New diagnostic criteria for Alzheimer's disease and mild cognitive impairment for the practical neurologist

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Abstract

Four articles in the journal ***Alzheimer's and Dementia*** in 2011 describe new criteria for Alzheimer's disease (AD) dementia and mild cognitive impairment (MCI) due to the AD pathophysiological process (MCI due to AD), as well as the underlying rationale for them. The new criteria also include preclinical AD criteria but these are intended purely for research purposes. The new criteria emphasise that the AD pathophysiological process starts years and perhaps decades before clinical symptoms, and that biomarkers can detect amyloid β deposition and the effects of neurodegeneration in the brain. The criteria are recommendations based upon consensus meetings and will require future validation. Nonetheless, the authors believe that they are immediately helpful to the practising clinician, providing more accurate and specific guidelines for the diagnosis of AD dementia and MCI due to AD. As new diagnostic tools and treatments for AD become available, diagnoses using these criteria will enable patients with AD dementia, MCI due to AD and eventually preclinical AD to receive the best possible care.

Rationale for new criteria

The National Institute on Aging and the Alzheimer's Association work group on diagnostic guidelines for Alzheimer's disease have updated the 1984 Alzheimer's disease criteria in four articles in the journal *Alzheimer's and Dementia* in 2011. In these, they describe new clinical criteria for Alzheimer's disease (AD) and mild cognitive impairment (MCI) due to the AD pathophysiological process (MCI due to AD).[1] Although these groups were not the first to update the 1984 criteria (see papers by Dubois and colleagues),[2 3] they currently have the greatest consensus in the scientific AD community and are likely to have a lasting impact.

The new criteria were developed due to several factors that have changed since 1984:

(1) The AD pathophysiological process likely starts years before cognitive changes and decades before onset of clinical dementia[4 5] (figure 1). The concept of the 'AD pathophysiological process' is thus separated from 'AD dementia.'
(2) Many patients whose cognition is not normal for age do not meet criteria for dementia.
(3) Other causes of dementia are more likely mistaken for AD than are thyroid disorders and B_{12} deficiency.
(4) Genetics of AD are better understood.
(5) Biomarkers of AD are available in some centres.
(6) New criteria are needed for research.
(7) Specific treatments for the AD pathophysiological process are being developed; when these treatments are available it will be critical to know if patients have that process.

There are three stages of AD:

- Preclinical AD requires measureable changes in biomarkers and/or poor performance on challenging cognitive tests.
- MCI due to AD manifests the first clinical changes. Patients and families notice mild changes in memory and other cognitive abilities; these changes can be detected through careful evaluation, but do not interfere with day-to-day activities.

- Dementia due to AD is characterized by changes in two or more aspects of cognition and behaviour that interfere with function in everyday life.

One model of AD is that many factors combine to cause the accumulation of amyloid β (Aβ) in the brain, which in turn produces synaptic dysfunction, tangle formation, and neuronal death, ultimately leading to cognitive decline (Sperling *et al*,)[5] (figure 2). Because events in this sequence likely take years or decades, there must be a prior 'preclinical' stage of AD (figure 3).

Table 1 presents several currently used biomarkers of Aβ deposition or neurodegeneration. Markers of Aβ deposition include low cerebrospinal fluid (CSF) $A\beta_{42}$ and positive positron emission tomography (PET) amyloid imaging. Markers of neurodegeneration include elevated CSF tau (both total and hyperphosphorylated tau), decreased metabolism in temporal and parietal cortex on ^{18}flurodeoxyglucose (FDG) PET, and atrophy on MRI in temporal (medial, basal, and lateral) and medial parietal cortex. In clinical practice, one tends to divide the biomarkers by how they are obtained: structural MRI, PET, and CSF studies.

Although volumetric MRI analyses are not routinely available, we encourage all clinicians to look for qualitative patterns of atrophy in temporal (medial, basal, and lateral) and medial parietal cortex.[6]

FDG PET scans show decreased metabolism in temporal and parietal cortex when the AD pathophysiological process has caused neurodegeneration.[6] FDG PET scans are available to the clinician now (and are covered by Medicare in the USA). We do not, however, recommend using these scans routinely when the history, physical examination, cognitive testing, and structural imaging are all consistent with AD: it is simply not necessary.[6] However, when one suspects an atypical neurodegenerative disease or the patient is younger than 66 years of age (when the prevalence of AD is similar to that of many other aetiologies), an FDG PET scan can help to distinguish AD from another disorder (such as

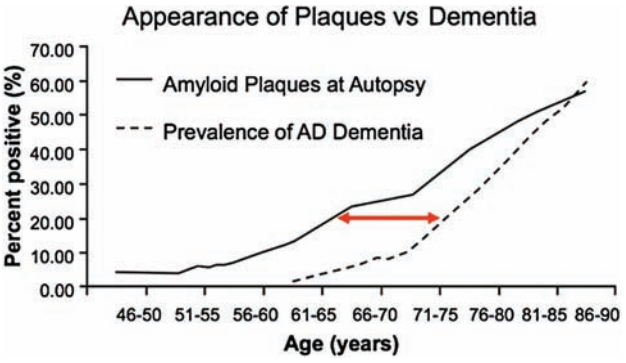

Figure 1 Postulated temporal lag between the deposition of amyloid β in amyloid plaques from an autopsy series and the development of clinical Alzheimer's disease (AD) dementia based upon three epidemiological studies (from Sperling *et al*).[5]

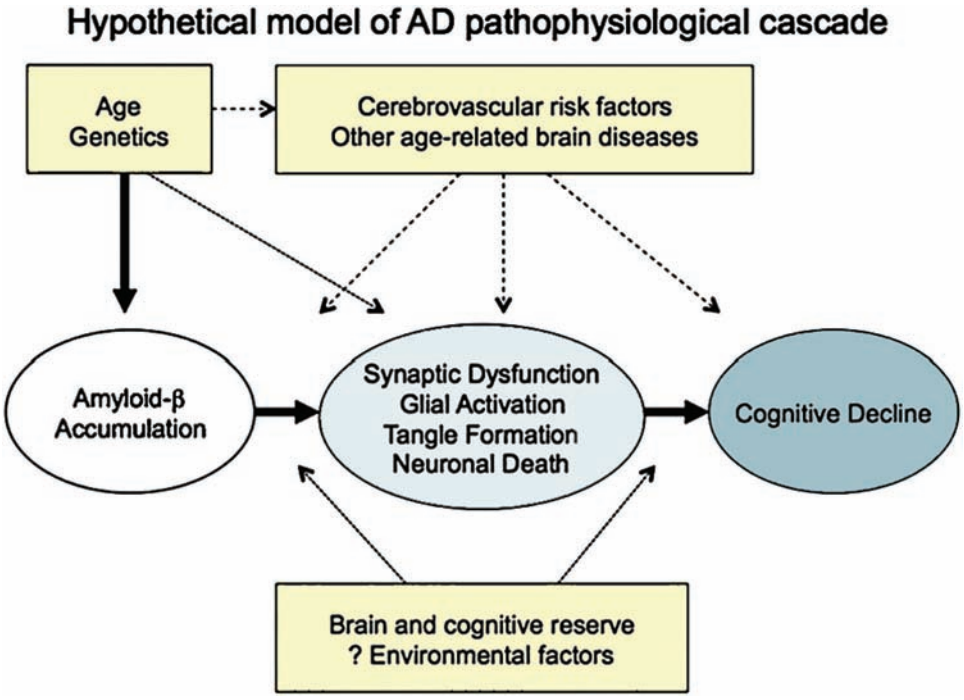

Figure 2 Hypothetical model of Alzheimer's disease (AD) pathophysiological cascade sequence (from Sperling *et al*).[5]

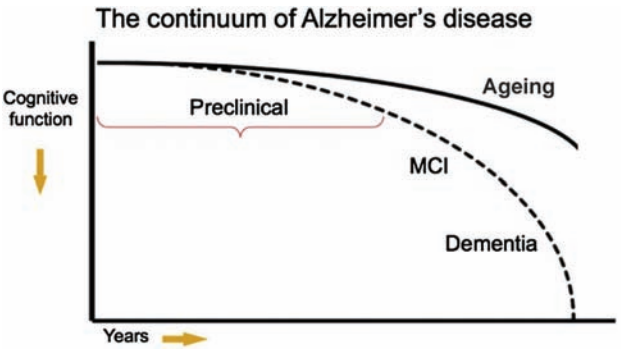

Figure 3 Model of the clinical course of Alzheimer's disease (from Sperling *et al*).[5] MCI, mild cognitive impairment.

Table 1 Putative biomarkers for the AD pathophysiological process currently being used

(1)	Markers of amyloid-β (Aβ) protein deposition in the brain
a.	Low CSF $A\beta_{42}$
b.	Positive PET amyloid imaging
(2)	Markers of downstream neurodegeneration
a.	Elevated CSF tau (total and phosphorylated)
b.	Decreased metabolism in temporal and parietal cortex on ^{18}flurodeoxyglucose PET
c.	Atrophy on MRI in temporal (medial, basal, and lateral) and medial parietal cortex

AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography.

dementia with Lewy bodies or frontotemporal dementia).

Several compounds that can identify Aβ deposition using PET are currently being used for research and/or are under commercial development, including Pittsburgh compound B and florbetapir. Because amyloid accumulation may occur years before clinical symptoms, PET identification of Aβ raises the possibility of identifying and treating patients with AD years before symptoms emerge—once a drug has been proven to be disease-modifying.

Standard CSF biomarkers for AD are $A\beta_{42}$, total tau, and hyperphosphorylated tau. When all three markers are combined, the accuracy of the diagnosis is the highest, with sensitivity and specificity of 85–90%. Although CSF analysis is already commercially available (http://www.athenadiagnostics.com) and some clinicians use it to aid diagnosis, we view this test as promising but not yet ready for routine clinical practice.[6]

Guided by these theoretical underpinnings, the new criteria are presented for all cause dementia, AD dementia, MCI due to AD, and—for research only—preclinical AD. (See figure 4 for an overall flow chart for the evaluation of a patient with cognitive impairment.)

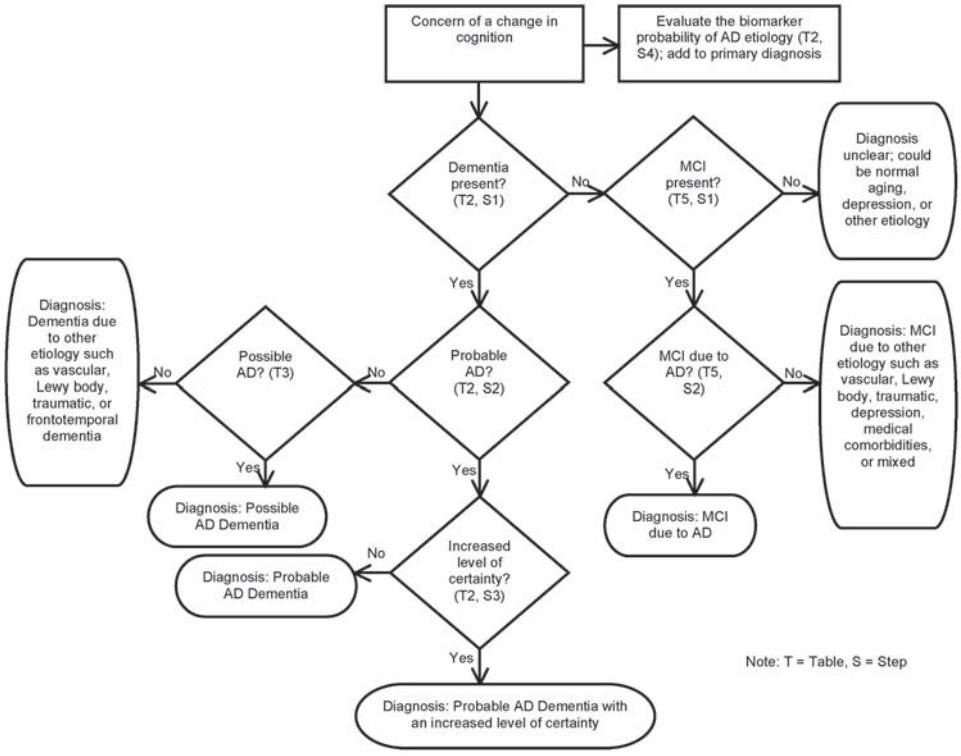

Figure 4 Flow chart for the evaluation of a patient with cognitive impairment leading to the diagnosis of mild cognitive impairment (MCI) and dementia using the new guidelines, with references to the tables (T) and steps (S) in the text.

Table 2 Clinical and cognitive evaluation for all cause dementia and AD

Guideline	Procedures
Step 1: criteria for 'all cause dementia'	
Interferes with the ability to function at work or with usual abilities and Represents a decline from previous ability and Cannot be explained by delirium or major psychiatric disorder	**History and observation** ■ Evidence of changes in functioning reported by either patient and/or informant or observed by clinician
Presence of cognitive impairment	**History, observation, neuropsychological testing** ■ History-taking from a knowledgeable informant ■ Objective mental status testing and/or neuropsychological testing ■ Neuropsychological testing is recommended when history and mental status testing cannot provide a confident diagnosis
The cognitive or behavioural impairment involves a minimum of two domains	**History, observation, neuropsychological testing** ■ Impaired ability to acquire/remember new information (eg, repeating questions, forgetting events or appointments, becoming lost in familiar places) ■ Impaired reasoning and handling of complex tasks, poor judgement (eg, inability to handle finances, poor decision making) ■ Impaired visuospatial abilities (eg, difficulty recognising faces or common objects) ■ Impaired language function (speaking, reading, writing; eg, difficulty thinking of common words while speaking, hesitations in speech) ■ Changes in personality, behaviour, comportment (eg, agitation, apathy, social withdrawal)
Difference between MCI and dementia	**History and observation** ■ The fundamental difference between diagnoses of dementia versus MCI depends upon whether or not there is a significant change in the ability to function at work or in daily activities. This will necessarily require clinical judgment based upon the information provided by the patient and a knowledgeable informant.
Step 2: criteria for 'probable AD dementia'	
Meets criteria for dementia	See criteria above for dementia, step 1
Insidious onset: symptoms have a gradual onset over months or years, not sudden over hours or days.	**History** ■ From patient and knowledgeable informant
Clear cut history of worsening of cognition	**History, serial neuropsychological testing** ■ From patient and knowledgeable informant
Initial cognitive deficits are evident and most prominent in one of the following categories ■ Amnestic presentation – the most common presentation ■ Non-amnestic presentations (1) Language presentation (2) Visuospatial presentation (3) Executive dysfunction	**History, neuropsychological testing** Amnestic presentation ■ Impairment of learning and recall of recently learned information ■ Deficit in at least one other cognitive area Non-amnestic presentations ■ Language: most prominent deficits are word finding, but should also be deficits in other cognitive areas ■ Visuospatial: most prominent deficits are spatial cognition, but should also be deficits in other cognitive areas ■ Executive: most prominent deficits are reasoning, judgment and problem solving, but should also be deficits in other cognitive areas
Diagnosis of AD should not be made when there is evidence of another dementing illness	**History, neuropsychological testing, imaging studies, laboratory studies** Disorders to rule out include: ■ Vascular cognitive impairment/vascular dementia ■ Dementia with Lewy bodies ■ Frontal-temporal dementia – behavioural variant ■ Primary progressive aphasia ■ Evidence of neurological disease or non-neurological condition or medication that could have a substantial effect on cognition
Step 3: criteria for 'probable AD dementia with increased level of certainty'	
Meets criteria for AD dementia	See criteria above for AD dementia, step 2
Probable AD dementia with documented decline	**History, serial neuropsychological testing** Evidence of progressive cognitive decline on subsequent evaluations from ■ knowledgeable informant or ■ cognitive testing (either formal neuropsychological evaluation or standardised mental status examinations)

Continued

Table 2 Continued

Guideline	Procedures
Probable AD dementia in a carrier of a causative AD genetic mutation	**Laboratory studies** Presence of an early-onset familial genetic mutation ■ APP, PSEN1, or PSEN2 (Note that the apolipoprotein E ε4 allele was not considered specific enough to meet criteria)
Step 4: evaluate the 'biomarker probability of AD aetiology' Evaluate for atrophy of temporal (medial, basal, and lateral) and medial parietal cortex and other biomarkers when available and clinically useful	**Biomarkers** ■ Although the use of biomarkers is not recommended routinely, they are available to the clinician when desired ■ There are two categories of biomarkers, those associated with Aβ protein deposition and those associated with downstream neurodegeneration (see table 1) ■ We recommend routine review of CT and MRI patterns of atrophy, a marker of downstream neurodegeneration ■ Presence of one biomarker category makes the 'biomarker probability of AD aetiology' 'intermediate;' both categories must be positive for a 'high' probability. The 'lowest' probability is present if both categories are negative

Note: patients who would have met criteria under the 1984 guidelines would also meet criteria under the current guidelines.
Aβ, amyloid β; AD, Alzheimer's disease; APP, amyloid precursor protein; MCI, mild cognitive impairment; PSEN, presenilin.

Table 3 Clinical and cognitive evaluation for possible AD

Guideline	Procedures
Criteria for 'possible AD dementia'	**History, neuropsychological testing, imaging studies, laboratory studies**
Atypical course	Meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either ■ has a sudden onset of cognitive impairment or ■ demonstrates insufficient historical detail or objective cognitive documentation of progressive decline
Aetiologically mixed presentation	**History, neuropsychological testing, imaging studies, laboratory studies** Meet all core clinical criteria for AD dementia but has evidence of ■ (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or ■ (b) features of dementia with Lewy bodies other than the dementia itself; or ■ (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition

AD, Alzheimer's disease.

Criteria for all cause dementia and AD

The new criteria propose four possible classifications of dementia caused by AD: (1) probable AD dementia, (2) probable AD dementia with increased level of certainty, (3) possible AD dementia and (4) probable or possible AD dementia with evidence of AD pathophysiological process.[7]

The new criteria suggest a four-step approach to diagnosing dementia due to AD (table 2). Step 1 determines that dementia is present, step 2 determines that the dementia is due to AD, step 3 provides an increased level of certainty to the diagnosis and step 4 evaluates the biomarker probability of AD aetiology. The authors do not advocate obtaining biomarkers for routine clinical

Table 4 Criteria for dementia unlikely to be due to AD

(1) Does not meet clinical criteria for AD dementia
(2) Regardless of meeting clinical criteria for probable or possible AD dementia
a. There is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington's disease or others that rarely overlap with AD
b. Biomarkers for both Aβ and neuronal degeneration are negative

Aβ, amyloid β; AD, Alzheimer's disease. Adapted from McKhann *et al*.[7]

Table 5 Clinical and cognitive evaluation for MCI due to AD

Guideline	Procedures
Step 1: establish clinical and cognitive criteria: determine that the clinical and cognitive syndrome is consistent with MCI and the patient is not demented	
Concern regarding a change in cognition	**History and observation** ■ Concern of a *change* in cognition from prior level ■ Reported by patient and/or informant or observed by clinician
Objective evidence of impairment in one of more areas of cognition (eg, memory, attention, language, visuospatial skills, executive function)	**Neurocognitive testing** ■ Impairment in episodic memory (learning and retention of new information such as word lists), the most common symptom and best predictor of progression to AD dementia ■ Other cognitive areas should also be evaluated ■ Sample battery: Rey Auditory Verbal Learning Test (memory), the Trail Making Test Parts A and B (executive function), the Boston Naming Test, letter and category fluency (language), figure copying (spatial skills) and digit span forward (attention) (see Budson and Solomon,[6] for discussion of these and other tests) ■ Patients with MCI typically score 1–1.5 SD below the mean on cognitive tests ■ Note that cognitive assessments are influenced by age, education, motivation, and cultural variation. Not all tests provide normative data taking these factors into account ■ Evaluation by a neuropsychologist is appropriate and helpful in these patients with mild deficits. Brief or informal office testing may not be sensitive enough to detect deficits.
Preservation of independence in functional abilities	**History, questionnaires** ■ MCI patients *maintain independence of function in daily life* although they may experience more difficulty or take longer in carrying out complex tasks (eg, balancing the books, household projects, meal planning and preparation) ■ Interviews with friends or family will usually detect these changes ■ Standardised and validated scales completed by family or friends can be helpful (see Budson and Solomon,[6] for a discussion of specific scales)
Not demented	**History, observation, questionnaires** ■ There is no significant impairment in occupational or social function
Step 2: examine aetiology of MCI consistent with AD pathophysiological process: determine the likely primary cause of signs and symptoms	
Rule out other possible causes of cognitive decline Possibilities include: vascular, Lewy body, other degenerative disease, traumatic, depression, medical comorbidities, mixed dementia, other (see Budson and Solomon,[6] for complete list and description of the various disorders)	**History, neurocognitive testing, imaging and laboratory studies** ■ History and testing may be consistent with various clinical phenotypes ■ CT and MRI may show vascular infarcts and patterns of atrophy ■ Laboratory studies (eg, B_{12}, TSH, Lyme titre) may find other causes of cognitive deficits
Provide evidence of longitudinal decline in cognition	**History, serial neuropsychological testing** ■ Documentation of progressive cognitive decline increases the probability of MCI due to AD ■ Decline can be determined by history and/or neuropsychological testing
Report history consistent with AD genetic factors	**Genotyping** ■ Although genotyping is not part of the routine workup for MCI or AD, if an autosomal dominant form of the gene is known to be present (ie, mutation in APP, PS1, PS2), then the development of MCI is highly likely to be the prodrome of AD ■ The vast majority of these cases develop early onset AD in the patient's 40s or 50s ■ The presence of one or two ε4 alleles in the apolipoprotein E increases the risk for late onset AD
Evaluate for atrophy of temporal (medial, basal and lateral) and medial parietal cortex and other biomarkers when available and clinically useful	**Biomarkers** ■ See table 2 step 4

AD, Alzheimer's disease; APP, amyloid precursor protein; MCI, mild cognitive impairment; TSH, Thyroid Stimulating Hormone.

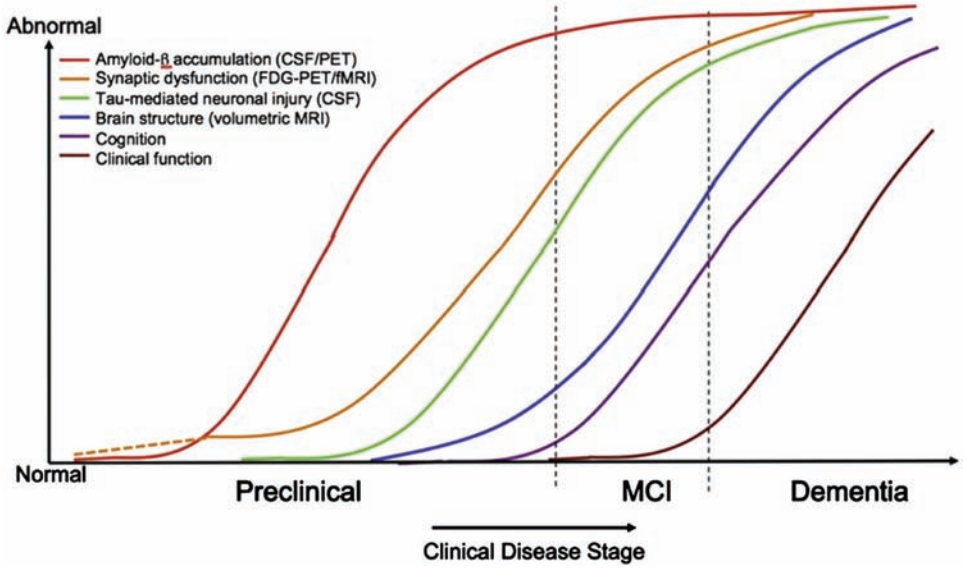

Figure 5 Model of how the different stages of Alzheimer's disease may be detected by changes in various biological, cognitive and clinical markers (from Sperling *et al*).[5] CSF, cerebrospinal fluid; FDG, ^{18}flurodeoxyglucose; fMRI, functional Magnetic Resonance Imaging; MCI, mild cognitive impairment; PET, positron emission tomography.

purposes at present, although they note that they may be used when available and deemed appropriate by the clinician.

Biomarkers enable the diagnosis of 'probable AD dementia with evidence of the AD pathophysiological process' (table 1). If one of the two biomarker categories is positive, the 'biomarker probability of AD aetiology' rises to 'intermediate,' and if both categories are positive the probability becomes 'high'.

'Possible AD' is used instead of 'probable AD' if the cognitive deficits look like AD but there is an atypical course (either sudden onset or no definite decline) or evidence of a mixed aetiology. Thus, the patient might meet the criteria for probable AD dementia but there is also evidence of significant vascular disease, features of dementia with Lewy bodies or other disease, or condition that could be contributing to the patient's dementia (table 3).

The next category is pathophysiologically proven AD, consisting simply of the unchanged criteria of patients meeting both the clinical and neuropathological criteria for AD. Finally, the authors discuss the criteria for dementia unlikely to be due to AD (table 4).

Criteria for MCI due to AD

MCI due to AD refers to the symptomatic phase of the AD pathophysiological process before the individual develops the functional impairment that defines dementia. The guidelines presented by Albert *et al* recognise that everyone who eventually develops AD goes through a transitional period of mild but detectable cognitive impairment.[8] However, not everyone who is diagnosed with MCI goes on to develop AD. MCI can be due to several disorders, including vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and others. Furthermore, distinguishing between normal cognition and MCI, and between MCI and dementia needs clinical judgment.

The criteria for MCI due to AD include:

- excluding patients with other causes of MCI, including extensive vascular disease, frontotemporal dementia, and dementia with Lewy bodies
- including patients with increasing cognitive decline over time
- including patients with mutations associated with early-onset familial AD (amyloid precursor protein, presenilin 1 or presenilin 2).

First, criteria are presented for the clinical and cognitive syndrome of MCI, and second, criteria are presented regarding the aetiology of the MCI syndrome being consistent with AD (table 5).

Criteria for MCI due to AD incorporating biomarkers (table 1) are next presented. Biomarkers of Aβ protein deposition may help determine aetiology, and markers of neurodegeneration may aid prognosis. If one of these two biomarker categories is positive, the 'biomarker probability of AD aetiology' rises to 'intermediate'; both categories must be positive for the

'highest' probability. The 'lowest' probability is present if both categories are negative.

Preclinical AD (for research only)

Sperling *et al*[5] discussed three stages of preclinical AD based upon biomarkers and cognitive change (figure 5). Stage 1 is asymptomatic cerebral amyloidosis, determined by the presence of a biomarker of Aβ, without a marker of neurodegeneration or evidence of subtle cognitive change. Stage 2 is asymptomatic cerebral amyloidosis plus neurodegeneration without subtle cognitive change. Stage 3 is amyloidosis plus neurodegeneration plus subtle cognitive or behavioural decline.

Case examples

Example 1

A 78-year-old man and his wife were both concerned that his memory was not as good as it was last year. He used to be able to remember a short grocery list in his head but now he needed to write it down or he would return with the wrong items. He continued to pay the bills, balance the books and do household projects although these tasks now took him longer to complete. Evaluation of memory testing in the office showed that he scored below normal when repeating a brief story containing 10 details. His laboratory data were unremarkable, and his MRI showed bilateral atrophy in hippocampus (basal temporal lobe), lateral temporal lobe, and parietal lobe.

Because this patient had concerns about a change in cognition, objective impairment in cognition and preservation of functional abilities, he meets the criteria for MCI (table 5 step 1). Because the history and cognitive testing are of memory impairment—the main phenotype of AD—and he has atrophy of the brain in a pattern consistent with the AD pathophysiological process, he meets the criteria for MCI due to AD, with an intermediate biomarker probability of AD aetiology (table 5 step 2).

Example 2

An 84-year-old woman was brought in by her daughter. Although the patient did not believe that anything was wrong, her daughter noted that her mother's thinking and memory had deteriorated slowly over 5 years. Her phone was disconnected because she forgot to pay the bills, and she kept buying the same canned food items whenever she went to the market. There was spoiled food in the refrigerator. When interviewed she had pauses in her speech and her daughter often filled in missing words for her. On a brief office test she was not orientated to the day, date, month, or year; she could not recall any of the few items she was instructed to remember; and she was unable to name even common items. A CT scan of head showed mild small vessel ischaemic disease (average for individuals in their 80s) and atrophy of hippocampi, lateral temporal lobes, and parietal lobes.

This patient had clear evidence of a decline in prior ability that interfered with function: she has had her phone disconnected, she bought the same food repetitively, and she had spoiled food in the refrigerator. Cognitive impairments in at least two domains (memory and language) are present. Thus, she meets criteria for 'all cause dementia' (table 2 step 1). That her memory deteriorated slowly over 5 years suggests a gradual onset; clear cut worsening of memory suggests an amnestic presentation, and the CT scan of head rules out a vascular dementia. There is nothing in the story to suggest another type of dementia or condition that could have a substantial effect on cognition. Thus, this patient's dementia meets criteria for the amnestic presentation of probable AD (table 2 step 2), and the atrophy on the CT suggests an intermediate biomarker probability of AD aetiology (table 2 step 4). There is nothing in the story either to provide an 'increased level of certainty' (table 2 step 3) or to suggest 'possible' instead of 'probable' AD (table 3).

Implications for the practicing clinician

These new guidelines are recommendations based upon consensus meetings and will require validation in the future. They encourage clinicians to:

- Recognise that AD is the end of a long process, spanning years or perhaps decades.
- Diagnose (and perhaps treat) AD at the earliest possible stage, at present MCI due to AD, but eventually (with new disease-modifying medications) preclinical AD. (Note that the criteria for preclinical AD are currently intended purely for research purposes.)

Suggestions for further reading

- Budson & Solomon Memory Loss: A Practical Guide for Clinicians, Philadelphia: Elsevier Inc., 2011.
- Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:280-92.

- Consider using biomarkers in the diagnosis of all stages of AD. Our current recommendation is to use biomarkers for those cases that present diagnostic quandaries.[6]
- Evaluate patients with cognitive impairment and dementia to determine aetiology, with special attention to amnestic and non-amnestic presentations of AD.
- Remember that because of the ageing population, numbers of patients with all stages of AD will likely triple in the next 50 years.

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