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Consensus Recommendations for the Postmortem Diagnosis of Alzheimer's Disease

THE NATIONAL INSTITUTE ON AGING, AND REAGAN INSTITUTE WORKING GROUP ON DIAGNOSTIC CRITERIA FOR THE NEUROPATHOLOGICAL ASSESSMENT OF ALZHEIMER'S DISEASE[1,2]

THE NATIONAL INSTITUTE ON AGING AND REAGAN INSTITUTE WORKING GROUP ON DIAGNOSTIC CRITERIA FOR THE NEUROPATHOLOGICAL ASSESSMENT OF ALZHEIMER'S DISEASE. *Consensus recommendations for the postmortem diagnosis of Alzheimer's disease.* NEUROBIOL AGING **18**(S4) S1–S2, 1997.—This report summarizes the consensus recommendations of a panel of neuropathologists from the United States and Europe to improve the postmortem diagnostic criteria for Alzheimer's disease. The recommendations followed from a two-day 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's disease published in 1985 (2). The consensus recommendations for improving the neuropathological criteria for the postmortem diagnosis of Alzheimer's disease are reported here, and the "position papers" by members of the Working Group that accompany this report elaborate on the research findings and concepts upon which these recommendations were based. Further, commentaries by other experts in the field also are included here to provide additional perspectives on these recommendations. Finally, it is anticipated that future meetings of the Working Group will reassess these recommendations and the implementation of postmortem diagnostic criteria for Alzheimer's disease. © 1997 Elsevier Science Inc.

Plaques Tangles Amyloid Aβ Tau Neurodegenerative disease

A. GUIDING PRINCIPLES FOR THE POSTMORTEM DIAGNOSIS OF ALZHEIMER'S DISEASE

1. Alzheimer's disease is a heterogeneous clinico-pathological entity. Thus, based on the pathological changes detected in the postmortem brain alone (i.e., Alzheimer's disease lesions), only probabilistic statements about the presence or absence of dementia can be made in a given patient. Similarly, the presence or amount of Alzheimer's disease lesions in the postmortem brain can only be inferred and not predicted with certainty when a progressive dementia has been documented antemortem in an elderly individual.
2. Because dementia in an elderly individual may arise from more than one disorder, more than one pathological process (i.e., stroke, Parkinson's disease, progressive supranuclear palsy, etc.) in addition to Alzheimer's disease lesions may contribute to the dementia in many patients.
3. Any Alzheimer's disease changes in the postmortem brain (i.e., diffuse amyloid or neuritic plaques, neurofibrillary tangles) are considered to be abnormal and should be recorded as such. In other words, these changes are considered to be pathological even in instances where they appear to be incidental.

B. NEUROPATHOLOGICAL ASSESSMENT

The following categories are recommended to provide an estimate of the likelihood that Alzheimer's disease pathological changes underlie dementia:

1. There is a high likelihood that dementia is due to Alzheimer's disease lesions when the postmortem brain shows the presence of both neuritic plaques and neurofibrillary tangles in neocortex (i.e., a frequent neuritic plaque score according to CERAD [*C*onsortium to *E*stablish a *R*egistry for *A*lzheimer's *D*isease; 5,4], and a Stage V/VI according to Braak and Braak; 1).
2. There is an intermediate likelihood that dementia is due to Alzheimer's disease lesions when the postmortem brain shows moderate neocortical neuritic plaques and neurofibrillary tangles in limbic regions (i.e., CERAD moderate, and Braak and Braak Stage III/IV).
3. There is a low likelihood that dementia is due to Alzheimer's disease lesions when the postmortem brain shows neuritic plaques and neurofibrillary tangles in a more limited distribution and/or severity (i.e., CERAD infrequent, and Braak and Braak Stage I/II).

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Criteria for the recognition of "incipient" dementia due to Alzheimer's disease remain to be determined. Further, it is expected that Alzheimer's disease may occur with combinations of neuritic plaques and neurofibrillary tangles in the postmortem brain other than those specified above. Finally, the contribution of diffuse Aβ deposits to cognitive impairments remains uncertain at this time, but the presence of these lesions should be noted.

C. SPECIFIC RECOMMENDATIONS

1. For the routine diagnosis of Alzheimer's disease in the postmortem brain by general pathologists and neuropathologists, it is recommended that semiquantitative methodologies (i.e., the CERAD approach) be used to assess neuritic plaques and neurofibrillary tangles. In addition to CERAD Guidelines, it is emphasized that the examination of the hippocampal formation and the neocortex for the presence of neurofibrillary tangles is essential to enhance confidence in the postmortem diagnosis of Alzheimer's disease.
2. In Alzheimer's disease research settings, it is recommended that topographic staging methods (i.e., that of Braak and Braak) be used as an important approach for establishing the extent of neurofibrillary lesions including neuritic plaques, neurofibrillary tangles and neuropil threads.
3. The CERAD protocols are recommended for tissue fixation, tissue processing, sectioning and tissue staining. Modified Bielschowsky, Gallayas, or Thioflavine S methods are appropriate.
4. It is recommended that the following regions be sampled in the coronal plane after careful macroscopic examination of the postmortem brain to evaluate Alzheimer's disease and to rule out potentially confounding disorders:
    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 to sample include: thalamus, caudate, putamen, cerebellum, motor cortex, cingulate cortex, mamillary bodies, and spinal cord. Any lesions seen on macroscopic examination also should be examined. Finally, the remaining brain should be saved until a microscopic diagnosis has been established.

5. In Alzheimer's disease research centers, it is recommended that specific immunostains be used to correlate immunostained Alzheimer's disease lesions (neuritic plaques, neurofibrillary tangles, Aβ deposits) with conventional stains that demonstrate these lesions.

D. ASSESSMENT OF MAJOR COEXISTING LESIONS IN ADDITION TO ALZHEIMER'S DISEASE LESIONS IN THE POSTMORTEM BRAIN

The most common confounding lesions are Lewy bodies and vascular lesions. The lesions that are present in the postmortem brain should be recorded and all diagnoses ascribed to the presence of these lesions should be specified. The relative extent to which Alzheimer's disease lesions and other coexisting pathological lesions contribute to clinical symptoms cannot always be determined with certainty. With regard to the Alzheimer's disease lesions, the CERAD score and the Braak and Braak stage should be noted. Immunohistochemical procedures using antiubiquitin antibodies were recommended by the International Workshop on Lewy Bodies (3) as an adjunct for the diagnosis of Lewy body disorders.

E. RECOMMENDATIONS FOR STRATEGIES TO IMPROVE THE POSTMORTEM DIAGNOSIS OF ALZHEIMER'S DISEASE

To improve upon currently recommended procedures for the postmortem diagnosis of Alzheimer's disease, the following goals were suggested:

1. Validate and refine the procedures recommended above.
2. Establish if heterogeneity in Alzheimer's disease changes reflect 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's disease.
4. Investigate the pathological, cellular, and molecular basis for mild cognitive impairment that does not progress to Alzheimer's disease in well characterized cohorts of individuals from age 50 to the end of the human lifespan and contrast this with normal aging as well as Alzheimer's disease.
5. Develop biochemical and molecular methods (i.e., soluble assays for hyperphosphorylated tau, Aβ, etc.) for the rapid postmortem diagnosis of Alzheimer's disease and compare data obtained using these methods with data obtained from the currently recommended pathological methods.
6. Seek to standardize diagnostic methods and reagents used for the postmortem diagnosis of Alzheimer's disease including the establishment of common sources or core facilities for the production and distribution of diagnostic reagents.
7. Seek to develop and standardize quantitative methods including stereology, for application to the postmortem diagnosis of Alzheimer's disease.
8. Determine the nature and significance of white matter pathological changes in Alzheimer's disease.

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