first identified granulovacuolar degeneration in 1911. This is a poorly understood lesion that consists of an intraneuronal cluster of small vacuoles measuring 2 to 4 μm in diameter, each containing a small, dense basophilic granule that typically measures approximately 1 μm in diameter. These granule-containing vacuoles are encountered almost exclusively within the perikaryal cytoplasm of pyramidal neurons of the hippocampus, typically in the neurons that form the junction between the cornu ammonis 2 (CA2) and CA1 sectors of Ammon's horn. They are also seen in lesser numbers in the neurons of the remainder of the CA1 hippocampal region. Ultrastructurally, they are described as membrane-bound structures with a clear vacuolar matrix containing an electron-dense central granule.[41] The central granules stain intensely with silver impregnation stains and with antibodies directed against phosphorylated neurofilaments, tubulin, *tau*, and ubiquitin.[42–44] Little is known about the nature of these lesions or their significance. They are seen in brain specimens derived from elderly individuals with normal cognitive function, but 2 studies have shown that large numbers of such lesions in the boundary zone between the CA1 and CA2 regions of the caudal aspect of the hippocampus correlate well with a diagnosis of Alzheimer's disease.[45,46]

Eosinophilic Rodlike Inclusions (Hirano Bodies)

Eosinophilic rodlike inclusions, or Hirano bodies, are intensely eosinophilic perineuronal lesions encountered within the CA1 region of the hippocampus. These lesions were first identified by Asao Hirano in his studies of amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, and they are now commonly called Hirano bodies.[47] This disease is mostly confined to the indigenous native population living on Guam, and in this setting, large numbers of Hirano bodies are commonly encountered. Identical inclusions in much smaller numbers are also noted in some, but not all, cases of Alzheimer's disease. Hirano bodies may also occasionally be encountered in the brains of normal aged individuals with intact cognition. Hirano bodies have a very characteristic ultrastructural appearance consisting of parallel fibers that interweave in a very regular crossing pattern reminiscent of the appearance of a tweed fabric. Immunohistochemical studies indicate the presence of actin, tropomyosin, and vinculin within these bodies.[48–50] The Hirano body is currently considered to be a nonspecific lesion of unknown significance.

Synaptic Loss

Masliah and coworkers[51–54] as well as Scheff and coworkers[55–59] have demonstrated that a substantial loss in synaptic profiles occurs in the brains of patients with Alzheimer's disease. This has been investigated by the quantification of immunohistochemical markers directed against synaptic proteins, such as synaptophysin, and by quantitative electron microscopy. In comparison with normal controls, Masliah and coworkers have shown a 45% loss of the extent of staining of presynaptic boutons in cases of Alzheimer's disease. These workers have argued that this loss of the critical element for neuron-to-neuron communication constitutes the major morphological counterpart to cognitive loss in Alzheimer's disease. Their data indicate that this loss correlates strongly with the degree of functional impairment.[52]

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EMERGING PICTURE OF NEUROPATHOLOGY IN EARLY PHASES OF ALZHEIMER'S DISEASE

Over the years, most of the neuropathological literature related to descriptions of Alzheimer's disease and its clinicopathological correlation has tended to involve detailed examinations of the end-stage or terminal phases of the disease. Because patients with Alzheimer's disease do not typically die as a direct result of the disease itself, many patients with the disorder, especially if they had a relatively young onset of disease, will tend to survive into its more advanced stages. Such patients typically tend to survive for many years in a severely impaired state until a superimposed pneumonia or other infection emerges to ultimately serve as the cause of death. Accordingly, the brain specimen obtained from such an end-stage case will demonstrate an extensive burden of neurodegenerative lesions in a widespread distribution. Specimens derived from such terminal cases will typically show a very heavy burden of both neurofibrillary tangles and senile plaques. In such cases, it is virtually impossible to dissect out meaningful clinicopathological correlational relationships.

It is clear that Alzheimer's disease is a slowly progressive disorder whose lesions accumulate within the brain over a period of many years. How long it takes before a sufficient extent of neuropathological damage occurs to produce a degree of functional impairment that might allow a clinical diagnosis to be considered is not known, but it is likely to take many years, if not decades, for this to occur. Additional years are likely needed for the further progression from the early stages to the middle stages of the disorder. Presumably, the progressive accumulation of a burden of the aforementioned neuropathological lesions underlies this clinical progression. Recognizing that advanced age, with its inherent frailties and multiple medical comorbidities, leads to a high death rate, we anticipate that many individuals of advanced age will die of unrelated causes while they are also passing through the early clinical and even preclinical stages of Alzheimer's disease. It can be argued that the neuropathological changes found in such preclinical cases of Alzheimer's disease might well have been considered to be within the range of normal aging.

This has led some to begin thinking about the progressive stages of involvement of the brain by Alzheimer's disease and to speculate on what the earliest phases of the disease might look like. In 1991, neuroanatomists Eva and Heiko Braak published a proposed sequence of progression of the neuropathology of Alzheimer's disease, breaking the disorder down into 6 stages with increasing involvement of the brain (the so-called Braak and Braak stages). Braak and Braak stages 1 and 2 show selective involvement by neurofibrillary tangles in the transentorhinal cortex. This is followed by stages 3 and 4 with increasing limbic lobe involvement, with the final 2 stages (stages 5 and 6) showing the more typical widespread pattern of involvement in the neocortex. These Braak and Braak stages were initially developed by the evaluation of the pattern of neurodegenerative changes (predominantly neurofibrillary tangles) present in a series of 83 brain specimens derived from elderly individuals. They devised the stages by mapping out the extent and distribution of lesions in these brain specimens, but no associated clinical data were available from the patients from whom the samples were obtained. Although it is clear that not all Alzheimer's disease patients progress precisely along the stages they described, the Braak and Braak stages do represent a useful concept and have provided a format for neuropathologists to use in evaluating the relative stage of development of the disease.

ALZHEIMER'S DISEASE AND ITS ASSOCIATED CONDITIONS

It is very common for both clinicians and researchers involved in studying Alzheimer's disease to approach a patient or brain specimen, for that matter, and assume that the diagnosis is solely Alzheimer's disease and nothing else. Although this may at times be true, more often the reality is that one or another pathological process is also present in the brain in addition to Alzheimer's disease. Indeed, certainly at autopsy, it is relatively uncommon to encounter Alzheimer's disease in its pure form, that is, in the absence of 1 or more coexisting conditions. This is particularly true when one is examining the brains of advanced elderly patients who suffered from dementia. It is very important to recognize this situation when one is designing experiments involving the use of postmortem brain tissues.

The most common coexisting condition with Alzheimer's disease is stroke and more specifically ischemic infarction, another very common

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age-related brain disease. Over the age of 75 years, ischemic infarctions of the brain are rather frequently encountered, and the prevalence of such lesions rises dramatically as the age at death increases. Accordingly, it is very common to encounter 1 or more such ischemic lesions in the brains of victims of Alzheimer's disease. Very often, clinical evidence of the onset of stroke that correlates with the presence of such lesions is missing. This can arise from a lack of a referral for a neurological evaluation or from the inability of the cognitively impaired individual to give a detailed history. Inevitably, the pathologist is left with a specimen demonstrating the full neuropathological picture of Alzheimer's disease, as described previously, plus superimposed ischemic infarct(s) typically involving the territory served by the middle cerebral arteries. Over the past 20+ years of examining the brains of deceased elderly patients who suffered from dementia within the Mount Sinai Brain Bank repository, approximately 20% of cases have shown evidence of both Alzheimer's disease and superimposed brain infarction. Such cases are generally referred to as mixed dementia, and one is often left unable to determine the relative contribution of the stroke(s) in producing the cognitive impairment, as opposed to the underlying Alzheimer's disease.

Another issue of comorbid pathological features is the common occurrence of neuropathological lesions of Alzheimer's disease coexisting with those of Parkinson's disease. Neuropathological studies of large numbers of patients who, during life, had a clinical diagnosis of Alzheimer's disease demonstrate not only the neuropathological features of this disease but also evidence of neuronal degeneration of the substantia nigra pars compacta with Lewy bodies in many remaining neurons. The later findings suggest a coexistent diagnosis of Parkinson's disease. In cases of this type, it is common to also see evidence of widely distributed cortical Lewy bodies, especially if appropriate immunohistochemical preparations are made. Such cases are now commonly diagnosed as suffering from dementia with Lewy bodies, and the criteria for both clinical and neuropathological diagnoses of this condition have been written and subsequently revised by consensus committees.[60,61] The boundary line between Alzheimer's disease and Parkinson's disease and the nosologic status of dementia with Lewy bodies remains a subject of debate, but this is an important instance in which the concept of the common age-related neurodegenerative diseases remaining in a pure state is challenged.

Neuropathological studies of large numbers of patients who, during life, had a clinical diagnosis of Alzheimer's disease also demonstrate [the characteristic lesions of Parkinson's disease, that is,] neuronal degeneration of the substantia nigra pars compacta with Lewy bodies in many remaining neurons.

CONCLUSION

It is over 100 years since Alois Alzheimer first described the neurofibrillary tangles associated with Alzheimer's disease and introduced the notion that this condition has an underlying neuropathological substrate. Many more details have been added over the past century. Despite this progress, there are still important gaps in our understanding of the condition and the nature of the pathological processes taking place in the brain. Although the neuropathological diagnosis can be established with relative precision among those patients with a relatively young onset, such cases are relatively rare in comparison with the vast burden of disease encountered in individuals of advanced age. Here, the distinction from normal aging and the correlations between structure and function are very difficult to delineate and will require considerable additional study. The continued morphological study of human brain specimens derived from longitudinally assessed patients will remain the cornerstone for such research.

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DISCLOSURES

Potential conflict of interest: Nothing to report.

REFERENCES

1. Terry RD. Interrelations among the lesions of normal and abnormal aging of the brain. *Prog Brain Res* 1986; 70: 41–48.

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2. Haroutunian V, Schnaider-Beeri M, Schmeidler J, et al. Role of the neuropathology of Alzheimer disease in dementia in the oldest-old. *Arch Neurol* 2008; 65: 1211–1217.
3. Alzheimer A. Ueber eine eigenartige erkrankung der hirnrinde. *Z Gesamte Neurol Psychiatr* 1907; 18: 177–179.
4. Dickson DW, Farlo J, Davies P, et al. Alzheimer's disease. A double-labeling immunohistochemical study of senile plaques. *Am J Pathol* 1988; 132: 86–101.
5. Yen SH, Dickson DW, Crowe A, et al. Alzheimer's neurofibrillary tangles contain unique epitopes and epitopes in common with the heat-stable microtubule associated proteins tau and MAP2. *Am J Pathol* 1987; 126: 81–91.
6. Iwatsubo T, Hasegawa M, Ihara Y. Neuronal and glial tau-positive inclusions in diverse neurologic diseases share common phosphorylation characteristics. *Acta Neuropathol (Berl)* 1994; 88: 129–136.
7. Kidd M. Paired helical filaments in electron microscopy of Alzheimer's disease. *Nature* 1963; 197: 192–193.
8. Wisniewski HM, Narang HK, Terry RD. Neurofibrillary tangles of paired helical filaments. *J Neurol Sci* 1976; 27: 173–181.
9. Lee VMY, Balin BJ, Otvos L Jr, Trojanowski JQ. A major subunit of paired helical filaments and derivatized forms of normal tau. *Science* 1991; 251: 675–678.
10. Perry G, Friedman R, Shaw G, Chau C. Ubiquitin is detected in neurofibrillary tangles and senile plaque neurites of Alzheimer's disease brains. *Proc Natl Acad Sci U S A* 1987; 84: 3033–3036.
11. Love S, Saitoh T, Quijada S, et al. Alz-50, ubiquitin and tau immunoreactivity of neurofibrillary tangles, Pick bodies and Lewy bodies. *J Neuropathol Exp Neurol* 1988; 47: 393–405.
12. Mesulam MM, Moran MA. Cholinesterases within neurofibrillary tangles related to age and Alzheimer's disease. *Ann Neurol* 1987; 22: 223–228.
13. Hyman BT, Van Hoesen GW, Beyreuther K, Masters CL. A4 amyloid protein immunoreactivity is present in Alzheimer's disease neurofibrillary tangles. *Neurosci Lett* 1989; 101: 352–355.
14. Morrison JH, Hof PR. Life and death of neurons in the aging brain. *Science* 1997; 278: 412–419.
15. Hof PR, Bierer LM, Purohit DP, et al. Neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. *Arch Neurol* 1995; 52: 81–88.
16. Arriagada PV, Growdon JH, Hedley-White T, Hyman BT. Neurofibrillary tangles and not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 1992; 42: 1681–1688.
17. Wisniewski K, Jervis GA, Moretz RC, Wisniewski HM. Alzheimer neurofibrillary tangles in diseases other than senile and presenile dementia. *Ann Neurol* 1979; 5: 288–294.
18. Masters CL, Multhaup G, Simms G, et al. Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. *EMBO J* 1985; 4: 2757–2763.
19. Beyreuther K, Masters CL. Nomenclature of amyloid A4 proteins and their precursors in Alzheimer's disease and Down's syndrome. *Neurobiol Aging* 1990; 11: 66–68.
20. Kang J, Lemaire HG, Unterbeck A, et al. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature* 1987; 325: 733–736.
21. Yamaguchi H, Hirai S, Morimatsu M, et al. Diffuse type of senile plaques in the cerebellum of Alzheimer-type dementia demonstrated by beta protein immunostain. *Acta Neuropathol* 1989; 77: 314–319.
22. Gentleman SM, Bruton C, Allsop D, et al. A demonstration of the advantages of immunostaining in the quantification of amyloid plaque deposits. *Histochemistry* 1989; 92: 355–358.
23. Wolf DS, Gearing M, Snowdon DA, et al. Progression of regional neuropathology in Alzheimer disease and normal elderly: findings from the Nun study. *Alzheimer Dis Assoc Disord* 1999; 13: 226–231.
24. Morris JC, Storandt M, McKeel DW Jr, et al. Cerebral amyloid deposition and diffuse plaques in "normal" aging: evidence for presymptomatic and very mild Alzheimer's disease. *Neurology* 1996; 46: 707–719.
25. Wisniewski HM, Vorbrodt AW, Moretz RC, et al. Pathogenesis of neuritic (senile) and amyloid plaque formation. *Exp Brain Res* 1982; S5: 3–9.
26. Selkoe DJ, Yamazaki T, Citron M, et al. The role of APP processing and trafficking pathways in the formation of amyloid beta-protein. *Ann N Y Acad Sci* 1996; 777: 57–64.
27. Selkoe DJ. The cell biology of beta-amyloid precursor protein and presenilin in Alzheimer's disease. *Trends Cell Biol* 1998; 8: 447–453.
28. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* 2001; 81: 741–766.
29. Prelli F, Castano E, Glenner GG, Frangione B. Differences between vascular and plaque core amyloid in Alzheimer's disease. *J Neurochem* 1988; 51: 648–651.
30. Castillo GM, Ngo C, Cummings J, et al. Perlecan binds to the beta-amyloid proteins (A beta) of Alzheimer's disease, accelerates A beta fibril formation, and maintains A beta fibril stability. *J Neurochem* 1997; 69: 2452–2465.
31. Maresh GA, Erezyilmaz D, Murry CE, et al. Detection and quantitation of perlecan mRNA levels in Alzheimer's disease and normal aged hippocampus by competitive reverse transcription-polymerase chain reaction. *J Neurochem* 1996; 67: 1132–1144.
32. Snow AD, Nochlin D, Sekiguichi R, Carlson SS. Identification in immunolocalization of a new class of proteoglycan (keratan sulfate) to the neuritic plaques of Alzheimer's disease. *Exp Neurol* 1996; 138: 305–317.
33. Namba Y, Tomonaga M, Kawasaki H, et al. Apolipoprotein E immunoreactivity in cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. *Brain Res* 1991; 541: 163–166.
34. Dickson TC, Saunders HL, Vickers JC. Relationship between apolipoprotein E and the amyloid deposits and dystrophic neurites of Alzheimer's disease. *Neuropathol Appl Neurobiol* 1997; 23: 483–491.
35. Nishiyama E, Iwamoto N, Ohwada J, Arai H. Distribution of apolipoprotein E in senile plaques in brains with Alzheimer's disease: investigation with the confocal laser scan microscope. *Brain Res* 1997; 750: 20–24.
36. Dickson DW, Rogers J. Neuroimmunology of Alzheimer's disease: a conference report. *Neurobiol Aging* 1992; 13: 793–798.

DOI:10.1002/MSJ

37. Rogers J, Cooper NR, Webster S, et al. Complement activation by beta-amyloid in Alzheimer disease. *Proc Natl Acad Sci U S A* 1992; 89: 10016–10020.
38. McGeer PL, Rogers J, McGeer EG. Neuroimmune mechanisms in Alzheimer disease pathogenesis. *Alzheimer Dis Assoc Disord* 1994; 8: 149–158.
39. Abraham CR, Shirahama T, Potter H. Alpha 1-antichymotrypsin is associated solely with amyloid deposits containing the beta-protein. Amyloid and cell localization of alpha 1-antichymotrypsin. *Neurobiol Aging* 1990; 11: 123–129.
40. Simchowicz T. Histologische studien über die senile dementz in histol. und histopathol. *Arbeiten Aber Grosshirnrinde* 1911; 4: 267–260.
41. Hirano A, Dembitzer HM, Kurland LT, Zimmerman HM. The fine structure of some intraganglionic alterations. Neurofibrillary tangles, granulovacuolar bodies and "rod-like" structures as seen in Guam amyotrophic lateral sclerosis and parkinsonism-dementia complex. *J Neuropathol Exp Neurol* 1968; 27: 167–182.
42. Kahn J, Anderton BH, Probst A, et al. Immunohistological study of granulovacuolar degeneration using monoclonal antibodies to neurofilaments. *J Neurol Neurosurg Psychiatry* 1985; 48: 924–926.
43. Dickson DW, Ksiezak-Reding H, Davies P, Yen SH. A monoclonal antibody that recognizes a phosphorylated epitope in Alzheimer neurofibrillary tangles, neurofilaments and tau proteins immunostains granulovacuolar degeneration. *Acta Neuropathol (Berl)* 1987; 73: 254–258.
44. Ikegami K, Kimura T, Katsuragi S, et al. Immunohistochemical examination of phosphorylated tau in granulovacuolar degeneration granules. *Psychiatry Clin Neurosci* 1996; 50: 137–140.
45. Tomlinson BE, Kitchener D. Granulovacuolar degeneration of hippocampal pyramidal cells. *J Pathol* 1972; 106: 165–185.
46. Ball MJ, Lo L. Granulovacuolar degeneration in the ageing brain and in dementia. *J Neuropathol Exp Neurol* 1977; 36: 474–487.
47. Hirano A. Hirano bodies and related neuronal inclusions. *Neuropathol Appl Neurobiol* 1994; 20: 3–11.
48. Galloway PG, Perry G, Gambetti P. Hirano bodies contain actin and actin-associated proteins. *J Neuropathol Exp Neurol* 1987; 46: 185–199.
49. Galloway PG, Perry G, Kosik K, Gambetti P. Hirano bodies contain tau protein. *Brain Res* 1987; 403: 337–340.
50. Goldman JE. The association of actin with Hirano bodies. *J Neuropathol Exp Neurol* 1983; 42: 146–152.
51. Masliah E, Terry R. The role of synaptic proteins in the pathogenesis of disorders of the central nervous system. *Brain Pathol* 1993; 3: 77–85.
52. Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol* 1991; 30: 572–580.
53. Masliah E, Terry RD, DeTeresa RM, Hansen LA. Immunohistochemical quantification of the synapse-related protein synaptophysin in Alzheimer disease. *Neurosci Lett* 1989; 103: 234–239.
54. Masliah E, Mallory M, Hansen L, et al. Quantitative synaptic alterations in the human neocortex during normal aging. *Neurology* 1993; 43: 192–197.
55. Scheff SW, Price DA, Sparks DL. Quantitative assessment of possible age-related change in synaptic numbers in the human frontal cortex. *Neurobiol Aging* 2001; 22: 355–365.
56. Scheff SW, Price DA. Synaptic density in the inner molecular layer of the hippocampal dentate gyrus in Alzheimer disease. *J Neuropathol Exp Neurol* 1998; 57: 1146–1153.
57. DeKosky ST, Scheff SW, Styren SD. Structural correlates of cognition in dementia: quantification and assessment of synapse change. *Neurodegeneration* 1996; 5: 417–421.
58. Scheff SW, Price DA. Synapse loss in the temporal lobe in Alzheimer's disease. *Ann Neurol* 1993; 33: 190–199.
59. Scheff SW, Sparks L, Price DA. Quantitative assessment of synaptic density in the entorhinal cortex in Alzheimer's disease. *Ann Neurol* 1993; 34: 356–361.
60. McKeith IG, Perry EK, Perry RH. Report of the second dementia with Lewy body international workshop: diagnosis and treatment. Consortium on dementia with Lewy bodies. *Neurology* 1999; 53: 902–905.
61. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies. Third report of the DLB consortium. *Neurology* 2005; 65: 1863–1872.

DOI:10.1002/MSJ