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Diagnostic Criteria for the Neuropathologic Assessment of Alzheimer's Disease

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POWERS, J. M. *Diagnostic criteria for the neuropathologic assessment of Alzheimer's disease.* NEUROBIOL AGING **18**(S4) S53–S54, 1997.—The provisional criteria proposed in 1985 by Khachaturian et al. emphasized numbers of plaques and neglected tangles, as did CERAD (Consortium to Establish a Registry for Alzheimer's Disease). The decision to set an arbitrary number of plaques as "pathologic" assumed that some neuritic plaques are a normal phenomenon in the aging brain. Neuritic plaques and neurofibrillary tangles are age-related lesions, but they are pathologic (i.e., lesions) no matter how many there are. In a clinically demented patient without vascular or other neurodegenerative lesions, a clinico-pathologic diagnosis of AD (a clinico-pathologic entity) can be made with a high level of confidence by demonstrating, and without counting, plaques and tangles. The vast majority of AD cases are straightforward, and diagnostic lesions can be appreciated with a simple silver stain. If patients' histories are unknown or uncertain, the clinical significance of the observed plaques and tangles must remain debatable. This is the essence of the consensus statement with which I wholeheartedly agree. In such cases without a dementia history, one can offer a neuropathologic diagnosis of Senile or Pre-senile Cerebral Disease (not "dementia") of the Alzheimer type. Precise clinico-pathologic correlations and some quantitative measures are needed for elucidating the pathogenesis of AD and for establishing a primary dementing diagnosis when AD is mixed with other dementing diseases. These correlations must be based on periodic and fairly extensive neuropsychological testing followed shortly thereafter by a detailed postmortem neuropathologic evaluation. © 1997 Elsevier Science Inc.

Plaques Tangles Diagnosis Alzheimer's disease Dementia

THE provisional criteria proposed in 1985 by Khachaturian et al. (3) were a good start. However, they had at least three limitations. Firstly, they emphasized numbers of plaques and neglected tangles. CERAD (Consortium to Establish a Registry for Alzheimer's Disease) decided on a similar approach. (5) Secondly, it did not distinguish diffuse from neuritic plaques. Diffuse plaques were unknown at that time, but they were displayed with the recommended stains (Bielschowsky or thioflavin S). It now seems that many diffuse plaques may be seen in intellectually intact individuals; hence, they are a poor morphologic correlate of dementia, and their pathologic significance is still uncertain. In retrospect, perhaps the Bodian stain should have been recommended for the detection of plaques, because it only demonstrates neuritic plaques. Thirdly, the decision to set an arbitrary number of plaques as sufficient to cause dementia was based to some extent on the long disputed assumption that some senile (neuritic) plaques are a normal phenomenon in the aging brain. I have always had a major problem with this postulate. Neuritic plaques and neurofibrillary tangles are age-related lesions; but, in my opinion they are pathologic (i.e., lesions), no matter how many there are. The decision to choose a numerical discriminator to distinguish demented from nondemented brains, even though based on age, also ignored the significant individual variations that typify many biological systems. Plaques and tangles are similar to lesions of many other disease processes throughout the body that possess threshold properties, such as atherosclerotic plaques. That is, a sufficient number of plaques and/or tangles need to be present in a given individual to cause dementia. The problem is to determine, if possible, how many plaques and/or tangles invariably cause dementia in all, or the vast majority, of people. Undoubtedly, many people can maintain normal cognitive functions, including memory, and still have some plaques and tangles in their neocortex. Conversely, some patients are clinically demented and yet only display small numbers of tangles in hippocampus/entorhinal cortex and a few neocortical plaques. Because it appears that education provides some measure of protection against Alzheimer's disease (10) and experimental studies suggest that the environment can promote supranormal dendritic and synaptic development, (9) most researchers probably would agree that one's brain reserve to withstand these dementing lesions varies from person to person. If this is true, then extensive discussions about sufficient numbers of (and elaborate methods to count) plaques and tangles for diagnostic purposes is somewhat unscientific and a poor utilization of our "inexorable enemy" time. I strongly believe that this exercise is largely unnecessary for diagnostic purposes. Similarly, staging the neuropathologic course of AD, such as the Braaks' classification (1), certainly can provide insights into the pathogenesis of AD and some meaningful clinical correlations, for we all have seen a number of cases where the predicted sequence of neurofibrillary progression does not occur. Finally, I would argue that even new or revised criteria would have limited usefulness if designed for both research and diagnostic purposes.

I have been astounded to see so many spending so much time talking about and counting plaques (and sometimes tangles) to make a neuropathologic diagnosis of AD. Is this exercise merely an example of the "safety in numbers" philosophy needed to embolden the diagnostically timid, or is it an affirmation of the words of Lord Kelvin: " . . . when you cannot measure it, when

you cannot express it in numbers . . . you have scarcely, in your thoughts, advanced to the stage of science." (8) I would like to think it is the latter, but much of morphologic diagnosis, as other forms of Medicine, is more art than science. In AD much of this quantitation is unnecessary, provided one follows the simple fundamental diagnostic steps that were outlined in the original Khachaturian publication. (3) That is, one starts out by excluding "any other obvious causes of organic dementia . . .". If the neuropathologist or pathologist has completed such an exercise through a careful review of medical records, the gross examination of brain, and the exclusion of non-Alzheimer microscopic degenerative lesions or infarcts in a clinically demented patient displaying neocortical neuritic plaques and/or tangles or many tangles in entorhinal cortex/hippocampus, then I believe that a clinicopathologic diagnosis of AD (a clinico-pathologic entity) can be made with a high level of confidence without counting these lesions. If patients' histories are unknown or uncertain, then the clinical significance of the plaques and tangles must remain debatable. This is the essence of the consensus statement with which I wholeheartedly agree. In such cases, I find refuge in the diagnostic nomenclature that I was trained to use. That is, one can offer a neuropathologic diagnosis of senile or presenile cerebral disease (not "dementia") of the Alzheimer type and qualify it as to mild-moderate-severe, localized or diffuse, plaque predominant, or classical (somewhat similar to CERAD). Let's be honest, the vast majority of AD cases are straightforward and their numerous neocortical neuritic plaques with at least some tangles can be appreciated with a simple silver stain, if one is solely interested in establishing a neuropathologic diagnosis and some measure of clinico-pathologic correlation. On the other hand, there are some patients where such counts may be necessary to establish a primary dementing diagnosis (e.g., diffuse Lewy body disease or mixed vascular-Alzheimer dementia). These are current clinical research issues that perhaps should be referred to dementia specialists in AD centers.

To offer unnecessary quantitative diagnostic criteria to community pathologists, or even neuropathologists who are primarily interested in other neurological or neurosurgical diseases, may do more harm than good. We neuropathologists often are viewed by general pathologists, including our chairs, as dilettantes who make few substantial contributions to their departments and usually cost them money. An esteemed colleague has expressed the following sentiment when discussing the too prevalent delays in autopsy reporting: "Never mind the neuropathology cases. This would need another article!" (7) Dementia neuropathologists are sometimes viewed by nondementia neuropathologists in the same way. More to the point, can one actually justify additional expenditures of time and resources on matters viewed as insignificant by informed "outsiders" who fiscally control us? Autopsy pathology has sustained major setbacks in the last 20 years. If we are to reverse this downward spiral, we must provide autopsy reports to physicians and families much more expeditiously (2). It is unlikely that we will be able to do so, if we complicate a process that is fairly straightforward. We need to conserve resources (our time and "their" money) to study other degenerative dementing diseases that presently require more detailed morphologic evaluations for a sound diagnosis. Fortunately, AD thus far has escaped the prevailing public sentiment that autopsies are somewhat important but not worth financing. Thus far! We need to proceed rationally and economically lest we kill another golden goose.

In summary, diagnostic criteria for AD should be simple enough for all pathologists to use (4,6), and the principles developed during the recent National Institute of Aging consensus conference are generally reasonable and practical. The inclusion of a hippocampal section and the emphasis on neuritic plaques with the presence of neurofibrillary tangles for the routine diagnostic evaluation are, in my opinion, modifications or updates of the Khachaturian (3) and CERAD (5) criteria that enhance our diagnostic abilities. I do not, however, think that Braak staging (1) (unless it is simplified) or including the additional sections of hippocampus at the uncus, locus coeruleus, and occipital cortex to permit staging are necessary to establish a diagnosis for the vast majority of patients with Alzheimer's disease.

On the other hand, I also maintain that precise clinicopathologic correlations are needed for AD research purposes and for elucidating the interrelationships between AD and other dementing diseases. These must be based on periodic and fairly extensive neuropsychological testing, especially near the time of death, followed by a detailed neuropathologic evaluation using specific silver stains (such as Bielschowsky and Gallyas) and immunostains of established sensitivity and specificity (such as to phosphorylated τ or paired helical filaments and β amyloid) on specified areas of brain that have been fixed, processed, and sectioned in a uniform manner. This uniformity would then allow meaningful correlations between laboratories and, in particular, between AD centers. I would recommend that, as a starting point, diffuse plaques, neuritic plaques, PHF + neuritic plaques, neurofibrillary tangles, neuropil threads, amyloid burden in blood vessels and neuropil, Braak staging, and perhaps synaptophysin immunohistochemistry in neocortex and archicortex (including hippocampus and entorhinal cortex) be evaluated quantitatively in research cases of pure AD or AD plus another dementing process.

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