Clinical and research value of the new diagnostic criteria for Alzheimer's disease

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Summary: The use of biomarkers in the diagnosis of Alzheimer's disease (AD) has been increasingly emphasized, but the feasibility and value of using biomarkers in clinical practice remain limited. However, the use of biomarkers in clinical and pharmaceutical research about AD may prove quite useful in clarifying the pathology underlying AD and, thus, help in the early identification of effective preventive and therapeutic interventions. Moreover, wide adoption of the new diagnostic criteria will improve comparability of research results across studies, and, thus, allow for the combination and comparison of study results using meta-analytic techniques – the types of analyses needed to definitively answer fundamental questions about the etiology, course, prevention, and treatment of AD.

Keywords: Alzheimer's disease; diagnostic criteria; biomarkers

As discussed in the Forum article by Yang and Xiao,[1] in recent years there has been an increasing emphasis on the role of biomarkers in the diagnosis of Alzheimer's disease (AD). Nonetheless, there are several potential serious problems in the clinical application of biomarker-based diagnostic criteria for AD:

a) The reliability of the biomarkers is not proven. Currently, there is a lack of consensus on the cutoff points that provide satisfactory sensitivity and specificity of the proposed biomarkers that would best distinguish 'normal' from 'abnormal'. More clinical studies are needed to unify and standardize the proposed cutoffs points. For instance, amyloid-beta (Aβ) accumulation is also detected in healthy individuals,[2] and the specificity of identifying AD using cerebrospinal fluid (CSF) $A\beta_{42}$ and CSF tau varies from 49% to 77%.[3] At present the diagnosis of AD cannot rely solely on such biomarkers.

b) The feasibility of assessing biomarkers is limited in clinical settings. The lack of an ideal tracer for PET and differences in Aβ and tau standards at different research institutes limits the broad application of these techniques. More importantly, the use of the tests for biomarkers is limited to locations that have the advanced (and expensive) equipment needed to make the assessments and the highly trained technicians who can operate and maintain the equipment and interpret the results. In low- or middle-income countries, these facilities are only available in prestigious health centers in large urban areas. Additional limitations may occur in countries

where cultural factors make it difficult to acquire samples (e.g., CSF).

c) There are ethical concerns about the early diagnosis of AD. The new diagnostic criteria stress the importance of early detection and propose the concept of a prodromal phase of AD. Some scholars suggest that the early detection of AD using biomarkers is little different from identifying carcinoma in situ (CIS) or using laboratory tests to identify prodromal phases of type-II diabetes, hypertension, renal insufficiency, and osteoporosis. However, the situation with AD is different because there is, as yet, little evidence that early detection and treatment of high-risk individuals (i.e., individuals with mild cognitive impairment) has any beneficial effects.[4,5] Furthermore, the psychological burden that is experienced by the individual and the individual's family when an early diagnosis is made by a treating clinician can be as great as that caused by the disease itself.[6] Thus, there are serious ethical issues related to the early diagnosis of AD that are more prominent than those related to the early diagnosis of other conditions for which effective treatments are already available.

d) The theoretical foundation of the new diagnostic criteria is inadequate. The new diagnostic criteria are completely based on theories about disturbed metabolism of Aβ and the resultant accumulation of Aβ. But this is only one of many etiological mechanisms that result in AD, so the markers only identify a subset of cases. Moreover, the

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proposed biomarkers are not pathognomonic, some individuals with these markers never develop AD.

Despite these problems, it is undeniable that the emphasis on biomarkers in the new diagnostic criteria is an improvement. Studies on biomarkers have demonstrated that the conventional symptomology-based diagnostic criteria of AD can delay treatment because clinical symptoms greatly lag behind the actual onset of the disease. This delayed diagnosis delays both the clinical treatment of affected individuals and the development of new medications of other interventions to prevent or treat AD. Despite the uncertainty of their use in clinical practice, adopting biomarkers in clinical research and pharmaceutical studies can help distinguish AD from other types of dementia, advance our understanding of the pathology of AD, promote the initiation of interventions and treatments earlier in the course of the condition, improve the quality of the evaluation of effectiveness, and, thus, help in the development of new drugs and other treatments.

A search on Web of Science found that many researchers are already publishing results based on these new diagnostic criteria. As of 5 April 2015 there have been 1059 articles published using the NINCDS-ADRDA criteria, 864 articles published using the NIA-AA criteria, and 21 articles published using the IWG-2 criteria. The widespread use of these new diagnostic criteria in research studies can help homogenize the selection of samples and, thus, greatly improve the comparability of the studies. It would then be feasible to combine such studies in meta-analysis with large pooled samples, the type of comprehensive analyses that will be needed to provide clear answers to many of the perplexing issues that need to be resolved before it will be possible to identify effective interventions for this disabling condition. Additional work in the future will be needed to identify a subset of relatively easy to identity biomarkers that can be used in routine clinical care, particularly in low-resource settings in low- and middle-income countries.

Conflict of interest

The author reports no conflict of interest related to this manuscript.

阿尔茨海默病新诊断标准的临床研究价值

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概述： 在阿尔茨海默氏病（Alzheimer's disease, AD）的诊断中采用生物标志物已日益得到重视，但在临床实践中使用生物标志物的可行性和价值仍然是有限的。然而，AD 临床和制药研究中生物标志物的使用也许可以证明对明确 AD 的病理基础是非常有用的，并有助于提高在有效预防和治疗措施下的早期识别。此外，新诊断标准的广泛采用将提高不同研究结果之间的可比性，并为使用 meta 分析方法合并和比较不同研究的结果创造了可能性 —— 这种分析能够明确回答关于 AD 的病因、病程、预防和治疗等基本问题。

关键词：阿尔茨海默氏病；诊断标准；生物标记物

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