Alzheimer's & Dementia
Translational Research
& Clinical Interventions

SPECIAL TOPIC SECTION

CCCDTD5: research diagnostic criteria for Alzheimer's Disease

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Abstract
The CCCDTD5 reviewed the research diagnostic criteria for Alzheimer's disease proposed in the NIA-AA Research Framework and supports their use in research but not in clinical practice

KEYWORDS
Alzheimer, criteria, diagnosis, research

1 | INTRODUCTION

The first Canadian Consensus Conference on the Diagnosis and Treatment of Dementia took place in 1989 and put emphasis on history taking, physical examination, a basic set of laboratory tests, indications for a head computerized scan, and for a referral to a specialist.[1]

The second CCCDTD in 1998 reaffirmed these recommendations,[2;3] using the definition of Alzheimer's Disease (AD) proposed by the NINCDS-ADRDA Work Group.[4]

The third CCCDTD in 2006 reaffirmed the clinical diagnosis by primary care practitioners as the main strategy for timely diagnosis, adding that brief cognitive tests such as the Montreal Cognitive Assessment may be more accurate than the Mini Mental State Examination in discriminating between dementia and the normal state, whereas neuropsychological testing may be useful in the differential diagnosis of dementia and other syndromes of cognitive impairment, that B12 serum levels should be determined in all older adults suspected of cognitive decline or dementia.[5]

The fourth CCCDTD in 2012 had to deal with the shift to an earlier diagnosis of AD in its prodromal stage[6] and the definition of AD proposed by the National Institute on Aging – Alzheimer Association (NIA-AA) Work Groups in the preclinical stage,[7] the mild cognitive impairment stage[8] and the dementia stage,[9] all these criteria using biomarkers. The consensus reached in 2012 was that the NIA-AA criteria for AD should be adopted for use in research settings. Additional recommendations were made regarding the diagnosis of early onset dementia, and about rapidly progressive dementia, which should lead to referral to specialty clinics.

The fifth CCCDTD in 2019 studied the research definition of AD proposed by the NIA-AA Research Framework,[10] in addition to seven other topics summarized in a core article.[11] The current article goes more in details on the reasons we supported this framework, but for research only.

2 | THE NIA-AA RESEARCH FRAMEWORK

The NIA-AA Research Framework proposed a biological definition of AD, intended for observational and interventional research, not routine clinical care.[10] The diagnosis of AD would not be based on the clinical consequences of the disease (i.e. symptoms/signs), but rather on biomarkers of ß amyloid deposition, pathologic tau accumulation and neuronal injury [AT(N)]. The NIA-AA framework extends the neuropathological definition of AD (abnormal amyloid-ß and tau) to living individuals with the use of in vivo amyloid-ß (A) and tau (T) biomarkers. Amyloid and tau biomarkers are used to identify AD as a unique biological process that contributes to cognitive decline. The N is placed in brackets as it is not unique to AD and is instead a feature of all neurodegenerative diseases. The authors did emphasize that it was premature and inappropriate to use this research framework in general medical practice.

A concern about the AT(N) definition of AD is the use of the medical term Alzheimer's 'disease' in asymptomatic persons who are amyloid and tau positive, whereas the natural history of progression to symptoms remains uncertain.[12;13] However, one might claim that a diagnosis of AD in predementia stage if the disease legitimizes early therapeutic interventions targeting disease pathophysiology.

Another critique to the AT(N) system refers to a certain disregard to co-pathologies such as cerebrovascular disease, neuro-inflammation or age-related protein aggregates such as transactive response DNA binding protein 43 kDa (TDP43), and alpha-synuclein.[14] As these co-pathologies might change the course of the disease, it is imperative to recognize them. For example, a recent study conducted in memory clinic patients has highlighted that severe white matter hyperintensities differentiated between A-T+N+ and A+T+N+ cases.[15]

The lack of affordable clinically approved biomarkers for large scale use represents another concern. Although certain amyloid PET agents have clinical certifications, only cerebrospinal fluid biomarkers have obtained clinical certifications for detection of amyloid ß42, total tau and phosphorylated tau on the 181 fragment (p-tau-181).

Tau PET agents remain to be approved for clinical use, but there are encouraging reports about plasma p-tau-181 levels correlating with brain amyloid and tau content.[16]

Early results from using the AT(N) classification in observation research databases such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) demonstrate that AT(N) positivity does predict faster clinical progression from cognitively normal to incident prodromal stage of AD, and from MCI to dementia.[17] Population-based cohort studies also indicate that the AT(N) classification system demonstrates better prediction of memory decline over 5 years than readily available clinical and genetic information.[18] This classification may provide prognostic information useful in targeted recruitment into clinical trials. Another population-based cohort study demonstrated that biologically defined AD is more prevalent than clinically defined AD at any age, and three times more prevalent at age 85 among both women and men.[19] The prevalence of biological AD resembled the prevalence of clinical AD 10+ years later.

Research in context

1. Systematic review: the authors did a systematic review of the English medical literature after the publication of the NIA framework for research diagnostic criteria for Alzheimer's disease.
2. Interpretation: We think that they adequately cover the classic pathological features of amyloid deposition (A), tau hyperphosphorylation (T) and neurodegeneration (N), but important comorbid factors modulate the disease expression, particularly small vessel disease and neuroinflammation.
3. Future research: the ATN classification is currently the best available for research, but not for clinical practice. Future studies must establish to relative weight of comorbidity on top of the core pathological features.

Another finding from using primarily in vivo biomarkers to diagnose AD is the number of persons with dementia that are both amyloid and tau negative, indicating that their cognitive decline is due to another etiology. Furthermore, a small percentage of individuals with dementia are amyloid negative but tau positive. This may increase interest in primary age related tauopathy (PART[20]); for the A-T+ dementias, and the limbic-predominant age-related TDP-43 encephalopathy (LATE[21]); for the A-T- group.

3 | RECOMMENDATIONS APPROVED BY THE CCCDTD5

1. We recommend the adoption of the criteria for the biological definition of Alzheimer's disease proposed by the NIA-AA working group in 2018 only for observational and interventional research.
2. We recommend the addition to this biological definition of other pathological factors such as vascular, inflammatory, synuclein and TDP-43 as soon as there are validated instruments to reliable measure their levels.
3. Given that the presence of brain amyloid and/or tau in cognitively normal people is of uncertain significance, we discourage the use of amyloid and tau imaging without memory decline, outside of the research setting. The medical community should be clear in its discussion with patients, the media and the general population that the presence of brain amyloid and/or tau in normal people is of unclear significance at the present time.

CONFLICT OF INTEREST STATEMENT

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