The prevalence of dementia has increased with life expectancy: more than one third of individuals over the age of 80 are likely to develop a dementia. Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that remains the most common cause of dementia and accounts for more than 60% of all cases. Although AD mainly concerns aged populations, it can also affect younger patients below 60.

The stage at which a diagnosis of AD is made impacts the therapy advised, the counseling given to patients and family, and the approach to long-term care. For more than 25 years, the diagnosis of Alzheimer’s disease has been based on the NINCDS–ADRDA criteria, according to which the diagnosis is classified as definite (clinical diagnosis with histological confirmation), probable (typical clinical syndrome without histological confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histological confirmation). The diagnosis of AD can also be based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision (DSM-IV-TR). Generally speaking, the current diagnostic criteria are characterized by a two-step procedure with: i) the identification of a dementia syndrome; and ii) the exclusion of other etiologies of a dementia syndrome, using biological and neuroimaging exams.

The issue in AD diagnosis today is to recognize the disease before the cognitive deficits have reached the threshold of dementia, ie, at its prodromal stage, in light of current drug development aimed at slowing AD progression. There is a need, today, for improving the diagnosis of AD with a double objective: i) to reach a diagnosis earlier; and ii) to be more specific.

Is it possible to make an earlier diagnosis? The answer is yes, because Alzheimer’s disease is already symptomatic...
long before dementia. This raises the issue of the definition of Alzheimer’s disease: what is Alzheimer’s disease? Should it be clinically defined by a reference to dementia? Should it be recognized earlier in the symptomatic phase, before threshold of the dementia syndrome, in case of specific cognitive changes? Can it be biologically defined by the evidence of specific biomarkers—today available in vivo—in the absence of any clinical symptoms? As we treat patients and not only lesions, we think that AD should remain defined as a disease with a clinical expression. However, it should encompass the full spectrum of the clinical expression, including both the predementia and dementia phases. Indeed, there is no fundamental reason to link the diagnosis of a disease (AD) to a certain threshold of severity and to exclude ipso facto from the diagnostic and treatment perspectives a large number of patients who have already expressed the diagnosis clinically. In other words, there is no reason to wait until the patients reach the threshold of a full-blown dementia for making the diagnosis of Alzheimer’s disease. It is exactly as if, in Parkinson’s disease, we waited until the patients were bedridden to make the diagnosis. We currently make the diagnosis of Parkinson’s disease much earlier, when we see a resting tremor of one hand. The same should apply for Alzheimer’s disease. Unfortunately, the stage of predementia—or prodromal AD—was integrated into the broad concept of mild cognitive impairment (MCI), a syndrome associated with many other causes than prodromal AD. The classical definition of AD, restricted to the concept of dementia, was mainly justified by the fact that the diagnosis was more difficult to make in the early, predementia phase in the last decades; and this was the reason for considering it a stage of MCI. However, the emerging literature on MCI has emphasized an intrinsic etiological heterogeneity and a diversity of outcomes within research studies. Efforts to address these issues have not succeeded, and the limitations of MCI are apparent. The risk of intervening on an etiologically heterogeneous sample of MCI subjects will include running the risk of “diluting” a significant treatment effect.

Recently, research has begun to focus on developing new tools, such as neuroimaging and cerebrospinal fluid (CSF) biomarkers, that could increase the specificity of the prodromal AD diagnosis. Before using such invasive or expensive tools, it is necessary to screen patients in memory clinics with neurological exams and neuropsychological assessment. The most prominent feature of AD is the decline in cognitive function. Memory impairment of recent events, unusual repeated omissions, and difficulty learning new information characterize the first clinical signs. This progression of cognitive deficits is related to the progression of the underlying cerebral lesions, as established by Braak and Braak. In the early stages of AD (Braak I-III), critical areas for episodic memory are already affected by neuropathological changes (neurofibrillary degeneration) in medial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex) and, consequently, episodic memory deficit is the initial and reliable neuropsychological marker of AD. As the condition progresses, deficits occur in instrumental functions (language, praxis, visuospatial capacities), which

![Image](image-url)
are consistent with the extension of lesions into the neo-
cortical associative areas (Braak V).

The situation faced by clinicians is easy to summarize: i) memory disorders are the most reliable sign of prodromal AD; ii) unfortunately, memory disorders are a very common sign, observed in many disorders: for example in depression, anxiety, sleep disorders, brain vascular lesions, frontal lobe dysfunction, and even in normal aging. Is it possible, therefore, to identify the memory disorders of AD? Here again, the answer is yes, because the memory disorders of AD are not like other memory disorders: there are very specific because they result from a hippocampal dysfunction.

This is why the neuropsychological evaluation is crucial at the prodromal stage, for establishing the nature of memory impairment. Specific memory tests are useful for distinguishing the true memory impairment (eg, failure of information storage and new memory creation) from attentional disorders or strategic impairment (such as normal aging or frontal disorders, Figure 1). Using a memory test that controls for encoding and provides semantic cueing to facilitate strategy of retrieval can improve accuracy of AD diagnosis.11, 12

The low performance of total recall in spite of retrieval facilitation indicates a poor storage of information. This amnestic syndrome that we have called “of the hippocampal type” differs from functional and subcorticofrontal memory disorders, which are characterized by a low free recall performance with normal total recall because of good cueing efficacy. In a recent study, we showed that the amnesic syndrome of the hippocampal type, defined by: i) a very poor free recall; and ii) a decreased total recall due to an insufficient effect of cueing can identify prodromal AD in patients with MCI with a high sensitivity of 79.7% and a specificity of 89.9%. At 36 months, the probability of developing AD dementia for patients with MCI who fulfilled both criteria defined by free and total recall was 90%, while it was 5.6% for those who did not fulfill both criteria. This is not surprising, because the test used assesses whether the given information has been truly encoded. This should be a requirement for testing the ability to store information. How can we interpret a recall deficit if the initial registration of information has not been tested? Unfortunately, none of the currently used memory tests are designed for such a test of encoding.

The evidence of an amnestic syndrome of the hippocampal type is therefore a major step for the diagnosis of prodromal AD. In addition, supportive features can improve the specificity for the diagnosis.7 Distinctive and reliable biomarkers of AD are now available through structural brain imaging with magnetic resonance imaging (MRI), molecular neuroimaging with positron emission tomog-

| Major criterion |
|------------------|
| Presence of an early and significant episodic memory impairment that includes the following features: |
| 1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months |
| 2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly, or does not normalize with cueing or recognition testing and after effective encoding of information has been previously assessed |
| 3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances. |

| Minor criteria: |
|----------------|
| A- Presence of medial temporal lobe atrophy |
| • Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with: |
| Qualitative ratings using visual scoring (referenced to well characterized population with age norms) or quantitative volumetry of regions of interest (referenced to well characterized population with age norms) |
| B- Abnormal CSF biomarkers: |
| • Low amyloid β 1-42 concentrations, increased total tau and/or increased phospho-tau concentrations |
| • Other well-validated markers to be discovered in the future |
| C. Specific pattern on functional neuroimaging with PET: |
| • Reduced glucose metabolism in bilateral temporal parietal regions |
| • Other well-validated ligands, including those that foreseeably will emerge such as PiB or FDDNP. |
| D. Proven AD autosomal dominant mutation within the immediate family |

Table I. New diagnostic criteria for Alzheimer’s disease (AD): 1 major criterion plus 1 (or more) minor criterion. MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; PET, positron emission tomography; PiB, Pittsburgh compound B; FDDNP, amyloid ligand
raphy (PET) and CSF, analysis of A-beta 42 concentration, total tau and phospho-tau levels. The presence of at least one biological footprint of the disease should improve the specificity for the diagnosis. This is at the origin of the new diagnostic criteria that were proposed in 2007 (Table I). These criteria no longer refer to the dementia threshold. They move away from the traditional two-step approach of first identifying dementia according to degree of functional disability and then specifying its cause. Rather, they aim to define the clinical, biochemical, structural, and metabolic presence of AD, even at early stages. Therefore, we consider that the new diagnostic criteria which capture the early pre-dementia phase of the disease reach the two objectives: to be earlier and to be more specific. According to these criteria, the diagnosis of early AD can be made on the objective evidence of significantly impaired memory upon testing, and the presence of hippocampal atrophy on MRI, or an abnormal pattern of CSF biomarkers, or a specific pattern on PET neuroimaging. We recognize that these criteria represent a cultural shift requiring a more biologically focused workup than previous approaches; however, this seems to be the best way to integrate the profound advances into the clinical arena. When effective disease-modifying medications are available, the argument for such biologically based studies will be even more compelling. Some research needs will be better addressed with a more stringent approach requiring that each diagnostic criterion be met. For example, proof-of-concept studies may benefit from the most highly selected AD study samples where the presence of all supportive features might be specified. This could maximize specificity for AD, but impose a substantial loss of sensitivity that would need to be readdressed in later stages of development. Their usefulness of these new criteria will be determined in the future as investigators apply the criteria in a variety of research studies, and as key issues in their application are resolved.

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**Detención precoz de la Enfermedad de Alzheimer: nuevos criterios diagnósticos**

Ha habido un crecimiento sin precedentes acerca del conocimiento científico de la Enfermedad de Alzheimer (EA). Tanto la descripción de biomarcadores característicos y confiables de los cuales se dispone actualmente a través de las imágenes cerebrales estructurales de la resonancia magnética, de las neuroimágenes moleculares de la tomografía por emisión de positrones y del análisis del líquido céfalo-raquideo, como una mejor definición del perfil clínico de los trastornos amnésicos que se producen precozmente durante la evolución de esta patología, permiten identificar la EA con bastante precisión, aun en etapas precoces de la enfermedad. De acuerdo con esto, se han propuesto nuevos criterios para el diagnóstico que centran la atención tanto en las etapas prodromáticas como en las etapas de demencia más avanzadas de la enfermedad dentro del mismo esquema diagnóstico.

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**Détection précoce de la maladie d’Alzheimer : nouveau critère diagnostique**

La connaissance scientifique de la maladie d’Alzheimer (MA) a fait récemment des progrès importants. Il est maintenant possible d’identifier la MA avec précision, même aux stades précoce de la maladie, grâce à la mise en évidence de biomarqueurs caractéristiques et fiables désormais disponibles par imagerie cérébrale structurale avec l’imagerie par résonance magnétique, la neuroimagerie moléculaire par tomographie par émission de positrons et l’analyse du liquide céphalo-rachidien, ainsi qu’une meilleure définition du profil clinique des troubles mnésiques intervenant de façon précoce au cours de la maladie. De nouveaux critères de diagnostic ont par conséquent été proposés pour appréhender à la fois les stades prodromaux ou prédémentiels et les stades plus avancés de la maladie dans le même cadre diagnostique.
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