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Editorial on Consensus Recommendations for the Postmortem Diagnosis of Alzheimer Disease from the National Institute on Aging and the Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer Disease

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This editorial summarizes recommendations of a panel of neuropathologists who sought to develop improved postmortem diagnostic criteria for Alzheimer disease following a workshop sponsored by the National Institute on Aging (NIA) and the Ronald and Nancy Reagan Institute of the Alzheimer's Association to reassess the original NIA criteria for the postmortem diagnosis of Alzheimer disease published in 1985 (1). The consensus recommendations for improving the neuropathological criteria for the postmortem diagnosis of Alzheimer disease, along with a series of commentaries, will be published shortly (2). To make these criteria known to the readership of this journal, the essential findings of the panel follow here.

The current Khachaturian criteria for Alzheimer disease diagnosis rely on numerical cutoffs of senile plaques counts (1). The specific number of senile plaques per field required for the diagnosis of Alzheimer disease changes with age. The rationale for updating the Khachaturian criteria is that subsequent studies suggested that they fell short of the goal of distinguishing controls from cases of Alzheimer disease. For example, numerous studies demonstrated individuals who met Khachaturian criteria in terms of senile plaque number, but had no history of clinical symptoms of dementia. Secondly, the idea of changing diagnostic criteria based on the patient's age has not been supported. Thirdly, the absence of assessment of neurofibrillary tangles in the current criteria stands in contrast to numerous studies that show that tangle number and distribution more closely parallel dementia than plaque number or distribution. Finally, there was a move away from setting absolute numerical criteria given both technical issues of how to stain and how to count, and the inherent uncertainties of correlating specific brain lesions with degree of clinical impairment in individual patients, especially where the impairment may be in the early stages.

Another issue addressed was the biological significance of subclinical numbers of neurofibrillary tangles or senile plaques. The consensus group felt that any neurofibrillary tangles or senile plaques, even if almost certainly clinically irrelevant and asymptomatic, should be viewed as abnormal brain lesions and recorded as incidental findings. This process is distinguished from the idea inherent in the Khachaturian recommendations that some senile plaques are a normal concomitant of aging.

The new recommendations are intended to address these issues, and to take into account the last 12 years of clinical-pathological correlation studies performed both in the United States and Europe. Moreover, the new recommendations take advantage of insight into the biology and progression of disease afforded by the observations of hierarchical vulnerability of different brain areas (5), as embedded for example by the Braak and Braak staging scheme (6). In general, the methodological systems developed by CERAD including the use of standardized brain areas to examine and semiquantitative analysis of neuritic pathology were endorsed. The goal of the working group was to formulate probabilistic statements, rather than a dichotomous yes/no, about the contribution of Alzheimer disease pathology to cognitive decline. It is anticipated that future meetings of the Working Group as well as studies conducted by interested investigators will reassess these recommendations and the implementation of postmortem diagnostic criteria for Alzheimer disease. An abbreviated version of the recommendations follows.

Guiding Principles for the Postmortem Diagnosis of Alzheimer disease

1. Alzheimer disease is a heterogeneous clinicopathological entity. Thus, only probabilistic statements about the presence or absence of dementia can be made based on pathological findings alone, and postmortem brain pathology can only be inferred when a progressive dementia has been documented in a living elderly individual.
2. Since dementia may arise from more than one disorder, more than one pathological process may contribute to dementia.

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3. The panel was of the opinion that any Alzheimer lesions should be considered as pathological even where they appear to be incidental.

Neuropathological Assessment of the Likelihood that Alzheimer Disease Accounts for a Dementia Should be Judged As Follows:

1. The likelihood is high when the postmortem brain shows both neuritic plaques and neurofibrillary tangles in neocortex (i.e. a frequent neuritic plaque score according to CERAD [3, 4]) and Stage V/VI according to Braak and Braak (5).
2. Likelihood is intermediate when there are moderate neocortical neuritic plaques and neurofibrillary tangles in limbic regions (i.e. CERAD moderate, and Braak and Braak Stage III/IV).
3. Likelihood is low when there are neuritic plaques and neurofibrillary tangles in a more limited distribution and/or severity (i.e. CERAD infrequent, and Braak and Braak Stage I/II).

Specific Recommendations

1. For the routine diagnosis of Alzheimer disease in the postmortem brain, it is recommended that semiquantitative methodologies (i.e. the CERAD approach) be used to assess neuritic plaques and neurofibrillary tangles. In addition to CERAD, examination of the hippocampal formation and the neocortex for the presence of neurofibrillary tangles is essential.
2. In Alzheimer disease research settings, topographic staging methods (i.e. Braak and Braak) should be used to establish the extent of neurofibrillary lesions including neuritic plaques, neurofibrillary tangles and neuropil threads.
3. CERAD protocols are recommended for tissue fixation, tissue processing, sectioning and tissue staining (e.g. Bielschowsky, Gallayas, Thioflavine S methods).
4. The following regions should be sampled in the coronal plane after macroscopic examination:

   a. Neocortical areas: superior temporal gyrus, inferior parietal lobe, mid-frontal cortex, occipital cortex (including primary visual cortex and association cortex).
   b. Hippocampal formation at the level of the lateral geniculate nucleus.
   c. Hippocampal formation including entorhinal cortex at the level of the uncus.
   d. Substantia nigra and locus coeruleus.

Optional regions include: thalamus, caudate, putamen, cerebellum, motor cortex, cingulate cortex, mamillary bodies, and spinal cord. Any macroscopic lesions also should be examined, and the remaining brain should be saved until a diagnosis has been established.

Assessment of Major Co-existing Lesions in Addition to Alzheimer Disease Lesions

Since the relative extent to which Alzheimer disease lesions and other co-existing pathological lesions contribute to clinical symptoms cannot always be determined with certainty, other disorders or lesions should be listed together with the CERAD score and the Braak and Braak stage. Immunohistochemical procedures using anti-ubiquitin antibodies have been recommended by the International Workshop on Lewy Bodies (7) as an adjunct for the diagnosis of Lewy body disorders and immunostains for amyloid and neurofibrillary pathology can be used to confirm the detection of these lesions.

Strategies to Improve the Postmortem Diagnosis of Alzheimer Disease in the Future

To improve current procedures for the postmortem diagnosis of Alzheimer disease, the following goals were suggested:

1. Validate and refine the procedures recommended above.
2. Establish if heterogeneity in Alzheimer disease changes reflects genetic and gender-based factors.
3. Investigate well-characterized cohorts of demented patients to determine the effects of age on the clinical and pathological criteria for the diagnosis of Alzheimer disease.
4. Investigate the pathological, cellular and molecular basis for mild cognitive impairment that does not progress to Alzheimer disease and contrast this with normal aging as well as Alzheimer disease.
5. Develop biochemical and molecular methods (i.e. soluble assays for hyperphosphorylated tau, Aβ, etc.) for the rapid postmortem diagnosis of Alzheimer disease and compare data obtained using these methods with data obtained from the currently recommended pathological methods.
6. Standardize diagnostic methods and reagents used for the postmortem diagnosis of Alzheimer disease including the establishment of common sources of diagnostic reagents.
7. Standardize quantitative methods, including stereology, for application to the postmortem diagnosis of Alzheimer disease.
8. Determine the nature and significance of white matter pathological changes in Alzheimer disease.

Implementation

The working group did not directly address specific implementation of these criteria beyond endorsing the general strategies employed by CERAD (3, 4) for standardized tissue blocks expanded to include an anterior

hippocampus, entorhinal cortex, and inferior temporal gyrus (Brodmann area 20) block and a visual cortex (Brodmann areas 17 and 18) block. The use of modified Bielschowsky silver staining protocols was endorsed. The Braak and Braak staging scheme was initially described using very thick (polyethylene glycol embedded) sections (6), but can be readily adapted to standard paraffin sections (8, 9). It is hoped that interested investigators will test these new criteria, and that they will continue to evolve.

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