Harmonized diagnostic criteria for Alzheimer’s disease: recommendations

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Background. Two major sets of criteria for the clinical diagnosis of Alzheimer’s disease (AD) recently have been published, one from an International Working Group (IWG) and the other from working groups convened by the National Institute on Aging (NIA) and the Alzheimer’s Association (AA) in the United States. These criteria both aim to support a clinical diagnosis with in vivo evidence of AD pathology, using imaging methods and detection of biofluid biomarkers, and emphasize an aetiological diagnosis even in the prodromal stages of the disorder. Nonetheless, there are substantial differences in these two sets of criteria.

Methods. An international group of investigators with experience in the clinical diagnosis of AD met at the Key Symposium in Stockholm, Sweden on 6 & 7 December 2012, to develop recommendations to harmonize these criteria. The group was led by individuals who were integral to the development of both the IWG and the NIA-AA criteria. The similarities and differences between the two sets of criteria were identified and open discussion focused on ways to resolve the differences and thus yield a harmonized set of criteria.

Results. Based on both published evidence as well as the group’s collective clinical experience, the group was tasked with achieving consensus, if not unanimity, as it developed recommendations for harmonized clinical diagnostic criteria for AD.

Conclusion. The recommendations are to: (i) define AD as a brain disorder, regardless of clinical status; (ii) refer to the clinically expressed disorder, including its prodromal stages, as symptomatic AD; (iii) after the successful completion of standardization efforts, consider incorporating biomarkers into diagnostic algorithms for AD; and (iv) allow non-amnestic, atypical presentations to be included as symptomatic AD, especially when there is supportive biomarker evidence.

Keywords: Alzheimer biomarkers, Alzheimer’s disease, clinical diagnostic criteria, preclinical Alzheimer’s disease.

Introduction

Two major sets of clinical diagnostic criteria for Alzheimer’s disease (AD) were recently proposed. First, an International Working Group (IWG) of dementia experts, initially meeting at the 2005 Congress of the International Society for Vascular Behavioral and Cognitive Disorders, developed guidelines that incorporated new knowledge about the prodromal symptomatic stage of AD and biomarkers of the disorder [1]. The original 2007 guidelines were updated in 2010 to address atypical clinical presentations of AD and identify clinically asymptomatic individuals who are positive for biomarkers of AD pathology [2]. Secondly, the National Institute on Aging (NIA) of the National Institutes of Health in the United States, in partnership with the Alzheimer’s Association (AA), convened three work groups beginning in 2009 to update original standards published 25 years ago.
earlier for the clinical diagnosis of probable AD [3]. The NIA-AA work groups adopted the concept of AD as a pathophysiological continuum with three major stages: (i) asymptomatic, or preclinical [4]; (ii) prodromal symptomatic, or mild cognitive impairment (MCI) due to AD [5]; and (iii) fully symptomatic, or AD dementia [6].

The IWG and NIA-AA criteria recognize that the rapidly evolving research with AD biomarkers will eventually be translated into practical diagnostic algorithms to improve diagnosis, and both emphasize that the aetiology of the prodromal/MCI stage should be ascertained. However, there are also important differences in terms of how AD is conceptualized, the terminology used for common aspects of the disorder, and whether biomarkers should be incorporated into the diagnostic algorithm. Examining these differences and developing a proposal for their reconciliation were the principal aims of the 2012 Key Symposium held in Stockholm, Sweden, on 6 & 7 December 2012, which was supported by the Journal of Internal Medicine and the Royal Swedish Academy of Sciences. Led by experts who contributed to the NIA-AA criteria for AD dementia (JCM) and the 2007/2010 IWG criteria (BD), a distinguished group of clinical investigators reached a consensus on simple, common terminology to harmonize these sets of clinical diagnostic criteria for AD. To put these recommendations into context, the panel of AD biomarkers are briefly reviewed and the IWG and NIA-AA criteria are compared.

**AD biomarkers**

Biomarkers function as surrogates for pathophysiological lesions in AD. The molecular pathology of AD is complex; however, senile plaque (SP) and neurofibrillary tangle (NFT) constitute the classic neuropathologic hallmarks of AD [7]. Disruption in the cerebral homeostasis of soluble amyloid-beta (Aβ) – owing to overproduction, impaired clearance or both – promotes aggregation (particularly of the Aβ42 isoform) into insoluble, toxic species, which are deposited extracellularly in the cerebral cortex and form SPs. Tau protein hyperphosphorylation and other modifications destabilize intraneuronal microtubules, resulting in the formation of NFTs. Current laboratory and neuroimaging procedures can identify these abnormalities, which can therefore serve as in vivo biomarkers of AD: for instance, a reduced level of Aβ42 in the cerebrospinal fluid (CSF) or an increase in total or phosphorylated tau (p-tau) in the CSF is highly correlated with AD neuropathology [8, 9]. Moreover, tracers have been developed that allow detection of fibrillar Aβ deposits in the cerebral cortex by positron emission tomography (PET), including [11C]Pittsburgh Compound-B (PIB) [10], Florbetapir [18F] [11], [18F]Flutemetamol [12], [18F]Florbetaben [13] and [18F] AZD-2184 [14]. Thus, cortical amyloid burden in the brain at early stages of AD can be evaluated and correlated with SPs found in post-mortem examinations [11, 15]. [18F] Florbetapir (Amyvid®) and [18F] Flutemetamol (Visy®) have been approved for clinical use by the Food and Drug Administration in the United States (2012–2013), and [18F] Florbetapir has been approved by the European Medicines Agency (2013). PET tracers that detect cerebral tau burden are currently being developed.

The neurodegeneration that characterizes AD is initially manifested by decreased neuronal function and ultimately leads to synaptic loss and neuronal death. Neuroimaging can thus identify downstream biomarkers of AD that measure neuronal dysfunction and brain atrophy, particularly in brain regions that are the most vulnerable to the pathophysiological process. The most commonly used degeneration (also known as injury or topographical) biomarkers are medial temporal lobe atrophy and reduced glucose metabolism in temporoparietal regions, as determined by structural magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG) PET, respectively. Other potential MRI-derived degeneration biomarkers include cerebral cortical thinning [16] and resting state functional connectivity [17], and additional PET-derived measures include changes in regional cerebral blood flow [18]. Degeneration biomarkers are less specific for AD than molecular biomarkers.

**Key elements of the IWG and NIA-AA criteria**

The IWG criteria are as follows

**Terms and definitions**

The term AD refers only to the clinically expressed disorder that features cognitive, behavioural and neuropsychiatric changes that interfere with daily life. The spectrum of clinically manifest AD is subdivided into predementia and dementia phases [1] (Table 1).

a Predementia AD is represented by prodromal AD, with episodic memory impairment that is insufficient to disrupt the performance of accustomed instrumental activities of daily living (IADL).
AD dementia indicates that episodic memory loss and other cognitive symptoms are sufficient to interfere with the usual performance of IADL.

c The IWG team proposed for future consideration that AD alone might replace prodromal AD and AD dementia so as to unify the symptomatic phase of AD under one diagnostic label.

Preclinical AD refers to the stage of AD that is not clinically expressed; that is, although the molecular pathology of AD is present in the brain, symptoms are absent. The use of preclinical signifies that this stage can only be detected by AD biomarkers, and not by currently available clinical methods.

a Cognitively normal individuals with evidence of AD molecular pathology are considered as asymptomatic at risk for AD, as it is currently unknown whether progression to symptomatic AD is inevitable.

b Asymptomatic carriers of a dominantly inherited gene mutation causing AD are characterized as presymptomatic AD, as symptoms will almost certainly develop in these individuals.

Additional terms are proposed for variations in the clinical phenotype (typical versus atypical AD) or when comorbid disorders with the potential to cause or exacerbate cognitive and neuropsychiatric symptoms are present in an individual who also fulfills diagnostic criteria for AD (mixed AD). These will not be further addressed here.

The neuropathological AD entity is Alzheimer’s pathology, regardless of clinical status.

Diagnostic algorithm

The diagnosis of AD requires a characteristic pattern of episodic memory impairment and the presence of in vivo AD pathology, as indicated by one or more abnormal biomarkers that demonstrate either the molecular pathology of AD or the consequences of that pathology. The same requirements apply to the subcategories of prodromal AD and AD dementia, which are differentiated solely by the absence or presence, respectively, of functional impairment.

Preclinical AD, by definition, lacks symptoms of memory or other cognitive impairment. To diagnose asymptomatic at risk for AD, abnormal AD biomarkers that indicate the molecular pathology of AD must be present. Presymptomatic AD is characterized by the presence of a causative mutation for AD.

The NIA-AA work groups were instructed to focus on the spectrum of AD, regardless of clinical status.

Terms and definitions

Recognizing that the pathologic process of AD is not always clinically expressed, the NIA-AA criteria suggest that AD is conceptualized as a continuum in which the initially asymptomatic AD pathophysiological cascade eventually results in symptoms. (Table 2) [19].

Preclinical AD refers to the pathophysiological stage when in vivo molecular biomarkers of AD are present, but symptoms are absent.

MCI due to AD is defined as the symptomatic predementia phase of AD.

Table 1  

<p>| International working group (IWG) for new research criteria for the diagnosis of Alzheimer's disease |</p>
<table>
<thead>
<tr>
<th>AD Dx</th>
<th>Presence of impairment on memory tests</th>
<th>Evidence of biomarkers in vivo</th>
<th>Additional requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodromal AD</td>
<td>Y</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>AD dementia</td>
<td>Y</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Preclinical AD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic at risk for AD</td>
<td>N</td>
<td>Not present</td>
<td>Required</td>
</tr>
<tr>
<td>Presymptomatic AD</td>
<td>N</td>
<td>Not present</td>
<td>Not required</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>N</td>
<td>Not required</td>
<td>Not required</td>
</tr>
</tbody>
</table>

**AD dementia** refers to dementia caused by the pathophysiology of AD and encompasses the mildest to the most severe dementia stages.

Atypical presentations are addressed with the term *possible AD dementia*. Etiologically mixed presentations refer to the presence of comorbid disorders that could affect cognition when criteria for AD dementia also are met. These will not be further discussed here.

### Diagnostic algorithm

A model for staging preclinical AD was based on a hypothetical temporal ordering of biomarker changes: 

- **Stage 1** is marked by Aβ peptide dysregulation (reflected in reduced levels of CSF Aβ42 or by elevated cerebral cortical amyloid burden as determined by PET amyloid imaging);
- **Stage 2** adds synaptic/neuronal dysfunction and loss (i.e. neurodegeneration), as evidenced by increased CSF p-tau levels, or hypometabolism or cortical thinning/hippocampal atrophy as determined by FDG PET and MRI, respectively; and
- **Stage 3** features the abnormalities in Stages 1 and 2 plus subtle cognitive decline (the operationalization of this subtle decline remains to be determined).

A diagnosis of *MCI due to AD* requires evidence of intra-individual decline, manifested by

- a A change in cognition from previously attained levels, as noted by self- or informant report and/or the judgment of a clinician.

- b Impaired cognition in at least one domain (but not necessarily episodic memory) relative to age-and education-matched normative values; impairment in more than one cognitive domain is permissible.

- c Preserved independence in functional abilities, although the criteria also accept ‘mild problems’ in performing IADL even when this is only with assistance (i.e. rather than insisting on independence, the criteria now allow for mild dependence due to functional loss).

- d No dementia, which nominally is a function of c. (above).

- e A clinical presentation consistent with the phenotype of AD in the absence of other potentially dementing disorders. Increased diagnostic confidence may be suggested by

1. **Optimal:** A positive Aβ biomarker and a positive degeneration biomarker

2. **Less optimal:**
   - a) A positive Aβ biomarker without a degeneration biomarker
   - b) A positive degeneration biomarker without testing for Aβ biomarkers

A diagnosis of *AD dementia* requires

- a The presence of dementia, as determined by intra-individual decline in cognition and function.

- b Insidious onset and progressive cognitive decline.

- c Impairment in two or more cognitive domains; although an amnestic presentation is most common, the criteria allow for diagnosis based on nonamnestic presentations (e.g. impairment in executive function and visuospatial abilities).

- d Absence of prominent features associated with other dementing disorders.

- e Increased diagnostic confidence may be suggested by the biomarker algorithm discussed in the *MCI due to AD* section above.

The IWG and NIA-AA criteria have in common the recognition of a preclinical stage of the disease, the acceptance of a diagnosis of AD prior to dementia and the incorporation of AD biomarkers to...
diagnose (IWG) or provide support for the diagnosis (NIA-AA) of AD (Table 3). To the extent that biomarkers are used in the clinical diagnosis of AD, the diagnostic process is shifted from a nonspecific syndromic approach to one in which AD is considered as a clinico-biological entity.

The applicability of the IWG criteria has been demonstrated by some reported experiences. Two individuals enrolled in a natural history study of cognition were diagnosed with MCI based on isolated memory deficits at baseline as well as CSF molecular biomarker changes consistent with AD and reduced hippocampal volumes, thus fulfilling IWG criteria for AD. Both individuals demonstrated cognitive and functional decline over 12 months, which was interpreted as a preliminary validation of the IWG criteria [20]. Other reports from a memory clinic population [21] and from another natural history study of MCI [22] found good specificity of the new criteria relative to cognitively normal individuals and showed that the biomarkers provided incremental diagnostic information to the clinical assessment, whilst also suggesting that more than one AD biomarker was useful when the clinical diagnosis is in doubt. Another study, however, found that the IWG criteria were inaccurate for half of patients with AD dementia who were evaluated in a clinical setting [23], underscoring the point that to date most biomarker data have been derived from highly selected research samples rather than in clinical settings where biomarkers must be well characterized prior to routine use in clinical diagnostic processes.

The NIA/AA criteria also are being assessed, most notably with the criteria for staging preclinical AD stage [24]. Investigators from the Mayo Clinic Study of Aging used imaging results (MRI, FDG PET and PIB PET) to stage 296 cognitively normal older adults in accordance with the proposed model for preclinical AD as discussed above. Within 15 months, individuals progressed from cognitive normality to symptomatic AD (MCI or dementia) at rates proportional to their preclinical stage at baseline [e.g. five of 80 (11%) Stage 1 individuals versus three of seven (43%) Stage 3 individuals] [25]. A similar study of 311 cognitively normal older adult participants at the Knight Alzheimer Disease Research Center at Washington University used CSF Aβ42 and tau concentrations to stage preclinical AD, which was present in 31% of the cohort, and found that the 5-year progression rate to symptomatic AD was only 2% for participants who lacked any AD biomarkers (termed Stage 0) but was 11% for Stage 1, 26% for Stage 2 and 56% for Stage 3 preclinical AD [26]. These and other reports [27, 28] demonstrate a strong association between biomarker-defined preclinical AD and subsequent cognitive decline.

The Key Symposium group agreed that the two sets of criteria are useful in attempting to extrapolate biomarker research results to diagnostic guidelines.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison of international working group criteria and NIA-AA criteria for clinical diagnosis of Alzheimer’s disease</th>
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<tbody>
<tr>
<td><strong>Similarities</strong></td>
<td></td>
</tr>
<tr>
<td>Incorporate biomarkers for AD into the diagnostic process</td>
<td></td>
</tr>
<tr>
<td>Move towards an aetiological diagnosis for MCI</td>
<td></td>
</tr>
<tr>
<td>‘Prodromal AD’ (IWG)</td>
<td>‘MCI due to AD’ (NIA-AA)</td>
</tr>
<tr>
<td><strong>Differences</strong></td>
<td><strong>NIA-AA</strong></td>
</tr>
<tr>
<td>‘AD’ refers only to symptomatic stage</td>
<td>‘AD’ refers to the pathologic process, whether asymptomatic or symptomatic</td>
</tr>
<tr>
<td>Replace ‘MCI’ with ‘Prodromal AD’</td>
<td>Retain ‘MCI’</td>
</tr>
<tr>
<td>Requires objective impairment in memory</td>
<td>Subjective and/or objective impairment in memory and/or nonmemory domains</td>
</tr>
<tr>
<td>Biomarker abnormalities required for diagnosis</td>
<td>Biomarker abnormalities support diagnosis but not required</td>
</tr>
</tbody>
</table>

and that most individuals who meet one set of criteria most likely will meet the other set. However, there remain substantive differences between these sets of criteria (Table 3), as well as other challenges. First, the two criteria offer opposing views of what is meant by disease. Secondly, the multiple terms and definitions may be confusing and cumbersome. Thirdly, it may be premature to require the use of biomarkers in diagnosis as standardization of CSF and the imaging of biomarkers has not been accomplished even in research studies, much less in clinical settings, and there are unresolved questions about their costs and accessibility. Fourthly, whether AD must be represented by amnestic deficits is unresolved.

**Meaning of Alzheimer's disease**

The most frequently used disease categorization system is the International Statistical Classification of Diseases and Related Health Problems (ICD) published by the World Health Organization (WHO). The ICD classification is based primarily on clinical information and does not always incorporate remarkable advances in the understanding of molecular mechanisms and genetic and environmental factors that interact to cause disease and pathology. For example, the WHO’s definition of disease typically requires the presence of signs (malfunction) and symptoms (suffering). However, new biological and medical information are prompting a reconsideration of this definition. The National Research Council of the National Academy of Sciences (United States) proposed a new taxonomy of human disease based on molecular biology, recommending that diseases be defined not only by the traditional dependence on signs and symptoms but also in regards to their biology [29].

The temporal ordering of molecular and degeneration markers of AD has been shown for asymptomatic mutation carriers with autosomal dominant forms of AD [30]. The validity of biomarker abnormalities is underscored by their presence only in mutation carriers who are destined to develop symptomatic AD with virtual 100% certainty. It is not known what percentage of biomarker-positive, asymptomatic older adults will develop sporadic symptomatic AD, although there is increasing evidence to suggest that they are at great risk of doing so [25–28, 31, 32]. The absence of symptoms should not dissuade the use of the term disease to describe asymptomatic but biomarker-positive individuals. Although some individuals with coronary heart disease escape experiencing a myocardial infarction, nonetheless, the condition is recognized as an asymptomatic disease and is medically treated. In a similar manner, based on advances in the molecular pathology of AD, the Key Symposium group recommends that AD be used to represent the brain disorder itself, regardless of clinical status. It is appreciated that when truly effective therapies for AD, including its asymptomatic stages, are developed adoption of this recommendation will be accelerated.

The consensus recommendation to define AD as a pathophysiological disorder regardless of clinical status was not unanimous. A minority view from the Key Symposium group favoured the IWG position that separates the clinically expressed disorder (term AD) from the underlying pathology until a clearer understanding is reached regarding the relationship between the presence of the pathological lesions and symptomatic expression. That the IWG and NIA-AA criteria currently differ on the definition of AD reflects the need for ongoing and future studies to clarify the symptomatic consequences of the preclinical stage of the disorder and thus lead to a standard lexicon.

**Terms and definitions**

The IWG and NIA-AA criteria together offer a plethora of nonharmonized terms to describe the different stages and aspects of AD. This is partly because some clinicians have long been reluctant to label individuals in the earliest symptomatic phase as having dementia, and thus, this stage has been variously considered as representing MCI, predementia and prodromal AD, as well as other terms. Reasons for this reluctance include the apparent absence of functional loss in this stage, the difficulty in ascertaining whether mildly affected individuals will subsequently demonstrate the AD phenotype of progressive cognitive and functional decline, and the perceived stigma of labelling an individual as demented or having AD when symptoms are very mild.

With experience, it is now recognized that mild functional losses are present in at least some individuals in the MCI/ prodromal AD stage [33–35] and that the frequency of functional impairment increases when the clinician carefully probes an observant informant as to whether the affected individual has declined in performance of his or her accustomed activities (intra-individual decline). The NIA-AA criteria allow impaired functional abilities to be consistent with MCI due to AD [5]. Hence,
a requirement for preserved functional abilities no longer distinguishes MCI/prodromal AD from AD dementia. It may be beneficial to absolve clinicians of the difficulties of trying to impose a dichotomous classification on a continuous process of cognitive and functional decline by eliminating the artificial distinction between MCI due to AD and AD dementia. The aetiologically based term, symptomatic AD, encompasses the entire clinical spectrum of symptom severity from very mild (in MCI due to AD) to advanced dementia.

Not all individuals considered to have MCI/prodromal AD will have progressive cognitive and functional decline consistent with an AD phenotype, nor will all be AD biomarker-positive or have AD neuropathology. That is, not everyone with MCI has underlying AD. It is well accepted that many non-AD conditions (including those that are reversible) can produce MCI. This is identical to dementia, which is also not always caused by AD. In MCI/prodromal AD and dementia, the same diagnostic process can help in determining whether MCI/prodromal AD and dementia are likely caused by AD. This process includes obtaining a history of intra-individual cognitive and functional decline (from an informant whenever possible), ascertaining the essential features of the AD phenotype (e.g. gradual onset and progression) and documenting objective impairment with cognitive testing whilst evaluating the potential contributions of any comorbid disorders. This clinical approach alone can yield neuropathologically confirmed diagnostic accuracy rates for AD of 92% for individuals in the MCI/prodromal AD stage [36, 37]. When there is clinical diagnostic uncertainty (e.g. when the cognitive impairment is very mild), AD biomarkers can support (or refute) that underlying AD is present.

Terms such as AD and dementia can be stigmatizing, although greater awareness of AD due to its growing prevalence may be helping to reduce that stigma. Concern about psychological distress in affected individuals and their families resulting from a dementia diagnosis, particularly in the earliest symptomatic stages, has been an argument against disclosure [38]. There are several anecdotal reports of catastrophic reactions, including suicide [39, 40], following a dementia diagnosis. However, when risk of suicide after disclosure of a dementia diagnosis was systematically assessed in a research cohort of older adults, only two of 2660 individuals (<0.1%) evaluated over 25 years attempted suicide (one successfully) [41]. Individuals with a high-risk phenotype for suicide (male, high educational level, retention of insight [more common in early symptomatic AD], depressive features prior to dementia onset and suicidal ideation) [41] should be identified and treated [39]. On the other hand, the risk of suicide in dementia is generally quite low. Although an elevated risk for suicide was noted when dementia had been diagnosed in 21 394 individuals hospitalized for psychiatric (65%), somatic (30%) or psychiatric and somatic (5%) indications, an 11-year observation period of 5699 individuals who died by suicide found that only 136 (0.2%) were demented [42].

The vast majority of individuals in the MCI stage of early symptomatic AD do not experience catastrophic reactions after disclosure of the diagnosis. One study found that not only did depression not worsen but anxiety notably decreased in both the individuals and their families after diagnostic feedback [43]. Although clinicians may be reluctant to disclose a dementia diagnosis to avoid the (rare) provocation of psychological distress [44], both affected individuals and their family members consistently indicate that they wish to receive the diagnosis because it provides a cause for the observed symptoms and allows future planning to be better informed [45, 46].

The Key Symposium group proposes that the term symptomatic AD be used to describe the entire clinical spectrum of AD, from the earliest symptomatic stages (MCI/prodromal AD) to the most severe. Advantages of this term include simplicity and directness regarding the clinically determined aetiology. It also avoids the ambiguity associated with nonaetiological terms, such as MCI. Widely accepted clinical global staging systems such as the Clinical Dementia Rating [47] and/or cognitive test performance can be used with the term to provide an index of severity: for example mild symptomatic AD.

**Incorporating biomarkers into the clinical diagnostic algorithm**

Until standardization efforts are successfully completed to minimize within- and between-centre variability and allow uniform cut-off levels to be established, the Key Symposium group recommends that CSF biomarker assays should not be mandatory for the clinical diagnosis of AD. Additional issues that need to be resolved for CSF biomarkers include how they will be used operationally, their accessibility (e.g. not all physicians...
are comfortable performing lumbar punctures) and the cost of the assays. Nonetheless, they likely will be increasingly used to select participants with the appropriate phenotype for investigations, including clinical trials of experimental agents for AD [48], and in clinical settings for patients presenting with atypical dementia. This experience will be valuable in ascertaining the potential utility of incorporating CSF biomarkers with the clinical diagnostic algorithm for AD once standard procedures have been adopted.

Memory difficulties are the initial and prominent feature for the vast majority of individuals with symptomatic AD. Nonetheless, nonamnestic presentations of AD are well established [49]. The Key Symposium group recommends that the routine clinical diagnosis of symptomatic AD, in which biomarker evidence of AD is not required, be based on the presence of amnestic deficits. However, atypical or focally presenting cases with minimal or no memory impairment at the time of clinical presentation may also be diagnosed as symptomatic AD when the diagnosis is supported by biomarker evidence.

Summary

The Key Symposium workgroup on the harmonization of clinical diagnostic criteria for AD capitalized on the substantial contributions of the IWG and the NIA-AA groups. The recommendations of the Key Symposium workgroup presented here (Table 4) are offered to improve the concordance between two sets of criteria, simplify and standardize AD terminology, and move to aetiological based diagnoses. The future perspective on the role of AD biomarkers in clinical diagnostic algorithms involves resolving the current challenges associated with moving molecular and degeneration biomarkers from the research setting into clinical practice. These challenges include maximizing biomarker reliability and validity, standardizing sample collection and processing procedures and implementing quantitative assays with high sensitivity, precision and high-throughput capabilities [50]. If these can be accomplished, the clinical diagnosis of AD will evolve from the current dependence on syndromic presentations to biomarker-guided diagnoses that will provide another opportunity for updating the criteria for the clinical diagnosis of AD.

Conflict of interest statement

The authors have declared no conflict of interests.

Reference


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