# Clinical research

# Age-related mild cognitive deficit: a ready-to-use concept?

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While promising therapeutic strategies are being explored, our capacity to diagnose dementias early in their evolution remains poor. Degenerative dementias are insidious and progressive in nature. It is therefore conceivable that a dementia picture is preceded by a "preclinical state" (ie, pathognomonic cerebral lesions coexisting with normal cognition) as described in Alzheimer's disease (AD),[1,2] followed by mild deficits first experienced by patients themselves, then suspected by their family members, and eventually demonstrated through neuropsychological examination.

It is generally assumed that normal aging involves cognitive changes, displaying large inter- and intraindividual variability.[3] Some studies challenged this common view, showing that the use of strict criteria for the inclusion of cognitively normal subjects in longitudinal studies demon-

For better management of mild cognitive impairment in elderly patients, clinicians should be provided with instruments to detect early changes and predict their progression. To define this cognitive status between optimal and pathological aging, many concepts have been proposed, which actually describe various conditions and provide more or less precise criteria, leaving room for variable implementation. As a consequence, application of these criteria gave highly variable prevalence rates. Neuropathological studies indicate that the different criteria have variable power in detecting incipient Alzheimer's disease (AD) and suggest that the transition between mild cognitive impairment and AD is not merely quantitative. Follow-up studies have produced, according to the criteria used, a 2.5% to 16.6% annual rate for progression toward dementia, and have also shown that the criteria differ in their stability and predictive power. Baseline cognitive performances have some predictive value, but are difficult to apply in first-line medicine. Investigational techniques (structural and functional imaging, magnetic resonance spectroscopy, magnetization transfer imaging, cerebrospinal fluid neuro-chemistry, and apolipoprotein E genotype) are promising tools in the early diagnosis of AD, which remains the most frequent type of dementia in elderly people and probably the most frequent type developed by patients with mild cognitive deficit. The final goal is to offer early treatment to those patients who will evolve towards dementia, once they can be identified. In the case of AD, recent findings question the adequacy of cholinergic replacement therapies. In its current state, the criteria for mild cognitive deficit are hardly transferable to first-line medicine. However, disseminating the concept could help increase the sensitivity of general practitioners to the importance of cognitive complaints and signs in their elderly patients.

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# Clinical research

strated long-term stability.[4-7] It was therefore argued that the elderly populations who were the basis of the "normal cognitive aging" concept were contaminated by individuals with very mild dementia.[1,8,9]

As a result, there is currently no consensus on the definition or on the meaning of mild cognitive deficit in an older individual, or on the attitude it should trigger in physicians. Periodic reassessment until the criteria for a dementia syndrome are fulfilled, as is currently practiced, avoids the risks of overdiagnosis, but conveys those of delaying the initiation of an effective treatment. This daily clinical dilemma would be resolved if physicians were provided with simple instruments allowing a clear differentiation between normal and prodromal cognitive status in a given elderly patient. The goal of this review is to assess to what extent this need is currently met.

## Main concepts and criteria

Since Kral's benign senescent forgetfulness,[10] several concepts have been proposed to understand this shadowy zone between optimal and pathological cognitive aging *(Table I)*.[10-23]

Cognitive impairment–no dementia (CIND) identifies cognitive impairment associated with various conditions, ranging from age-associated memory impairment (AAMI)[15] to cerebrovascular or general vascular diseases, to depression.[22,24] Mild cognitive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*[20] and mild cognitive disorder in the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*[18] refer to the cognitive consequences of somatic disorders. Limited dementia[12] and minimal dementia[14] clearly refer to a dementia state. AAMI[15] and age-consistent memory impairment (ACMI)[16] address normal cognitive aging. Zaudig's mild cognitive impairment,[17] mild cognitive decline,[13] and questionable dementia[11] rely on global scores on cognitive-behavioral rating scales. The major drawback of this approach is that the same score can reflect different clinical profiles, making clinicopathological correlation and between-study comparison difficult. Late life forgetfulness (LLF)[16] assesses cognitive deficits relative to what is considered as normal for age, and aging-associated cognitive decline (AACD)[19] compares in addition with an education- and gender-matched relatively healthy sample. Both provide explicit inclusion and exclusion criteria and—in the case of LLF—examples of tests. LLF focuses on memory impairment, whereas AACD considers additional cognitive domains (attention and concentration, problem-solving and abstraction, language, and visuospatial function) and enforces a 6-month duration of decline. The Mayo Clinic criteria for mild cognitive impairment (MCI)[21] are less precise and their formulation has changed with time *(Table II, page 66)*.[21,25-33] As a consequence, the heading "MCI" covers highly variable diagnostic methodologies, hampering comparisons of studies from different research teams.

These different concepts and criteria have seldom been compared in the same population. In a recent study,[34] 111 subjects with informant evidence of cognitive decline were classified as AAMI (n=37, 33.3%) after clinical assessment. When AACD criteria were also applied, they were fulfilled by 39 subjects (35.1%), including 20 (54%) of the AAMIs. Moreover, as illustrated in *Figure 1 (see page 66)*, the cognitive profiles of subjects with AACD or AAMI were different, with 35.9% of AACDs vs 27% of AAMIs impaired in the memory and learning domain according to AACD criteria (ie, at least 1 SD below age-appropriate norms), and 35.9% AACDs vs 18.9% AAMIs impaired in more than one cognitive domain.[34]

As expected according to their individual definitions and goals, the AAMI and AACD concepts only modestly overlap one another; the latter captures a more severe impairment.

- **Benign senescent forgetfulness (1962)[10]**

  Poor retrieval of details of a recent experience, without loss of the memory of the experience itself, with awareness of and ability to compensate for memory troubles. The picture remained stable over time and was not associated with increased mortality rate.

- **Questionable dementia, CDR=0.5 (1982)[11]**

  Consistent slight forgetfulness, partial recollection of events, but fully orientated except for slight difficulty with time relationships, slight impairment in solving problems, slightly impaired functioning in job, shopping, and social groups, life at home, hobbies, and interests slightly impaired.

- **Limited dementia (1982)[12]**

  **1.** Subjective report of memory decline.

  **2.** Increased reliance on notes and reminders.

  **3.** Occasionally forgets names of acquaintances, forgets appointments, or misplaces objects.

  **4.** Occasionally has destructive or dangerous memory lapses, such as burning cooking or leaving on gas taps.

  **5.** Has one or two errors on cognitive testing: forgets current or past President, exact date, telephone number, postcode, dates of marriage or moving to present location, or cannot remember interviewer's name, even on third challenge.

- **Mild cognitive decline (1982)[13]**

  GDS score of 3, cognitive tests performances ≥1 SD below mean for age-group, and memory complaints.

- **Minimal dementia (1986)[14]**

  A CAMDEX category, refers to individuals with a mild impairment of recall, minor and variable errors in orientation, a blunted capacity to follow arguments and solve problems, and occasional errors in everyday tasks.

- **AAMI (1986)[15]**

  *Inclusion criteria*

  **1.** ≥50 years of age.

  **2.** Complaints of memory loss reflected in everyday problems. Onset of memory loss described as gradual, no sudden worsening.

  **3.** Memory test performance that is ≥1 SD below the mean established for young adults on a standardized and adequately normed test of secondary (recent) memory. Example of tests and cutoffs provided: BVRT form A ≤6; WMS logical memory subtest ≤6; associate learning subtest ≤13.

  **4.** Evidence of adequate intellectual function reflected in a standard score of ≥9 on the WAIS.

  **5.** Absence of dementia reflected in an MMSE score ≥24.

  *Exclusion criteria*

  **1.** Delirium, confusion, or other disturbance of consciousness.

  **2.** Any neurological disorder (determined by history, clinical neurological examination or neuroradiological examination) that could produce cognitive deterioration.

  **3.** History of infective or inflammatory brain disease.

  **4.** Evidence of significant cerebral vascular pathology as determined by an HIS ≥4.

  **5.** History of repeated minor head injury or single head injury with >1 h loss of consciousness.

  **6.** Current psychiatric diagnosis of depression, mania, or major psychiatric diagnosis.

  **7.** Current diagnosis or history of alcohol or drug dependence.

  **8.** Evidence of depression as determined by an HRSD score ≥13.

  **9.** Any medical disorder, determined by history, clinical examination and laboratory tests that could produce cognitive deterioration.

  **10.** Psychotropic drug use during the month before psychometric testing.

**Table I.** Age-related mild cognitive deficit: definitions and criteria.[10-23] AACD, aging-associated cognitive decline; AAMI, age-associated memory impairment; ACMI, age-consistent memory impairment; BVRT, Benton Visual Retention Test; CAMDEX, Cambridge Examination for Mental Disorders in the Elderly; CDR, Clinical Dementia Rating; *DSM-III-R, Diagnostic and Statistical Manual of Mental Health Disorders*. 3rd ed, revised; GDS, Global Deterioration Scale; HIS, Hachinski Ischemia score; HRSD, Hamilton Rating Scale for Depression; *ICD-10, International Statistical Classification of Diseases and Health-related Problems*. 10th revision; LLF, Late-life forgetfulness; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

- **AAMI (1989)[16]**

*Inclusion criteria*

1. Adults 50–79 years of age.
2. Perceived decrease in day-to-day memory corroborated by standardized self-report memory questionnaires.
3. Memory test performance, in a battery of at least four memory tests, which meets one of the following: (i) *AAMI*: performance ≥1 SD below the mean established for young adults on one or more test; (ii) *ACMI*: performance on ≥75% of the tests that is within 1 SD of the mean established for subject's age; (iii) *LLF*: performance on ≥50% of the tests that falls between 1 and 2 SD below the mean for age. Examples of tests provided: BVRT; WMS, visual reproduction with 30-min delay; Rey Osterreith complex figure with 3-min delay; WMS, logical memory with 30-min delay; WMS, associated learning with 30-min delay; Rey Auditory Verbal Learning Test with 30-min delay.
4. Verbal and performance IQ score between 90 and 130 on WAIS or WAIS-Revised.

*Exclusion criteria*

1. Presence of any neurological or vascular disorder, determined by history, neuropsychological assessment and laboratory tests, that could affect cognitive processing, including dementia, delirium or attentional problems indicated by a forward digit span ≤5 and history of infective or inflammatory brain disease.
2. Current medical problems that reduce the ability to participate or directly decrease memory performance.
3. Current psychological or psychosocial stress that would interfere with assessment and treatment, including depression reflected by a score of ≥13 on the HDRS or on the Geriatric Depression Scale, current or past drug or alcohol dependence, and any *DSM-III-R* disorder that would interfere with assessment or treatment, including adjustment disorder.

- **MCI (1992)[17]**

Based on a performance in the test battery of the "Structured interview for the diagnosis of dementia of the Alzheimer's type, multi-infarct dementia and dementias of other etiology according to *ICD-10* and *DSM-III-R*" SIDAM (score 34-49), exclusion of dementia, no other specific etiological concept.

- **Mild cognitive disorder (1993)[18]**

A. Meets the general criteria for "Other mental disorders due to cerebral lesion or impairment or to a somatic disorder."
B. Presence, most of the time during at least 2 weeks, of cognitive functions disturbance, according to the subject or a reliable informant. The disorder is characterized by impairment in at least one of the following domains:
   1. Memory (particularly recent) or learning of new information.
   2. Attention or concentration.
   3. Thinking (eg, slowing of abstract thinking or of ability to solve problems).
   4. Language (eg, comprehension, word finding).
   5. Visuospatial functioning.
C. Presence of abnormalities or decline on neuropsychological testing (or other quantified cognitive evaluation).
D. None of the disturbances B1-5 is severe enough to meet the diagnosis of dementia, amnestic syndrome, delirium, postencephalitic syndrome, postconcussional syndrome or another persistent cognitive failure due to the use of psychoactive substances.

**Table I.** Continued.

In the Canadian Study of Health and Aging, specific criteria were applied in subjects classified as CIND.[22] Sixty-five percent did not meet any of them; none met the AAMI criteria of Bradford and LaRue.[16] When inclusion criteria were applied alone, 8.1% fitted the criteria for AAMI, 5.9% for ACMI, 7.4% for LLF, and 34% AACD; after applying exclusion criteria, these figures dropped to 1.2% (AAMI), 0.9% (ACMI), 0% (LLF), and 13% (AACD). These data highlight the importance of exclusion criteria resulting from comprehensive clinical evaluation. Only 24% of those meeting one set of criteria also met one other or more (19.2% met two, 3.8% three, and 0.8% four), suggesting that the different sets of criteria are mutually exclusive. In a sample of 60- to 64-year-old healthy people,[35] 13.5% met criteria for AAMI, 6.5% for ACMI, 1.5% for LLF, and 23.5% for AACD. Among subjects with AAMI, 22% met the criteria for ACMI, 11% for LLF, and 63% for AACD. All the LLF subjects also fulfilled criteria for both AAMI and AACD.

• **AACD (1994)[19]**

*Inclusion criteria*

  1. Report by the individual or a reliable informant that cognitive function has declined.

  2. Onset of decline must be described as gradual and have been present for ≥6 months.

  3. The disorder is characterized by difficulties in any one of the following areas: memory and learning; attention and concentration; thinking (eg, problem solving, abstraction); language (eg, comprehension, word finding); visuospatial functioning.

  4. There is an abnormality of performance on quantitative assessments (eg, neuropsychological tests or mental status evaluations) for which age and education norms are available for relatively healthy individuals. Performance must be ≥1 SD below the mean value for the appropriate population.

*Exclusion criteria*

  1. None of the abnormalities listed above is of sufficient degree for a diagnosis of mild cognitive disorder or dementia to be made (there must be no objective evidence from physical and neurological examination or laboratory tests and no history of cerebral disease, damage or dysfunction or of systemic physical disorder known to cause cerebral dysfunction).

  2. Depression, anxiety or other significant psychiatric disorders that may contribute to observed difficulties.

  3. Organic amnestic syndrome.

  4. Delirium.

  5. Postencephalitic syndrome.

  6. Persisting cognitive impairment due to psychoactive substance use or the effect of any centrally acting drug.

• **Mild neurocognitive disorder (1994)[20]**

  A. The presence of 2 or more of the following impairments in cognitive functioning lasting most of the time for a period of ≥2 weeks (as reported by the individual or a reliable informant):

    1. Memory impairment as identified by a reduced ability to learn or recall information.

    2. Disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting).

    3. Disturbance in attention or speed of information processing.

    4. Impairment in perceptual-motor abilities.

    5. Impairment in language (comprehension, word finding).

  B. There is objective evidence from physical examination or laboratory findings (including neuroimaging techniques) of a neurological or general medical condition that is judged to be etiologically related to the cognitive disturbance.

  C. There is evidence from neuropsychological testing or quantified cognitive assessment of an abnormality or decline in performance.

  D. The cognitive deficits cause marked distress or impairment in social, occupational, or other important areas of functioning and represent a decline from a previous level of functioning.

  E. The cognitive disturbance does not meet criteria for a delirium, a dementia, or an amnestic disorder and is not better accounted for by another mental disorder (eg, a substance-related disorder, major depressive disorder).

• **MCI (1995)[21]**

  1. Memory complaint by patient, family, or physician.

  2. Normal activities of daily living.

  3. Normal global cognitive function.

  4. Objective memory impairment or impairment in one other area of cognitive function as evidenced by scores >1.5 SD below age-appropriate mean.

  5. CDR=0.5.

  6. Not demented.

• **Cognitively impaired, not demented (1995)[22]**

  1. Modified MMSE[23] (3MS) score ≤77.

  2. No dementia, based on: history; informant interview; physical examination; detailed neurological examination; neuropsychological tests (if 3MS>50) comprising: memory, abstract thinking, judgment, constructional abilities, language, familiar object recognition, digit symbol substitution test.

**Table I.** Continued.

Together these results are not very surprising. First, the different sets of criteria refer to different concepts (AAMI and ACMI versus LLF and AACD, see above). Second, they basically consist of a priori constructs, differing in their criteria and cutoff scores, and not of the description
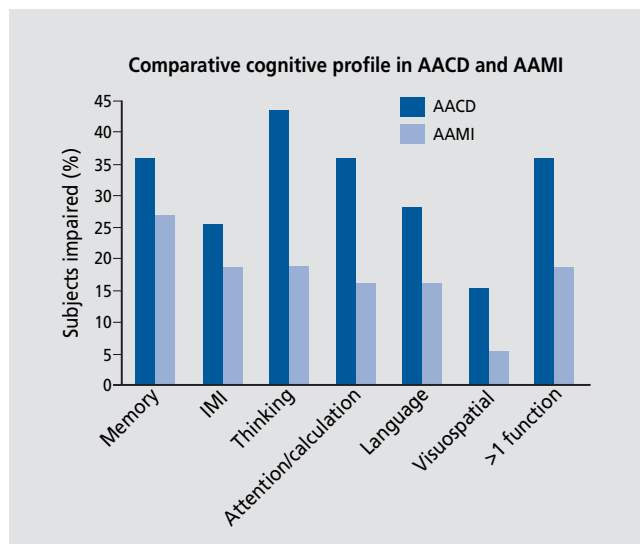
**Comparative cognitive profile in AACD and AAMI**



**Figure 1.** Cognitive profile in age-associated memory impairment (AAMI) and aging-associated cognitive decline (AACD) subjects, according to the data in reference 34. Memory: according to AACD criteria (at least 1 SD below age-appropriate norms). IMI, isolated memory impairment; >1 function, impairment in more than one function.

of clinical populations. Third, because of criteria's methodological vagueness (eg, no firm reference tests; no indication on whether one function should be assessed using one or several tests), they offer room for different implementation across teams. The impact of introducing changes in criteria is illustrated by the Eugeria Project.[36] Of 833 subjects recruited, 308 fulfilled the first two criteria for MCI (subjective memory complaint and normal general intellectual functioning, as assessed by performance on a vocabulary test); of these, 103 had a decrement of more than 1 SD on a memory task, relative to normal values for age and educational level (criterion 3); exclusion of subjects with difficulties in any other cognitive domain left only 27 subjects fulfilling the criteria; application of criterion 4 (normal activities of daily living) had no influence. Thus, modification of the third criterion reduced the prevalence of MCI from 12.4% to 3.2%. The AACD criteria applied to the same population identified 174 participants (20.8%), which included all the MCI subjects.

## Neuropathological correlates

To the best of our knowledge, the only concept that has been compared with neuropathological examination is MCI as defined by the Mayo Clinic team.[21] In a follow-up study,[37] 6 out of 6 subjects with a Clinical Dementia Rating (CDR)[32] score 0.5 resulting from memory impairment alone were found to meet modified[38] Kachaturian[39]

| | |
|---|---|
| 1995[21] | • Cognitive complaints (usually memory) |
| | • Cognitive screening tests in normal range for age (MMSE[27]/Short Test of Mental Status[28]) |
| | • Performances on memory tests >1.5 SD below age-appropriate norms |
| | • Preserved ADL (history, Blessed Dementia Scale,[29] Record of Independent Living[30]) |
| | • No dementia (*DSM-III-R*[31] criteria) |
| | • CDR=0.5[32] |
| 1999[25]* | • Memory complaint |
| | • Normal ADL |
| | • Normal general cognitive function |
| | • Abnormal memory for age |
| | • No dementia |
| 2001[26] | • Memory complaint, preferably corroborated by an informant |
| | • Objective memory impairment |
| | • Normal general cognitive function |
| | • Intact ADL |
| | • Not demented |

**Table II.** Definition and criteria for mild cognitive impairment (MCI).[21,25,26] ADL, activities of daily living; CDR, Clinical Dementia Rating; *DSM-III-R, Diagnostic and Statistical Manual of Mental Health Disorders*. 3rd ed, revised; MMSE, Mini-Mental State Examination. *Although CDR score[32,33] was not a criterion, MCI subjects had CDR=0.5.

neuropathological criteria for AD. This confirmed previous data[40] showing that 10 out of 10 subjects with CDR=0.5 had histopathological AD, versus none of 4 with a score of 0. In another study,[41] subjects with a CDR≥0.5 had large senile plaque densities in the neocortex and the degree of dementia seemed related to an increase in the ratio of neuritic to diffuse plaques. While cognitively healthy controls—and even individuals with preclinical AD—had no significant decrease in neuronal count in the entorhinal cortex (ERC) as a whole, in ERC layer II or in the CA1 hippocampal field, the brains of subjects with CDR=0.5 were characterized by a significant neuronal loss in these areas.[42] These studies suggest that "questionable dementia" or isolated memory impairment sufficient to yield CDR=0.5 actually represent very mild AD. It can be questioned whether CDR=0.5 equates to MCI. A series of studies[43-45] compared MCI subjects (defined as being impaired in one domain on neuropsychological testing, but not being found to have dementia by the examining neurologist according to NINCDS/ADRDA [National Institute of Neurological and Communicative Diseases and Stroke/ Alzheimer's Disease and Related Disorders Association] criteria[46]) with normal controls (NCs) and AD patients, all from a group of catholic clergy participating in the Religious Order Study *(Table III)*. Both AD patients and MCI subjects had a lower ERC layer II neuronal count, remaining neuronal volume, and global volume. However, MCIs

and AD patients significantly differed in layer II global volume only, despite a group effect in analysis of variance, while all the AD and NC values were significantly different. Global and neuronal atrophy were correlated with impairment of delayed and immediate recall.[44] Quantified ERC β-amyloid (βA) load[43] in MCIs was intermediate, but not significantly different from that found in NCs and AD patients respectively (again, NC vs AD values were significantly different), although analysis of variance revealed a significant group effect with a trend to linear increase from NCs to MCIs to AD patients. It is noteworthy that some NC or MCI subjects had βA load equal to or higher than that seen in many AD patients, and two MCIs had no detectable βA. The inverse correlation between Mini-Mental State Examination (MMSE)[27] scores (mean scores: 27.3 in NCs and MCI patients, and 24 in AD patients) and βA load was not significant. In this study, 6 of 12 MCI subjects had a neuropathological diagnosis of possible AD according to the criteria of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[47] In a third study,[45] neurofibrillary tangles (NFTs) and neuropil threads (NTs) were present in perirhinal cortex and ERC in NCs, MCI subjects, and AD patients; the average number of NFTs increased with the diagnosis from NC to MCI to AD. Between-group differences analysis again found that MCI subjects were intermediate, but not significantly different from either NCs or AD patients. NFT density was

| | Normal controls | MCI subjects | | AD patients |
|---|---|---|---|---|
| Layer II neuronal count | | S | -63.55% | NS | -58.13% |
| | | > | | < | |
| Layer II neuronal volume | | S | -24.1% | NS | -25.1% |
| | | > | | > | |
| Layer II global volume | | S | -26.5% | S | -43.4% |
| | | > | | > | |
| β-Amyloid load | | NS | +96% | NS | +245% |
| | | < | | < | |
| Neurofibrillary tangle density | | NS | | NS | |
| | | < | | < | |
| ***Neuropathological diagnosis (CERAD)*** | | | | | |
| No Alzheimer's disease | 11/20 | | 6/12 | | 0 |
| Possible Alzheimer's disease | 9/20 | | 6/12 | | 1/12 |
| Probable Alzheimer's disease | 0 | | 0 | | 4/12 |
| Definite Alzheimer's disease | 0 | | 0 | | 7/12 |

**Table III.** Neuropathological characteristics of mild cognitive impairment in the Religious Order Study.[43-45] CERAD, Consortium to Establish a Registry for Alzheimer's disease; MCI, mild cognitive impairment; NS, not significant; S, significant. Changes in MCI and AD group are given relative to normal controls.

inversely correlated with episodic memory score, but not with other, nonmemory, cognitive abilities across the three groups.

These studies first show that no more than 50% of MCIs were incipient AD. This is less than in the studies by Morris[37,40] and Price,[41] and suggests that the populations described were not equivalent, although the use of different neuropathological diagnostic criteria makes the comparison difficult. Approximately the same proportion of NCs (45%) were also diagnosed as possible AD; this finding suggests that the clinical diagnostic tools were neither sensitive nor specific in the detection of incipient AD. This can be explained by the fact that both the NC and MCI groups had high and similar MMSE scores, but the concept of MCI precisely intends to detect cases missed by more global testing. Nevertheless, MCI subjects globally were, for most ERC lesions, intermediate between NC and AD cases. This suggests that ERC lesions could be a better neuropathological marker of MCI than the presence of those required for a diagnosis of AD. However, the fact that group-to-group comparisons failed to distinguish MCIs from ADs makes currently impossible to determine practically useful cutoff values. If this failure is due to sample size, larger studies should solve it. However, it could also be due to heterogeneity; clinicopathological studies seeking pathological markers of both non-AD dementias and AD should confirm or rule out this possibility. Awaiting further studies, the lack of significant difference between MCI and AD, which was also found for high (trkA)[48] and low (p75[NTR])[49] expression of nerve growth factor receptors, suggests that the transition from MCI to AD is not merely quantitative.

## Predictive value

Another way of understanding these concepts and criteria is through their ability to predict the progression of patients. Follow-up studies[21,25,36,37,50-59] differ in their durations, making comparisons difficult; dividing the frequency of progression toward dementia by duration of follow-up gives an estimate of the annual rates of "conversion" *(Table IV)*.

Thus, a significant proportion of subjects did not become demented. It could be argued that a longer follow-up would increase the "conversion" rate. However, data from some studies reporting multiple evaluations[21,58,60-62] suggest that the incidence of dementia could decrease over time. In a recent study with assessments at 3 and 6 years in subjects with CIND, aged 80 years or older,[61] it was found that, according to the severity of impairment at baseline, 84% to 89% of those who were demented at 6 years had already received the diagnosis at 3 years. In another study in oldest old (84 to 90 years old at baseline) over 6 years,[60] a decrease in the progression from MCI to dementia with time was also reported. This attenuation of the rate of progression with time could be an artifact, since in these two studies—and also in one in slightly younger subjects[57]—MCI increased the risk of death by 1.7[58] to 7[60] during a 4-year period. In this case, there should be a correlation between the severity of cognitive impairment at baseline and the risk of death. Such a trend was found in one study,[58] but not in another,[61] and in a third[60] baseline performances in the deceased group were lower than those of survivors, but higher than for those who progressed to dementia. Thus, the issue of the slope of the rate of progression deserves further attention, particularly in relation to age at onset of cognitive impairment.

Because the main criteria were set to capture degenerative cognitive impairment (ie, without identifiable medical cause), an intriguing finding is that a substantial proportion of subjects were found to improve over time (4.8% after 3 years in subjects with CDR=0.5[63]; 19.5% after 2.7 years in MCI as defined by Zaudig[54]; 25% after 3 years and 12% to 17% after 6 years in CIND[61]). In clinical practice, such an outcome would be ascribed to a diagnostic error (ie, impairment was due to a unidentified medical condition). An alternative explanation is that the underlying process is different from AD. Indeed, a fluctuating course is classically described in vascular dementia (VaD)[64] and dementia with Lewy bodies (DLB).[65] In line with this hypothesis is the finding that, in a sample of MCI subjects, 20.5% developed VaD within 3.9 years; nothing in their baseline cognitive pro-

| Criteria | Conversion rate (%) |
|---|---|
| Age-associated memory impairment | 0–2.5 |
| Clinical Dementia Rating scale 0.5, no dementia | 4–16.6 |
| Mild cognitive impairment (Zaudig) | 6.5 |
| Age-associated cognitive decline | 9.5–16.6 |
| Mild cognitive impairment (Mayo Clinic) | 12–16 |

**Table IV.** Annual conversion rates according to classification criteria. Annual conversion rates were obtained by dividing the reported incidence by the length of follow-up in each study.

file or their progression (based on MMSE) differentiated them from those who progressed to AD (47.9%).[62,66] A third explanation is that the criteria do not describe a stable state. The Eugeria Project compared MCI (with impairment in memory, but not in any other domain) and AACD over 3 years,[36] and showed that 7.5% of MCI subjects retained the diagnosis from the first to second assessment and 17.4% from the second to third; the corresponding figures for AACD subjects were 56.3% and 59.4%. Apart from those who became demented, subjects met criteria for the alternative diagnosis (from MCI to AACD and vice versa) or were found to be normal. In this study, the AACD diagnosis had a sensitivity of 94.7% and a specificity of 54.1%, whereas the MCI diagnosis had a sensitivity of 5.3% and specificity of 91.3% in the prediction of progression toward dementia after 2 years. In another community-based French study,[59] the MCI diagnosis was also found to be unstable.

According to the cited studies, there is no doubt that mild cognitive deficit in elderly subjects, whatever its definition and criteria, increases the risk of developing dementia. The available data provide a rather broad range of annual incidence of dementia and are not all in favor of a linear prevalence–time relationship in mildly impaired patients. The proposed sets of criteria have different stability and predictive values. Also, they do not allow identification of individuals who will develop dementia or—more importantly—the type of dementia toward which they could evolve.

Beyond the criteria themselves, several studies found predictors of progression to dementia or even to AD in measures derived from the MMSE,[62] the CDR,[63] or impairment in memory, verbal fluency, and attention on more conventional neuropsychological tests.[52,67-69] As pointed out by Tuokko and Frerichs,[70] a major shortcoming of these data is that they are retrospective. No combination of cognitive tests has yet been assessed prospectively for its ability to predict outcome in mildly impaired patients. If it were done using neuropsychological batteries that were sufficiently refined for early identification of the characteristic signs of the major dementing diseases and determination of reliable cutoff scores, then this type of investigation would be reserved for specialized teams; however, the first person who people with cognitive complaints see is their general practitioner. It is expected that this dilemma will be partly solved in the near future by recourse to investigational techniques.

## Contribution of investigational techniques

For decades, the scientific community has been seeking biomarkers of AD, using genetics, neurochemistry, and imaging techniques. It was rational to apply these techniques to mild cognitive deficit, in order to characterize these states and identify predictors of progression to AD. Neuropathological studies have shown the hippocampus to be one of the earliest affected structures in AD,[71] and so it is a region of choice for neuroimaging studies. Although hippocampal atrophy, as measured by volumetric techniques is not entirely specific, it is now considered to be a hallmark of AD,[72] and its absence in addition to minor or unilateral atrophy is believed to be strong evidence against the diagnosis. In mild cognitive deficit, several studies have shown lesser[73-76] or similar[77] hippocampal atrophy to that found in AD. Age transformation of combined hippocampal and amygdala volume increases the accuracy of classifying AD, MCI, and normal elderly subjects.[78] MCI subjects had hippocampal volume correlated with cognitive and performance measures[79] and those who declined over time had also a greater annualized rate of hippocampal atrophy than nondecliners, close to that of AD patients.[80] Atrophy of various regions at baseline, including hippocampus[79,81,82] ERC,[83,84] fusiform gyrus,[85] caudal cingulate cortex,[83] and medial temporal lobe,[76] was found predictive of progression to AD. White matter lesions have been found to be associated with subjective cognitive decline,[86] lowered attention and speed of mental processing,[87] and progression to dementia.[88]

There is an agreement on the fact that established AD is characterized by altered cerebral blood flow (CBF) and metabolism in posterior parietal and temporal lobes as well as by, according to stage and neuropsychological profile, frontal cortex deficits, and hemispheric asymmetry.[89] That functional imaging is able to detect preclinical AD is suggested by positron emission tomography (PET) studies, which found regional cerebral glucose metabolism (rCMRGlu) alterations in nondemented subjects at risk of AD (ie, those carrying the apolipoprotein E type 4 allele [ApoE ε4] and with familial history of AD)[90,91]; those in the inferior parietal and posterior cingulate cortices correlated with later memory decline.[92]

Studies comparing CBF and rCMRGlu in normal and mildly impaired subjects found deficits in the latter, in various regions including bilateral parietal cortex,[56] hippocampus,[77] and posterior cingulate gyrus.[93-95] Prediction of outcome was found for defects in parietal or tem-

poroparietal cortex,[56,96] posterior cingulate gyrus,[94,95] and for temporoparietal asymmetry[97] and lowered posteroanterior ratio[89]; others were predictive when combined with performance on specific cognitive tasks[98,99] and/or demographic characteristics.[99]

Progress in functional imaging can come from activation studies. Comparisons of young to elderly healthy subjects have shown that poorer performances in tasks such as conflict resolution and episodic memory in the elderly corresponded to underactivation, whereas a performance similar to that of young controls in working memory tasks was accompanied with recruitment of additional brain regions.[100] Studies comparing activation during cognitive tasks in AD patients and controls[101-105] showed that, together with lower performances, AD patients had activation patterns characterized by absence of activation in some brain areas, activation with shifted peak foci, expansion of normally activated zones, and recruitment of remote areas.[103] These differences were generally interpreted as due to compensation efforts; complementary interpretations are disconnection between regions normally involved in the task and predominant processing of accessory aspects of the stimuli (eg, emotional appearance in face recognition).[105] Passive pattern-flash stimulation elicited less activation in AD patients; this failure requires a less demanding stimulation to be disclosed in the moderate-to-severe group than in the mild group.[106]

Cognitively normal subjects at risk for AD (defined as the presence of at least one ApoE ε4 allele, alone[107] or combined with a history of AD in at least one first-degree relative[108]) were compared with low-risk controls for activation induced by cognitive tasks they performed with the same accuracy level. In the high-risk group, some regions were activated to a greater extent or magnitude (eg, nearly twice as much as in controls in hippocampal regions[107]); others displayed lower activation.[108] After a 2-year follow-up,[107] decline in verbal recall correlated with the number of regions activated in the left hemisphere at baseline.

Using a functional magnetic resonance imaging (fMRI) protocol specifically developed for hippocampal region analysis, one study[109] compared cognitively NCs, subjects with isolated memory impairment (IMI), and AD patients during a simple task (gender discrimination of presented faces); all subjects performed the task with 100% accuracy. AD patients had lesser activation of the three regions studied, ie, ERC, subiculum, and the hippocampus proper. Among the IMI subjects, one third had an activation pattern similar to that of AD patients and the others displayed lesser activation in the subiculum only. Follow-up data would be necessary to determine whether the differences described in this study are predictive, but together these activation studies indicate that properly chosen activation paradigms could help identify AD in subjects with mild cognitive deficits.

Nuclear magnetic resonance affords additional approaches. Magnetic resonance spectroscopy (MRS) can assess the biochemical composition of living brain regions. To date, the most consistent findings in AD[110] have been obtained with proton MRS showing a decrease in $N$-acetylaspartate (NAA) and an increase in myoinositol (MI). NAA and MI changes are specific to neither AD nor brain disease, but the NAA/MI ratio can discriminate possible AD cases from NCs. In addition, NAA/MI, NAA, and the MI/creatine (Cr) ratio were shown to be correlated with MMSE score in controls and patients with probable AD[111]; in a 12-month follow-up study[112] NAA/Cr and NAA/MI at baseline were correlated with the progression of MMSE scores. Few studies have used MRS in mild cognitive deficit. MI/Cr was found to be higher in MCI subjects[113,114] and NAA lower in AAMI subjects[115] and AD patients than in controls, whereas MI values were intermediate between AD patients and controls.[115] Follow-up studies are necessary to confirm the predictive value of such findings.

The magnetization transfer imaging (MTI)[116] signal arises from the magnetization exchange between water- and macromolecule-bound protons; this technique is useful in the study of membranes and membrane-linked diseases such as multiple sclerosis, in which decreased magnetic transfer ratio (MTR) is a marker of demyelination[117] and axonal density loss.[118] MTI studies involving AD patients[119-125] agree on decreased values compared with NCs, expressing structural changes in the temporal lobe, and also the frontal lobe and the whole brain.[119,120] Hippocampal MTR had a discrimination rate relative to controls of 85% in mild AD (CDR=0.5), 89% in mild AD (CDR=1), and 100% in moderate AD (CDR=2); the values for visually rated atrophy were of 73%, 80%, and 91% respectively.[124] MTR was also able to differentiate AD from non-AD dementia with a success rate of 77%.[123] Studies comparing MCI subjects with AD patients and healthy controls[119-122] identified structural changes in MCI in the absence of significant atrophy; they were located in gray matter, whereas those

found in AD patients involved white and gray matters.[122] These changes were found to be correlated with cognitive impairment.[119,120] MTI thus seems able to identify structural changes before atrophy is manifest. Follow-up studies should confirm its predictive value and comparison with functional imaging should assess which technique detects the earlier changes.

The ApoE ε4 allele is acknowledged to be a risk factor for AD.[126,127] Few studies have specifically addressed its influence on the evolution of MCI subjects. The ApoE ε4 carrier status was found the best predictor of conversion to AD (risk ratio=4.36),[21] a nonsignificant predictor (relative risk of 1.49)[79] or to have no predictive value.[54,128] In subjects with memory impairment and Global Deterioration Scale (GDS) score of 2 to 3,[129] ApoE ε4 alone predicted progression to dementia with a 73.8% accuracy; combining genotype and memory scores increased the accuracy to 92.5%. In subjects with MMSE scores of 21 to 26, the ApoE genotype was found to be associated with an odds ratio for progression to dementia of 3.31[130] and with memory decline.[131]

Among the various substances that have been assayed in blood and CSF,[132] increased CSF-tau and decreased $\beta A_{1-42}$ proteins are the best markers for AD to date.[132-134] Their combination yielded a 94% and 88% sensitivity for probable and possible AD, respectively, and specificity of 100% versus psychiatric disorder, 89% versus no dementia, 67% versus DLB, and 48% versus VaD in clinical practice conditions.[135] CSF-tau levels were found to be higher in MCI than in healthy controls,[136-140] lower than[141] or similar to[139,140] those found in AD patients. In follow-up studies, it identified MCI subjects who evolved to AD with a sensitivity of 65% to 68% and a specificity of 100% versus patients with memory complaints[142] and 93% versus healthy controls[139]; baseline values in converters were higher than in nonconverters.[137] In one study,[139] combining CSF-tau and $\beta A_{1-42}$ values did not improve the predictability obtained with CSF-tau alone. In others, combined CSF-tau/$\beta A_{1-42}$ values differentiated converters from healthy controls with 88% sensitivity and 80% specificity[138] and from nonconverters with a 90% sensitivity and specificity.[140]

Medical diagnoses are rarely reached using a single marker; most often it results from the combination of different approaches, including thorough clinical evaluation. Once a consensus is obtained on cutoff values for the different techniques mentioned, it is likely that a combination of different markers for AD will allow early diagnosis with high sensitivity and specificity in individual cases.

## Therapeutic aspects

The final goal of constructing criteria for age-associated mild cognitive deficit is to treat it, and many therapeutic approaches are available.[143,144]

Some benefits have been reported, in terms of global stability and improved memory with the acetylcholinesterase inhibitors (AChEI) donepezil[145] and rivastigmine[146] and the dopamine receptor agonist/$\alpha_2$ antagonist piribedil[147]; trials are underway using donepezil and vitamin E, rivastigmine, the cyclooxygenase-2 (COX-2) inhibitors celecoxib and rofecoxib with the goal of delaying patients' progression to dementia[144] and the Ampakine® CX516 with the aim of short-term symptomatic improvement.[148] Treating MCI using approaches initially intended for AD premises either that MCI equates to early AD in all cases, which is unlikely, or that the underlying mechanism is the same in both cases, the difference being merely a matter of intensity, which is not confirmed by neuropathological data. Even if improved criteria or techniques were able to predict the progression to AD in a given patient, this strategy deserves discussion. As regards the cholinergic and glutamatergic systems in AD, it has been proposed that the final deficiency state is preceded, in the early stages, by a hyperactive state[149,150] originating in βA-induced *N*-methyl-D-aspartate (NMDA) receptor hypersensitivity. It was recently found that the number of choline acetyltransferase (ChAT)–positive neurons in the nucleus basalis of Meynert was no lower in MCI than in NCs.[151] Further, ChAT activity was shown to be increased in hippocampus and in the superior frontal cortex compared with NCs, and similar in anterior cingulate, superior temporal, and inferior parietal cortices.[152] Although such data are lacking for the glutamatergic system, these findings suggest that, among the currently available treatments, those aiming at downmodulating the NMDA receptor responsiveness could be more appropriate than replacement therapies in degenerative, AD-type MCI. Mild cognitive deficit will be the condition of choice for administration of future treatments addressing basic mechanisms of degenerative dementias, provided they can be reliably identified in these patients.

## Conclusion

Introducing criteria for mild cognitive deficit should:
• Help its detection, mostly in first-line medicine.
• Improve the accuracy of early dementia diagnosis.

• Through harmonization of practice in research settings, permit progress in pathophysiological and therapeutic research.

All the sets of criteria, whatever their formulation, require the input of a neuropsychologist and a thorough, comprehensive examination. This approach is available in specialized centers only, and not transferable to first-line medicine. The criteria by themselves do not predict which individual will progress to dementia and still less the nature of this potential disease. On the other hand, early, reliable diagnosis of AD through a proper combination of investigational procedures can be expected in the near future. Epidemiological data show that AD remains the most frequent dementia type in elderly people.[153] Follow-up studies suggest that it is also the most frequent dementia type developed by subjects with mild cognitive deficit. Therefore, early identification or rejection of AD would solve the majority of cases. It can thus be thought that the priority is to optimize our battery of investigational tools by defining appropriate cutoff values, comparing them in the same patient samples, and defining their individual powers.

From a practical and clinical point of view, refining the sets of criteria to improve their specificity, which implies skilled professional intervention, is probably useless. Efforts should rather be made to define simple, sensitive tools, usable by general practitioners.

From a research point of view, it seems mandatory to reach a consensus on several points. Should the reference population be matched for age only, or for gender and education as well? Using age-related references implies admitting that cognitive decline occurs in healthy aging; using education-related ones implies that low education is an independent risk factor for cognitive decline[154,155]; using gender requires taking into account the hormonal status of women. Should impairment in a cognitive domain be established on the basis of a single test, or of several ones addressing the same function? Should studies include subjects with memory impairment only, or with decline in other domains as well? Stratifying the participants according to their cognitive profile would allow assessment of the predictivity of this item, relative to the underlying disease, as proposed by Petersen et al.[156] It would also permit comparison of the effect of treatments in these subsets.

These issues cannot be solved by any single research team. Collaborative or, at least, comparable studies require the strict definition of common basic inclusion (eg, the tests to be used with standard cutoff scores) and exclusion criteria. Before being applicable in daily practice, the available sets of criteria need to be further defined and standardized. The current lack of treatment is a hurdle to its acceptance. However, disseminating the concept could help increase the sensitivity of general practitioners to the importance of cognitive complaints and signs in their elderly patients. ❏

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## El déficit cognitivo leve relacionado con la edad: ¿un concepto a punto de usarse?

*Para un mejor manejo del deterioro cognitivo leve en los pacientes ancianos, los clínicos deben contar con instrumentos para detectar cambios precoces y predecir su progresión. Para definir este estado cognitivo entre el envejecimiento óptimo y el patológico se han propuesto muchos conceptos, los cuales incluyen diversas condiciones y proporcionan criterios más o menos precisos, dejando libertad para una implementación variable. Como consecuencia de esto, la aplicación de estos criterios determinó frecuencias de prevalencia altamente variables. Los estudios neuropatológicos indican que los diferentes criterios tienen un poder variable para detectar la Enfermedad de Alzheimer (EA) incipiente y sugieren que la transición entre el deterioro cognitivo leve y la EA no es meramente cuantitativa. Los estudios de seguimiento han determinado– de acuerdo con los criterios utilizados –una frecuencia anual de progresión hacia la demencia entre un 2,5% y un 16,6%, y también han mostrado que los criterios difieren en su estabilidad y poder predictor. Los resultados cognitivos basales tienen algún valor predictor, pero son difíciles de aplicar en la atención primaria. Las técnicas paraclínicas (las imágenes estructurales y funcionales, la resonancia magnética por espectroscopía, las imágenes por transferencia de magnetización, la neuroquímica del líquido céfalo-raquídeo y el genotipo de la apolipoproteína E) constituyen herramientas promisorias en el diagnóstico precoz de la EA, la cual se mantiene como el tipo más frecuente de demencia en la población anciana y probablemente también el más frecuente que se desarrolla en pacientes con déficit cognitivo leve. El objetivo final es ofrecer un tratamiento precoz a aquellos pacientes que evolucionarán hacia la demencia, una vez que ellos se hayan podido identificar. En el caso de la EA los hallazgos recientes cuestionan la conveniencia de terapias colinérgicas de reemplazo. Actualmente los criterios para el déficit cognitivo leve son difíciles de aplicar a la atención primaria. Sin embargo, la divulgación del concepto podría ayudar a aumentar la sensibilización de los médicos generales respecto a la importancia de signos y quejas cognitivas en sus pacientes ancianos.*

## Troubles cognitifs légers liés à l'âge : un concept prêt à l'emploi ?

*La prise en charge efficace des troubles cognitifs légers chez les patients âgés implique que les médecins puissent disposer d'instruments capables de détecter des modifications précoces et de prévoir leur évolution. Divers concepts, décrivant en fait des situations variées et utilisant des critères plus ou moins précis, ont été proposés pour définir cet état cognitif intermédiaire entre vieillissement optimal et pathologique. Par conséquent, l'application de ces critères a fourni des taux de prévalence eux-mêmes très variables. Les études neuropathologiques montrent que les différents critères ont un pouvoir variable pour détecter une maladie d'Alzheimer débutante (MA) et suggèrent que la transition entre trouble cognitif léger et MA avérée n'est pas seulement d'ordre quantitatif. Les études de suivi ont montré que les critères utilisés diffèrent quant à leur pouvoir prédictif et leur stabilité, aboutissant à des chiffres annuels de progression vers la démence variant entre 2,5 % et 16,6 %. Les performances cognitives basales ont une certaine valeur prédictive mais sont difficiles à appliquer en médecine de premier recours. Les examens paracliniques (imagerie fonctionnelle et structurelle, spectroscopie par résonance magnétique, imagerie par transfert de magnétisation, neurochimie du liquide céphalorachidien et génotype des apolipoprotéines E) sont des outils prometteurs dans le diagnostic précoce de la MA qui reste le type de démence le plus fréquent chez les sujets âgés et probablement la pathologie qui se développe le plus souvent chez les patients atteints de troubles cognitifs légers. Le but final est d'offrir un traitement précoce à ceux qui évolueront vers la démence dès qu'ils auront pu être identifiés. Pour ce qui est de la MA, des observations récentes remettent en cause les traitements substitutifs cholinergiques. Dans leur état actuel, les critères du déficit cognitif léger sont difficilement applicables en médecine de premier recours. Néanmoins, la diffusion de ce concept pourrait aider à sensibiliser les médecins généralistes à l'importance des manifestations tant subjectives qu'objectives indiquant une atteinte cognitive chez leurs patients âgés.*

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