

## Position paper of the Italian Society for the study of Dementias (Sindem) on the proposal of a new Lexicon on Alzheimer disease

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**Abstract** A panel of Italian neurologists of the Italian Society for the study of Dementias (SINDEM) discussed the recently proposed new lexicon for Alzheimer disease (AD) and the related diagnostic criteria for the different phases of the disease (Preclinical AD, prodromal AD and Alzheimer's dementia) (Dubois et al. in *Lancet Neurol* 6:734–746, 2007; in *Lancet Neurol* 9:1118–1127, 2010). The aim of this discussion was to reach a consensus, among

the Italian neurologists involved in the study and care of persons with dementia, in particular in reference to the potential use of the proposed diagnostic criteria in clinical practice. After having critically revised the scientific evidence related to the new lexicon and to the new proposed diagnostic criteria, the panel concluded that the proposed new diagnostic criteria and the new proposed lexicon for AD are conceptually attractive. However, the evidence

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about the instrumental and laboratory markers for the diagnosis of the preclinical and asymptomatic states of the disease are, until to now, insufficient to support the routine clinical use of these investigations.

**Keywords** Alzheimer's disease · Diagnostic criteria · Biomarkers · Expert opinion

## Introduction

A panel of Italian neurologists members of the Scientific Committee of the Italian Society for the study of Dementia (SINDEM) discussed the diagnostic research criteria and the new lexicon for Alzheimer disease (AD) proposed by Dubois et al. [1, 2].

The adopted procedure was two steps: first all the participants discussed about the conceptual framework of the new lexicon expressing their agreement or disagreement on the new diagnostic classification. The principal aim of first step consensus procedure was to evaluate whether the entities introduced by the new lexicon could enter the scientific and clinical language of neurologists. The second step consisted in a critical appraisal of the scientific evidence that supports the operational criteria for defining the new entities. The evidence considered during the consensus process are all the scientific articles considered in the Dubois papers and any other evidence proposed by the panelists. The principal aim of this second step consensus

procedure was to evaluate the potentials and/or limitation for adoption of the new criteria and lexicon in clinical practice.

## Glossary

The Scientific Committee has accepted this glossary after a discussion in order to specify the meanings of the terms adopted.

*Dementia.* With the term dementia, we refer to the internationally accepted definition coded by DSM-IV and ICD-10; presence of a memory disturbance, and of impairment in at least one other cognitive domain, which interferes significantly with activities of daily living.

*Disease.* In this context, we define disease as the presence of the pathological process that can be the cause of the neuropathologic alterations characterizing AD (amyloid deposition and neurofibrillary tangles). These features may or may not be concomitant with the clinical signs of Dementia of Alzheimer type.

## Step 1

The new criteria reflect the widely agreed opinion that Alzheimer's disease preexists prior to the clinical manifestation of dementia. This is not only a diffuse opinion but is also supported by consistent scientific evidence. There is no doubt that, in the hereditary forms of AD, the pathological process, and consequently the disease, is present from birth but the clinical signs occur during middle- or late-life [3].

In the proposed new classification, the pre-dementia phase of AD is further divided sequentially into a pre-symptomatic and a symptomatic period. Finally, the latest stage of the disease is represented by Alzheimer's dementia. For many reasons, the panelists are positive to the idea of disentangling the diagnosis of AD from the diagnosis of dementia as defined in DSM-IV. The disease is present well before the full manifestations of dementia; the existence of a pre-dementia phase of AD is conditioning the entire diagnostic process and should be formalized into appropriate criteria. The attention to a pre-dementia phase of the disease is helpful for the differential diagnosis between AD and other forms of neurodegenerative disorders with cognitive involvement. All the criteria for the diagnosis of neurodegenerative diseases causing dementia state that cognitive involvement is different from AD at the beginning of the natural history, but eventually become indistinguishable in the advanced phases when dementia is fully present [4, 5]. A reliable recognition of AD before dementia can increase the efficacy of disease-modifying interventions. Therapies

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capable of modifying or possibly halting the rate of progression of the disease are expected in the next future. These therapies will be most effective when introduced early during the course of the disease.

The panelists agree the proposed division of AD prodromal phase into a condition of high-risk for AD and of prodromal AD. There is conclusive evidence that an early symptomatic phase of the disease precedes the development of dementia in AD, although this phase is difficult to distinguish from normal ageing. On the other hand, other consistent evidence supports the idea that groups of normal young and middle-aged people carrying different risk factors have a higher likelihood of developing AD than persons without these characteristics. The condition of Mild Cognitive Impairment (MCI), generally defined as a condition of cognitive impairment not severe enough to meet the criteria for dementia, is associated with a higher risk of having dementia in the ensuing years with respect to age and sex-matched cognitively normal individuals [6]. Epidemiological and clinical studies have shown that many factors that are present in normal persons are associated with higher risks of AD occurrence. Among the most widely accepted factors that increase the risk of having dementia are vascular risk factors (diabetes, dyslipidemia, hypertension) [7], low education [8] and the Apolipoprotein (ApoE) epsilon-4 allele [9]. Many of these factors are considered amenable of preventive interventions [10] although there is currently a lack of evidence from randomized clinical trials. Normal persons with laboratory or neuroimaging characteristics of AD have been shown to be at higher risk of AD, and these observations provide evidence for the new proposed lexicon [2]. All these evidences will be reviewed in the second part of this position paper.

The panelists consider positively the introduction of the new entity of prodromal AD as a separate entity from what was commonly considered as MCI. Studies on populations heterogeneously diagnosed with MCI [6], report that a higher than expected proportion of these persons evolved to AD or other forms of dementia, but others returned to a cognitively normal state or remained in the state of MCI [11]. This supports the theory that the population of persons with cognitive impairment not meeting the criteria of dementia is a mixed population composed both of persons destined to evolve towards Alzheimer's disease and by persons whose cognitive disturbance is caused by other factors. The need to distinguish these two populations seems highly useful for intervention planning.

## Step 2

### Preclinical states of AD

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Preclinical states of AD (including both “asymptomatic at-risk state for AD” and “presymptomatic AD”)

These terms refer to the long asymptomatic stage between the earliest pathogenic events/brain lesions of AD and the first appearance of specific cognitive changes. Traditionally, a preclinical or asymptomatic phase was recognised post mortem by the evidence of histological changes typical of Alzheimer's pathology in individuals considered as cognitively normal before death. Today, two preclinical states can be isolated in vivo:

- *Asymptomatic at-risk state for AD*: this state can be identified in vivo by evidence of amyloidosis in the brain (with retention of specific PET amyloid tracers) or in the CSF (with changes in amyloid  $\beta$ , tau, and phospho-tau concentrations). In the absence of knowledge about the value of these biological changes to predict the further development of the disease, the asymptomatic phase of AD should still be referred to as an “at-risk state for AD”
- *Presymptomatic AD*: this state applies to individuals who will develop AD. This can be ascertained only in families that are affected by rare autosomal dominant monogenic AD mutations (monogenic AD)”

Panel 1. Preclinical states of AD according to Dubois et al. [1]

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The preclinical states of AD are divided into two conditions: the asymptomatic at-risk state for AD and the presymptomatic AD.

*The asymptomatic at-risk state for AD* is identified by instrumental evidence of the presence of amyloid in the brain, reduced  $\beta$ -amyloid (A $\beta$ 42) and increased total-tau (T-tau) and phospho-tau (P-tau) concentrations in cerebrospinal fluid (CSF), in individuals not cognitively impaired. PIB-PET imaging studies have found elevated levels of brain amyloid in elderly subjects defined as normal [12–15]. However, the lack of cognitive symptoms in these normal individuals is not sufficiently documented or definitively ascertained in the available studies. Indeed, only two studies explored the cognitive performances of normal persons with normal and abnormal amyloid brain deposition at PIB-PET imaging reporting contradictory results [12, 15]. One study found no differences with a large battery of cognitive tests [12] whereas, the second one found a correlation between the level of amyloid deposition and episodic memory impairment [15].

The presence of amyloid brain deposition detected in vivo with PIB-PET imaging, and/or the CSF reduction of

amyloid and the increase in tau and/or phospho tau, have been reported to be associated with higher probabilities of cognitive decline during follow-up [16–19] in persons defined as normal or non-demented at baseline. Furthermore, reports also find an association between these measures and increased rates of brain atrophy [20]. These studies concerned a general risk of cognitive decline rather than the occurrence of dementia. Nonetheless, the evidence derived from these studies appears sufficient to consider that normal persons with amyloid brain deposition detected in vivo with PIB–PET imaging, and/or CSF abnormal concentrations in A $\beta$ 42 and P-tau have a higher risk of having AD. However, since it is not yet possible to predict who will develop dementia, and since specific preventive strategies suitable for this group are not available, the panel believes that PIB-PET imaging and CSF examination for A $\beta$ 42 and T-tau/P-tau should not be performed in asymptomatic persons. The construct of Asymptomatic at-risk state for AD maintains, however, a great interest for research purposes.

The *presymptomatic AD* category is suggested for individuals free of symptoms of AD but who carry fully penetrant genetic mutations. The most frequent mutations causing the familial forms of AD have been detected on the genes of amyloid precursor protein (APP) and of presenilin 1 and 2 (PSEN 1, PSEN 2). The panelists did not find formal studies on the penetrance of mutations on APP, PSEN 1, PSEN 2 and other genes causing AD and anecdotal reports describe incomplete penetrance for PSEN 1 and PSEN 2 mutations [21, 22]. Clinical descriptions of affected families showed a relevant variability in the age of onset of dementia and in phenotype expression [22, 23]. For these reasons, on the basis of the available evidence, the predictive value of the presence of a mutation causing AD in an otherwise healthy subject remains uncertain.

## Prodromal AD

Prodromal AD (also called “predementia stage of AD”)

This term refers to the early symptomatic, predementia phase of AD in which (1) clinical symptoms including episodic memory loss of the hippocampal type (characterised by a free recall deficit on testing not normalised with cueing) are present, but not sufficiently severe to affect instrumental activities of daily living and do not warrant a diagnosis of dementia; and in which (2) biomarker evidence from CSF or imaging is supportive of the presence of AD pathological changes. This phase is now included in the new definition of AD. The term of prodromal AD might disappear in the future if AD is considered to encompass both the predementia and dementia stages

Panel 2. Prodromal AD according to Dubois et al. [1]

The term prodromal AD concerns individuals presenting specific cognitive symptoms that do not cause limitations

in instrumental activities of daily living, in addition to positive CSF biomarkers or imaging markers consistent with AD pathology. The specific cognitive profile is episodic memory loss detected by free recall testing not normalized with cueing. This very strict definition of the cognitive symptoms of AD in the prodromal phase is supported by a longitudinal study in which elderly with memory subjective complaint and objective memory impairment who did not fulfill the DSM-IV criteria for dementia were followed for 36 months [24]. In that study, the authors report that the amnesic syndrome of the medial temporal lobe type characterize the prodromal AD of the subjects showing low performances at the Free and Cued Selective Recall Reminding Test. Using receiver operating characteristics (ROC) analysis for predicting the evolution to clinical AD, the Free and Cued Selective Recall Reminding Test had the highest area under the curve among the many cognitive tests performed. However, this finding is unique and has not been replicated, being also evident that impairment in cognitive domains different from memory has higher or similar capacities in discriminating between evolving and non-evolving persons with MCI [25]. This observation, and the fact that the cognitive profile of fully developed AD, is not strictly confined to the amnesic type and involves cognitive domains as attention and construction, leave open the question whether memory has to be always considered a necessary prodromal condition [26]. Although attractive, the specificity of episodic memory impairment as detected by the Free and Cued Selective Recall Reminding Test for subjects with prodromal AD has to be confirmed by well-designed longitudinal study in non-demented individuals with cognitive deficits [27].

Further, in addition to the discussion of the Free and Cued Selective Recall Reminding Test within the amnesic syndrome paradigm, the validity of biomarkers in predicting the presence of AD in persons with signs of cognitive impairment not severe enough to fulfill the criteria for dementia need to be discussed.

## Imaging

Studies have reported three different brain imaging markers that are consistent with the pathological model of the disease.

1. Brain atrophy and more specifically atrophy of the temporal mesial brain areas including hippocampus atrophy. The evaluation of these atrophies relies on structural MRI imaging using semi-quantitative and quantitative analyses.
2. Reduced brain glucose metabolism evidenced with PET imaging with quantitative assessment.

### 3. In vivo brain amyloid detection with PIB–PET imaging.

The validity of all these markers relies on two commonly accepted paradigms of AD. The first paradigm is that the disease starts with neuropathological alterations of the memory circuits connecting the entorhinal and transentorhinal cortex to hippocampus [28]. The second is that the disease is due to a process with neurotoxic effects leading to amyloid deposition in the form of amyloid plaques the so-called “amyloid cascade” [29]. Although potentially falsifiable by a relatively large number of evidences these paradigms represent the best explanations for the pathogenesis and clinical characteristics of AD.

The diagnostic validity of each marker can be established by well-designed longitudinal studies. These studies should compare the rates of conversion to clinical AD in non-demented persons with cognitive impairment and positive or negative markers. The judgment of the panelists was derived after a retrieval and critical reappraisal of all the studies before February 2011. In particular, the panelists judged the validity of individual predictions based on the markers. This mode of evaluation does not imply that the considered markers do not have a consistent validity (which is almost always the case) in discriminating between groups of patients with different risks of conversion to AD [30]. The panelists have considered a sensitivity of 80% or higher with a specificity of 85% or higher as cut-off values of validity of the marker as a predictor of conversion. These values were adopted since, with reference to a utilization of the markers in populations with a 3-year conversion rate from MCI to AD of 35–50% [11, 31], a marker with these characteristics of sensitivity and specificity would have predictive values (positive 74–84%; negative 81–89%) reasonably useful and safe for routine clinical practice.

#### Medial temporal lobe atrophy

Hippocampus atrophy through MRI investigation seems a quite valid method for a cross sectional discrimination of normal individuals from non-demented individuals with cognitive impairment [32]. However, in a longitudinal study age and AD were reported to exert independent effects on brain grey matter volumes, but these effects overlapped in hippocampus and entorhinal cortex—the brain areas considered more specifically involved in AD [33]. Moreover, temporal dynamics of spatial atrophy consistent with AD have been reported also in normal individuals [34]. In the most recent publication from the Alzheimer Disease Neuroimaging Initiative (ADNI) [35], the reported values of sensitivity and specificity were as follow:

Right entorhinal cortex thickness (%)	67.9	86.1
Left entorhinal cortex thickness (%)	74.1	84.2
Left hippocampus volume (%)	66.7	79.2
Right hippocampus volume (%)	65.4	85.1

Another recent paper from ADNI reported somewhat better values (sensitivity 79 specificity 82) [36] very near to our predefined cut-off values of validity. Also a recent paper from a group of researchers not involved in ADNI reported values not very dissimilar (sensitivity 73–77, specificity 74–80) [37] whereas previous studies reported almost always worse results [38, 39]. It is highly plausible that the more refined and standardized MRI measures recently adopted are the reason for better result in recent papers.

#### Reduced brain glucose metabolism at PET imaging examination

In principle, molecular neuroimaging has the capability to measure levels of neuronal activity. PET imaging with 2-[18F]fluoro-2-deoxy-Dglucose (FDG) is used to track AD-related brain changes by providing estimates of the cerebral metabolic rate of glucose (CMRglc). Moreover, CMRglc is a direct index of synaptic functioning and density. For these and other reasons, functional neuroimaging seems one of the best candidate markers to predict AD in subjects with initial cognitive impairment [40].

One study, in a limited number of individuals with MCI found a level of glucose metabolism in the right temporo-parietal areas that was lower in all the patients who converted to AD with respect to non-converters [41]. This result corresponds to a sensitivity and specificity of 100%. Another study in 30 persons with MCI reported a sensitivity of 92% and a specificity of 89% [42]. Another study that combined FDG PET with neuropsychological testing had a sensitivity of 93% and a specificity of 84% [43]. The recent results from ADNI are somewhat lower than those described above (sensitivity 79% specificity 82%) but nevertheless are close to the panel’s cut-off values [36].

#### PET amyloid imaging

The panelist retrieved a single study on 31 individuals with MCI followed for 3 years where amyloid PET imaging at initial observation was evaluated in association with conversion to AD during follow up [44] with a sensitivity of 93% and a specificity of 81%.

## Cerebrospinal fluid markers

Although the concentration of T-tau in CSF seems to increase in normal aging [45] a decreased concentration of A $\beta$ 42 and increased concentrations of T-tau and P-tau are the CSF characteristics of AD. The predictivity for AD conversion for persons with these CSF parameters has been evaluated in a large multicenter cohort study on 750 individuals with MCI [46]. The combination of A $\beta$ 42/P-tau ratio and T-tau identified incipient AD with a sensitivity of 83% and a specificity of 72%. Considering that 271 individuals with MCI had AD and 59 other dementias, we can calculate that the “a priori” probability of AD in the studied sample was 40% (271/691) and the post-test improvement in the positive predictive value (62%) was really poor. The reasons for these unsatisfactory results were individuated in the large variability and thus in the insufficient accuracy of the determinations of the CSF concentrations of A $\beta$ 42, T-tau and P-tau. A recent study that adopted strictly standardized procedures of evaluation of CSF parameters found satisfactory inter laboratory coefficients of variation around 5% [47]. Unfortunately, in that study the intra laboratory coefficients of variation confirmed the high intra laboratory variability of CSF determinations.

A previous study in a single center reported consistently better results (sensitivity 95% and specificity 87%) [48]. However, most previous studies had results similar to the large 2009 multicenter study [49]. The most recent results of the Descripa study [50] reported on 158 subjects with subjective memory complaints, non-amnesic MCI, and amnesic MCI. After a follow-up of 3 years, 35 (22%) subjects with AD dementia were observed. All the subjects with AD at follow-up had an AD-like CSF profile, which corresponds to a sensitivity of 100%. However, since 105 subjects had an AD-like CSF profile it can be derived that 70 of these were false positives, and that specificity was 57%. The values of specificity were somewhat worse in the subgroup of non-amnesic MCI (54%) and better in the subgroup of amnesic MCI (67%) persons.

## Conclusions

The proposed new diagnostic criteria and the new proposed lexicon for AD are conceptually attractive. However, the evidence about the instrumental and laboratory markers for the diagnosis of the preclinical and asymptomatic states of the disease are, until to now, insufficient to support the routine clinical use of these investigations.

Although not specifically evaluated in this position paper, it is panelists' opinion that selected dementia centers, with recognized expertise, may provide CSF analysis

and morphological and functional imaging in selected patients both for differential diagnosis in dementia with atypical presentations and for population enrichment in clinical trials.

The limited usefulness of present laboratory and instrumental markers in clinical practice does not extend to the field of research, where the markers maintain huge interest for the purpose of improving human health.

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