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New lexicon and criteria for the diagnosis of Alzheimer's disease

Hamid Sohrabi
Edith Cowan University

Michael Weinborn

Johanna Badcock

Kristyn A. Bates

Roger Clarnette
Edith Cowan University

See next page for additional authors

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Authors

Hamid Sohrabi, Michael Weinborn, Johanna Badcock, Kristyn A. Bates, Roger Clarnette, Darshan Trivedi, Giuseppe Verdile, Tom Sutton, Nat P. Lenzo, Samuel Gandy, and Ralph Martins

Letter to the Editor

“Revising the definition of Alzheimer’s disease: a new lexicon”

Authors:

Sohrabi, Hamid R.^{1,2}; Weinborn, Michael³; Badcock, Johanna⁴; Bates, Kristyn A.⁵; Clarnette, Roger^{1,2}; Trivedi, Darshan¹; Verdile, Giuseppe^{1,2}; Sutton, Tom^{2,6}; Lenzo, Nat, P.^{1,7}; Gandy, Samuel, E.⁸; Martins, Ralph N.^{1,2,6*}

¹School of Exercise, Biomedical and Health Science, Edith Cowan University, Western Australia, Australia.

²The Sir James McCusker Alzheimer’s disease Research Unit, Hollywood Private Hospital, Australia.

³School of Psychology, University of Western Australia, Australia.

⁴Centre for Clinical Research in Neuropsychiatry (CCRN), Graylands Hospital, University of Western Australia, Australia.

⁵School of Animal Biology, University of Western Australia, Australia.

⁶School of Psychiatry and Clinical Neurosciences, University of Western Australia, Australia.

⁷Department of Nuclear Medicine, Fremantle Hospital, Western Australia, Australia.

⁸Department of Neurology, One Gustave L Levy Place, Box 1137, New York, USA.

*** Corresponding author**

Dear Editor,

We have been closely following the proposed diagnostic criteria for Alzheimer's disease (AD) over the last few years (Foster et al., 2008). Recent revisions of the AD criteria proposed by Dubois et al. (2010) represent a clear improvement of their previously published position paper (Dubois et al., 2007). In the new revision, Dubois et al. propose an important distinction between the *clinical disorder* (AD), and the *neuropathological condition* ("Alzheimer's pathology"). They also describe a number of distinctions within the clinical disorder, including two preclinical conditions ("Asymptomatic at-risk for AD" and "Presymptomatic AD"), a prodromal condition ("Prodromal AD"), and AD dementia with varying presentations ("Typical AD," "Atypical AD" and "Mixed AD").

The authors provide an evidence-based structure to improve the clarity of pre-dementia conditions; particularly the new classification of individuals previously diagnosed with MCI, but with biomarker evidence of AD pathology, as having "Prodromal AD". However, the definitions provided for "Atypical and Mixed AD" may result in some confusion and lack of diagnostic clarity. For example, "Atypical AD" refers to the less common clinical features of the disease accompanying other clinical syndromes such as primary progressive non-fluent aphasia and logopenic aphasia. It should be recognized that in these conditions, AD is not a prominent feature of the disease and applying atypical AD as the diagnosis may increase the possibility of a misleading or incorrect diagnosis. Further, in the recently suggested frontal variant of AD that was mentioned as an example of "Atypical AD" by Dubois et al., the antemortem diagnoses is very uncertain (Larner, 2006) and may not be very reliable.

Similarly, the “Mixed AD” refers to a condition where patients must “present with full diagnostic criteria of “Typical AD” plus the clinical and pathophysiological evidence of other diseases or disorders”. It is unclear what diagnostic, treatment or research benefit is achieved with this classification approach rather than simply applying “Typical AD” diagnosis in concert with the associated co-morbid diagnosis (e.g. vascular disease). We believe that specifying the co-occurring pathology based on co-morbidity with AD may be more useful for the patients’ management.

Most importantly, however, the authors have not acknowledged the importance of including “age at onset” as a factor in diagnostic classification. Specifically, there is a need for differential diagnoses of early onset AD (EOAD) versus late onset AD (LOAD). Neurochemical and neuropathological differences between EOAD and LOAD have been previously reported (Iversen, 1987). Additionally, age at onset has been shown to influence clinical presentation of AD. Therefore, using the EOAD versus LOAD diagnostic distinction may promote differentially effective management approaches for each group of patients (Emery and Oxman, 2003). Although, current knowledge about the clinical course of EOAD as compared to the LOAD remains incomplete, there are at least three reasons that this dichotomy should be included in the diagnostic criteria:

1. The neuropsychological profile for pre and post-diagnostic phases could be different for these two groups, with subsequent implications for functional status;
2. The covariant factors affecting treatment (e.g. other diseases and clinical conditions, the medications used by each group of patients, psychosocial support and responsibilities, etc.) are likely to vary across the diagnostic groups;

3. As age at onset may determine the prototype of the disease, incorporating it may change the clinical management of the patient, as well as the disease prognosis.

In summary, the revised criteria proposed by Dubois et al. (2010) represent an important step forward in the development a “new lexicon for Alzheimer’s disease” for researchers and clinicians. However, further refinement of some diagnostic categories, as well as consideration of age of onset as an important clinical feature, are important next steps in this endeavor.

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