A NOTE ON CHANGING APPROACH TO DIAGNOSIS OF ALZHEIMER'S DISEASE

***Antonio Tartaglione,[1,2] Massimo Del Sette[1]**

1. Department of Neurology, Ospedale S. Andrea, La Spezia, Italy
2. Laboratorio della Memoria, RSA Felicia, La Spezia, Italy
**Correspondence to ntntartaglione@gmail.com*

Disclosure: No potential conflict of interest.
Received: 04.03.14 **Accepted:** 23.04.14
Citation: EMJ Neurol. 2014;1:87-94.

ABSTRACT

This short review summarises the conclusions of two different series of studies set out to revise the 1984 National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria for the diagnosis of Alzheimer's disease (AD). The role of AD-pathology (AD-P), the characteristics of AD clinical expression, and the importance of positivity of biomarkers are concisely surveyed, and the diverging position of different research groups in reference to predementia AD are outlined. The importance of other factors such as age, inflammatory changes, and vascular pathology, which can variably interact with the main feature of AD, is signalled and some clinical questions are raised.

Keywords: Mild cognitive impairment, Alzheimer's disease, dementia, neurodegeneration, biomarkers.

INTRODUCTION

25 years after the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) position paper on Alzheimer's Disease (AD),[1] the vast amount of clinical and biological data available urged for a revision of the argument. The results were summarised in two series of recommendation papers, one from the International Working Group for New Research Criteria for the Diagnosis of AD (IWG),[2-4] the other, from the National Institute on Aging-Alzheimer's Association (NIA-AA).[5-7] Later, the Italian Society for the study of Dementias (SINDEM)[8] adhered to part of the IWG positions.

In December 2012, researchers from both groups convened to a symposium held in Stockholm to summarise the respective positions as recently reported.[9,10] This short review is intended to approach some aspects of the two positions, summarising the common starting points and revising their different conclusions in the light of old and new findings. Clinical syndromes outlined in the Key Symposium[9] are reported in Tables 1 and 2 which respectively refer to IWG and NIA-AA criteria.

As it can be seen, the Symposium proposes that the term 'symptomatic AD' be used to describe the entire clinical spectrum of AD, from the earliest symptomatic stages (mild cognitive impairment (MCI)/prodromal AD) to the most severe. The two positions, however, differ mainly with respect to the criteria adopted to define the predementia state. Therefore, our analysis will focus on this early phase of sporadic late-onset AD. Although recommendations are addressed to research, their relevance will be examined by the viewpoint of the clinician.

THE REFERENCE MODEL

NINCDS-ADRDA criteria for AD diagnosis required the initial identification of a specified type of dementia.[1] The absence of alternative pathologies, which decline might be referred to, completed the requirements. Thus, AD diagnosis implied that dementia was inescapably associated to AD-pathology (AD-P), and by converse, neuropathological lesions were excluded in absence of AD dementia.

Contrariwise, the new criteria maintain that AD-P can exist in the absence of dementia. Such a position shared by all the groups[4,5] is related to the progress in knowledge of AD markers and of the corresponding biology. Namely, biomarkers shown in neuropathologically-confirmed AD[11] can be found also in normal patients where they predict the future conversion to full-blown dementia with fair accuracy.[12] Their presence broadens the range of AD-clinical syndromes (AD-C), allowing identification of an early phase, which starts long before the appearance of AD dementia (Tables 1 and 2).

Two series of biomarkers have been identified,[3,5] one related to the AD-associated amyloid deposition, and the other, to neuronal dysfunction. The biomarkers of amyloidosis are: 1) increase in amyloid β (Aβ) burden as shown by positron emission tomography (PET) imaging with Pittsburgh Compound B (PiB-PET);[13,14] 2) reduction of amount of Aβ peptide in cerebrospinal fluid (CSF). The biomarkers of neuronal damage or dysfunction are: 1) elevated CSF tau protein; 2) hypometabolism in an AD-like pattern (i.e. in posterior cingulate, precuneus, and/or temporoparietal cortices) on fluorodeoxyglucose-PET (FDG-PET); and 3) hippocampal atrophy on volumetric magnetic resonance imaging (MRI) and cortical thinning in specific areas, as lateral and medial parietal, posterior cingulate, and lateral temporal cortices.

Relevance of biomarker changes is credited by both approaches as reported in Tables 1 and 2. According to IWG criteria biomarkers function as surrogates for pathophysiological lesions in AD and are incorporated to diagnosis.

Conversely, NIA-AA considers them simply a support for the diagnosis. Cautiously, indeed, NIA-AA reviewers observed that more work is needed to establish the optimal PET, MRI, biofluid techniques, their normal thresholds, and their reliability.[6] Furthermore, questions have been raised by the weak intra-individual correlations among amyloid accumulation at PET, reduction of CSF amyloid, and increase of CSF tau.[15] Finally, it has been shown that a positive PiB-PET scan does not necessarily imply the presence of AD-P neuropathology, as cerebral amyloid angiopathy[16] can lead to dementia with a typical AD distribution scan[17] even in absence of AD-P. Therefore, NIA-AA operates with 'core clinical criteria' - also for MCI - and suggests that biomarkers are only used for research purposes. IWG criteria do not sufficiently address this issue.

Overall the model refers to the amyloid cascade hypothesis whose core signs are represented by formation of amyloid plaques and aggregation of neurofibrillary tangles (NFT).[18] AD-P starts with the deposition of Aβ, which, once it reaches toxic concentration, is followed by changes of the properties of tau, a microtubule-associated protein and the major constituent of NFT. These first emerge during normal ageing in the basolateral cortical strip where cholinergic axons arising from the nucleus basalis of Meynert travel towards the mesial temporal cortex.

Table 1: International Working Group for new research criteria for the diagnosis of Alzheimer's disease (AD) (*Modified from Morris et al.*[9]).

		Presence of impairment on memory tests	Evidence of biomarkers *in vivo*	Additional requirements
Alzheimer's Disease	Prodromal AD	Required	Required	Absence of dementia
	AD dementia	Required	Required	Presence of dementia
Preclinical AD	Asymptomatic at risk for AD	Not present	Required	Absence of AD Symptoms
	Presymptomatic AD	Not present	Not required	Absence of AD Symptoms; presence of AD mutation
	Mild cognitive impairment	Not required	Not required	Absence of AD Symptoms or biomarkers

Table 2: National Institute of Aging and the Alzheimer's Association (NIA-AA) for new research criteria for the diagnosis of Alzheimer's disease (AD) (*Modified from Morris et al.[9] and Petersen et al.[31]*).

AD Dementia	Key criteria remain unchanged from the 1984 McKhann et al.[1] criteria for 'probable AD' except now allow nonamnestic presentations of AD dementia; Identify intra-individual decline in cognition and function as the salient clinical features AD biomarkers enhance confidence in clinical diagnosis
Preclinical AD	Refers to the pathophysiological stage when *in vivo* molecular biomarkers of AD are present, but symptoms are absent. Establish that AD has a long asymptomatic stage Can only be identified with *in vivo* AD biomarkers
Mild cognitive impairment	A diagnosis of MCI due to AD requires evidence of intra-individual decline, manifested by: Self or informant reported complain Objective cognitive impairment Preserved independence un functional abilities Increased diagnostic confidence may be suggested by positive Aβ biomarker and a positive degeneration biomarker

Here, in its component structures as piriform cortex, amygdala, hippocampus, and enthorinal cortex, NFT reach their maximum concentration in MCI and AD.[19,20] Once filamentous tau has been formed, it can be transmitted to other brain regions, likely along different network systems.[21,22]

NIA-AA criteria suggest a model for staging preclinical AD grounded on a hypothetical temporal ordering of different biomarkers. According to the model, biomarkers of Aβ deposition become abnormal early, before neurodegeneration and clinical symptoms occur. Biomarkers of neuronal injury, dysfunction, and neurodegeneration become abnormal later in the disease. Cognitive symptoms are directly related to biomarkers of neurodegeneration rather than biomarkers of Aβ deposition. Thus, hippocampal atrophy is followed by episodic memory impairment, grey matter atrophy, and finally, by changes in non-memory cognitive domains.[23,24]

Aβ deposition was estimated to start around 17 years before the onset of dementia, whereas hippocampal atrophy and memory impairment were considered to become abnormal about 3–6 years before the onset of dementia. Although this statement raises some doubt,[25] it evidences how lengthy the processes involved in AD may be.

ASYMPTOMATIC AT RISK OR PRECLINICAL STAGE?

According to the IWG criteria, this stage includes cognitively normal (CN) individuals presenting changes of one or both series of biomarkers (i.e. of amyloidosis and of neuronal damage).

Recommendations differentiate 'presymptomatic AD' from 'asymptomatic at risk state for AD'.[3,4] The first category refers to an individual who certainly will develop AD due to the presence of a fully genetic mutation. The second one includes patients who might develop AD as shown by autopsies of CN patients which document the occurrence of AD-P.[26,27]

Such a possibility is well known and many examples are offered of severe AD-P in ageing patients,[28] defined as 'healthy' for their normal levels of cognitive performances and their adequacy in functional abilities.[29] It has been observed that neuropathologic lesions can be associated with an incredible range of clinical manifestations from no symptoms to severe deficits.[30] No direct relationship exists between symptoms and the severity of lesions. Mostly lesions are mild or moderate but there can also be a very severe spread of AD-P[30] to the whole brain.

Conversion from prodromal at risk state to AD might depend on the degree of pathology present in the brain of the individual as well as the degree of resistance to the clinical expression of lesions related to individual susceptibility, including genetic factors (e.g. Apolipoprotein E ApoE genotype), risk or protective factors (e.g. vascular factors, diet, etc.), compensatory mechanisms (e.g. cognitive reserve), and comorbidities (e.g. diabetes).[3] These factors can modulate the risk of developing clinical symptoms, but from present data it is not possible to determine whether an individual is in a position to maintain a state of healthy ageing, remaining asymptomatic, and why. From the practical point of view, this category is profitable in so far as it offers the rationale for looking at factors able to influence the clinical picture, and for orienting the search for suitable treatments.

Opposite to this position, NIA-AA recommendations see biomarker changes in CN individuals as a starting point of the AD pathway so that, if they live long enough, they will progress to MCI and then to dementia. The syndrome is identified as a preclinical stage and – with the limitations already mentioned in the previous paragraph - its fate seems to be unavoidable along a continuum where AD-P modifications are the beginning of the path and dementia the end-stage of pathologic accumulation.[5]

Admittedly patients in the group might present subtle cognitive decline (SCD), namely a low cognitive performance,[6] which does not yet meet the standardised criteria for MCI.[7] The meaning of SCD and its relationship with MCI are not clear and they have been a matter of discussion.[31,32] Operationally, their cognitive performance has been conventionally set below a cutpoint corresponding to the 10th percentile of normal performance.[33-35] In keeping with the hypothesis of the ordered change of biomarkers, such a condition has been partitioned into three stages of growing severity.[6] Namely: 1) stage of asymptomatic cerebral amyloidosis with biomarker evidence of Aβ accumulation and normal cognitive and behavioural performances; 2) stage of amyloid positivity plus evidence of one or more markers of neuronal injury in absence of cognitive changes; 3) stage of amyloid positivity plus evidence of neurodegeneration and SCD. The attempt to validate the stage hypothesis revealed a more composite picture. Besides the three stages early predicted, a further condition had to be added, identified as suspected non-AD pathophysiology (s-NAP).[34,35] Individuals in this class, with or without signs of SCD, were characterised by pathological changes in biomarkers of neuronal damage in presence of normal biomarkers of amyloidosis. A Stage 0, characterised by normal biomarkers and an 'unclassified' category, completed the scheme.

Figure 1 presents the distribution of the preclinical subjects (green bars) as computed by averaging the data of frequency distributions reported by two studies[34,35] whose results coincided perfectly with each other, as noted,[31] despite the different techniques applied.

PRODROMAL AD OR MCI?

MCI definition is the point of maximal divergence between IWG and NIA-AA groups. On one side, the patient population is split into a Prodromal-AD (Prod-AD) group and a more generic MCI group. In the other, the classic definition holds true.[10,36-38]

Prod-AD refers to the patients who have AD both neuropathologically and clinically, before they meet the criteria for dementia, since AD signs are already present in these early stages, as reported.[3]

Prodromal AD neuropathology is characterised by a reduction of hippocampus volume,[39] whose atrophy has a predictive value.[40] These data fit well with pathological studies, which point at the mesial temporal lobe structures as the starting point of the degenerative process. Given the role of these structures in memory trace consolidation, such anatomic notion is in keeping with early and severe deficits of episodic memory presenting the characters of AD defect which regards encoding and retrieval of memorandum. Prod-AD patients present the same defect at a much lower degree. Tests asking for free and cued recall performances (e.g. the Grober-Buschke paradigm) seem to identify AD memory changes more effectively than traditional measures of free recall. Thus, a defective performance to such a paradigm can identify Prod-AD and predict incipient AD, differentiating its specific memory change from that of normal elders. According to IWG group, the Prod-AD category allows a more reliable estimate of incipient AD with respect to the common definition of MCI.

The relevance of this type of defect and the specificity of a particular test performance raised much interest and debate. Inconsistencies among

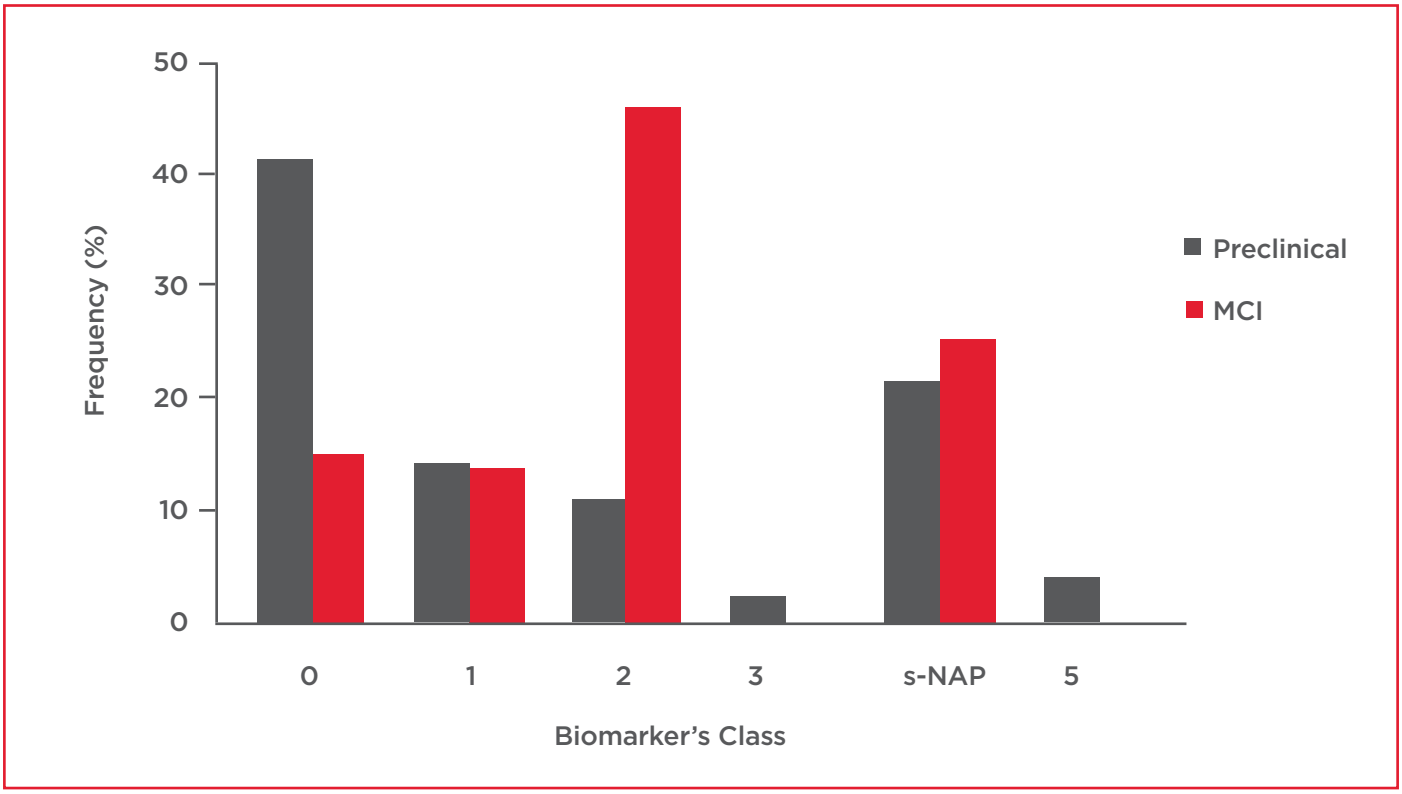

Figure 1: There is no apparent order in biomarker changes when passing from preclinical stage to mild cognitive impairment (MCI). Frequency distribution of biomarker classes in preclinical stage are obtained by averaging data from Jack et al.[34] and Vos et al.,[35] and those in MCI are drawn from Petersen et al.[44]
Biomarker class definition: 0 - Biomarkers negative; 1 - Amyloid only; 2 - Amyloid + neurodegeneration; 3 - Amyloid + Neurodegeneration + Subtle Cognitive Decline; 4 - suspected non-Alzheimer's disease pathophysiology- Neurodegeneration only; 5 - Unclassified.

results, however, suggest further studies before accepting the conclusion that AD conversion can be predicted by simply using a specific test paradigm.[41]

NIA-AA criteria still consider MCI a useful diagnostic category,[7] however difficult its definition might be. The diagnosis of MCI due to AD requires evidence of objective memory or cognitive impairment, adequacy in activities of daily living, and absence of dementia.[10] Patients in this group evolve toward dementia more frequently than CN individuals, though AD is not necessarily their final evolution.

Heterogeneity of MCI population, however, is great depending on many different factors. It is clear that MCI population varies within and among case series since the diagnosis applies to elderly individuals complaining of cognitive changes, irrespective of the aetiology or potential evolution of these changes. It includes, for example, physiological changes of ageing, functional disturbances of depression or drug-induced states, and pathological entities of brain degenerative processes or early AD. The same defect - lack of memory - may depend on the impairment of different functional processes (encoding, consolidation or retrieval) and may underlay distinct, non-overlapping, neuropathologic states.[3]

Furthermore, MCI variability mirrors the uncertain limits of normal ageing, whose definition may differ among studies. Lack of operational criteria for the identification of tests relevant to discriminate 'normal' versus 'pathological' performance may influence the individual diagnosis of MCI.[41] Stimulus modality, structure of the memorandum facilities to improve encoding and recall, the protocol itself (including one or more memory tests), and the level of normal cut-off (set at 1 or 1.5 standard deviation[42]) are influential. All these parameters can identify different sectors of the population and yield different predictions about their outcome.[41]

At the other extreme of the continuum, the definition of dementia can influence the prevalence of MCI patients. Dementia can vary from 13-31% depending on whether Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or International Classification of Diseases (ICD-10) criteria are applied.[43] Provided that the normal cut-off is held constant, the definition of dementia can influence the prevalence of MCI in a trade-off between the extension of the demented population and that of MCI. In the presence of a more demanding definition, e.g. ICD-10, the prevalence of MCI broadens to include patients who would be considered demented by the more lenient DSM-IV definition. Attention, therefore, is to be paid to all these parameters in order to reduce the heterogeneity of the group and to avoid bias in the analysis.

Increased diagnostic confidence may be suggested by positive Aβ biomarker, associated or not to an abnormal degeneration biomarker. As reported in Figure 1 (orange bars) the definition of MCI patients[44] includes patients who are in Stage 0 with normal biomarkers, or fall in the group of s-NAP where the lack of amyloidosis is associated with positive markers of neuronal damage.

FACTORS OF COMPLEXITY

The relationship between clinical picture and biomarkers, however, needs additional specifications. It has been shown that the within-subject levels of β-amyloidosis, measured by CSF Aβ, are minimally correlated with tau[45] and both correlate significantly with PiB-PET. This suggests that independent processes, one reflected by CSF Aβ and one by CSF tau, contribute to the preclinical development of fibrillar amyloid plaques.[45]

In a search[46] for differences in pathophysiological mechanisms at work in the normal elderly population, s-NAP subjects were compared to individuals with β-amyloidosis (i.e. in Stage 2 and 3; cfr Figure 1). Results showed that the two groups were similar in all the parameters investigated (PiB-PET, FDG-PET, hippocampal atrophy). The outcome confirms that β-amyloidosis is not the initial and causal AD event in CN elderly but that AD is to be considered as a multiparameter pathology subtended by several, partly independent, pathological processes.[45-47] The amyloid cascade hypothesis, indeed, does not take into account the role of other factors in modulating late changes of the brain; some of them will be listed below.

Age is an important risk factor, as implied by Perusini[48] when noting that neurofibrillary alterations very closely resembled 'the histo-pathological findings occurring in the involution of the brain during old age'. Since then, interpretation has been swinging from a position which sees AD as an exaggerated caricature of brain ageing, to the other, which views AD as a process that drops into age changes, mingling with its mechanisms.[49]

Actually, the relationship between AD-P and dementia changes as a function of age. The correlation between plaque and tangle burden versus cognitive status, which holds in younger AD patients, does not in older ones.[50]

Since elderly people without dementia may have pathological features of AD,[27,30] it has been possible to compare the neuropathological data of patients who have died with and without dementia. The results indicate that the prevalence of AD-P in patients who died from dementia remains constant or tends to decline with age, whereas the burden of Alzheimer's-type disease in patients dying without dementia increases with the age at death. There is a convergence of AD-P features in people with and without dementia at a very advanced age, so that the same burden of pathological features can be frequently found in age-related people who did not have dementia.[51]

In contrast, cortical atrophy, which reflects many other factors beyond plaque and tangle burden,[52] increases with age and continues to differentiate people with dementia from those without it in all age groups. Atrophy emerges as a robust marker of the accumulation of pathological lesions, not only plaques and tangles, and of the failure of compensatory mechanisms, both of which lead to dementia.[53]

Inflammation and activation of microglia, the predominant macrophage species within the brain, are the main features of AD. PET imaging of microglia and fibrillar amyloid, indeed, shows that levels of respective markers in the cortex of patients with AD are higher than those of non-demented controls. Microglial cells which accumulate around amyloid plaques in the brains of individuals with AD, may adopt a proinflammatory profile with deleterious effects on neurons, synapses, and cognition.[53,54]

Useful information comes from amyloid-β immunisation which, unsuccessful as therapy, significantly reduced microglial responses long after treatment finished. Tau pathology is downgraded as well, witnessing the role of inflammatory changes on AD and confirming the relevance of microglia in neurodegenerative disorders.[55]

Comorbidity due to vascular changes may interfere with the clinical picture as shown by a large body of data.[56] Although the Hachinski Ischaemic Score helps to identify the vascular component in diagnosis, the application of standard clinical and pathological criteria leads to the reclassification of many clinical diagnoses of AD as mixed dementia.[57,58] On the other hand, it is well known that the most severe AD cases present a significant vascular component.[29,59]

CONCLUSION

Summing up, the data so far outlined, which are simply fragments of an enormous body of knowledge, highlighted some aspects of progress in AD debate. Further studies are expected to hit the central heart of the disease where clinical signs, biological parameters, and neuropathological processes compound into a unifying model.

NOTE

While this review was still in press, the IWG group presented a new version[60] of the diagnostic framework, confirming the previously published lexicon. Thus diagnosis of typical AD was allowed long before the appearance of dementia, if a specific memory defect (i.e. low free recall not normalised by cueing) occurred in the presence of biomarker changes. Likewise, the asymptomatic at-risk state was confirmed when biomarker changes occurred in the absence of a clinical phenotype.

REFERENCES

1. McKhann G et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34:939-44.

2. Dubois B. 'Prodromal Alzheimer's disease': a more useful concept than mild cognitive impairment? Curr Opin Neurol. 2000;13:367-9.

3. Dubois B et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007;6:734-46.

4. Dubois B et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9:1118-27.

5. Jack CRJ et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:257-62.

6. Sperling RA et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:280-92.

7. Albert MS et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270-9.

8. Musicco M et al. Position paper of the Italian Society for the study of Dementias (Sindem) on the proposal of a new lexicon on Alzheimer disease. Neurol Sci. 2012;33:201-8.

9. Morris JC et al. Harmonized diagnostic criteria for Alzheimer's disease: recommendations. J Intern Med. 2014;275:204-13.

10. Petersen RC. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014;275:214-28.

11. Blennow K et al. Alzheimer's disease. Lancet. 2006;368:387-403.

12. Hansson O et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol. 2006;5:228-34.

13. Rowe CC, Villemagne VL. Brain amyloid imaging. J Nucl Med. 2011;52:1733-40.

14. Masdeu JC et al. The neurobiology of Alzheimer disease defined by neuroimaging. Curr Opin Neurol. 2012;25:410-20.

15. Toledo JB et al. Factors affecting Aβ plasma levels and their utility as biomarkers in ADNI. Acta Neuropathol. 2011;122:401-13.

16. Bugiani O. A beta-related cerebral amyloid angiopathy. Neurol Sci. 2004;25 Suppl 1:S1-2.

17. Ducharme S et al. Does a positive pittsburgh compound B scan in a patient with dementia equal Alzheimer disease? JAMA Neurol. 2013;70:912-4.

18. Ballard C et al. Alzheimer's disease. Lancet. 2011;377:1019-31.

19. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging. 1997;18:351-7.

20. Mesulam M. Cholinergic aspects of aging and Alzheimer's disease. Biol Psychiatry. 2012;71:760-1.

21. Mesulam M. Defining neurocognitive networks in the BOLD new world of computed connectivity. Neuron. 2009;62:1-3.

22. Seeley WW et al. Neurodegenerative diseases target large-scale human brain networks. Neuron. 2009;62:42-52.

23. Jack CRJ et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119-28.

24. Villemagne VL et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study.

Lancet Neurol. 2013;12:357-67.

25. Schneider LS. Quantifying an amyloid β model for Alzheimer's disease. Lancet Neurol. 2013;12:327-8.

26. Tomlinson BE et al. Observations on the brains of non-demented old people. J Neurol Sci. 1968;7:331-56.

27. Bennett DA et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006;66:1837-44.

28. Snowdon DA. Aging and Alzheimer's disease: lessons from the Nun Study. Gerontologist. 1997;37:150-6.

29. Tyas SL et al. Healthy ageing in the Nun Study: definition and neuropathologic correlates. Age Ageing. 2007;36:650-5.

30. Snowdon, DA. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med. 2003;139:450-4.

31. Petersen RC. Do preclinical Alzheimer's disease criteria work? Lancet Neurol. 2013;12:933-5.

32. Fagan AM, Vos SJB. Preclinical Alzheimer's disease criteria. Lancet Neurol. 2013;12:1134.

33. Knopman DS et al. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. Neurology. 2012;78:1576-82.

34. Jack CRJ et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. Ann Neurol. 2012;71:765-75.

35. Vos SJ et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol. 2013;12: 957-65.

36. Petersen RC et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56:303-8.

37. Gauthier S et al. Mild cognitive impairment. Lancet. 2006;367:1262-70.

38. Petersen RC et al. Mild cognitive impairment: ten years later. Arch Neurol. 2009;66:1447-55.

39. Fox NC, Schott JM. Imaging cerebral atrophy: normal ageing to Alzheimer's disease. Lancet. 2004;363:392-4.

40. Rusinek H et al. Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging. Radiology. 2003;229:691-6.

41. Gainotti G et al. Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer's disease. J Alzheimers Dis. 2014;38:481-95.

42. Busse A et al. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). Br J Psychiatry. 2003,182:449-54.

43. Erkinjuntti T et al. The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med. 1997;337:1667-74.

44. Petersen RC et al. Mild Cognitive Impairment due to Alzheimer Disease in the Community. Ann Neurol. 2013;74: 199-208.

45. Storandt M et al. Toward a multifactorial model of Alzheimer disease. Neurobiol Aging. 2012;33:2262-71.

46. Knopman DS. Brain injury biomarkers are not dependent on β-amyloid in normal elderly. Ann Neurol. 2013;73:472-80.

47. Chételat G. Alzheimer disease: Aβ-independent processes-rethinking preclinical AD. Nat Rev Neurol. 2013;9: 123-4.

48. Perusini G, "The nosographic value of some characteristic histopathological findings in senility" [Sul valore nosografico di alcuni reperti istopatologici caratteristici per la senilità], Rivista Italiana di Neuropatologia, Psichiatria ed Elettroterapia. 1911;4:193-213), Bick K et al (eds.), The early story of Alzheimer's disease (1987), Italy: Liviana Press, pp. 129-47.

49. Bugiani O. Alzheimer's disease: ageing-related or age-related? New hypotheses from an old debate. Neurol Sci. 2011;32:1241-7.

50. Prohovnik I et al. Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. Neurology. 2006;66:49-5.

51. Savva GM et al. Age, neuropathology, and dementia. N Engl J Med. 2009;360:2302-9.

52. Terry RD et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991;30:572-80.

53. Cagnin A et al. In-vivo measurement of activated microglia in dementia. Lancet. 2001;358:461-7.

54. Edison P et al. Microglia, amyloid, and cognition in Alzheimer's disease: an [11C](R)PK11195-PET and [11C]PIB-PET study. Neurobiol Dis. 2008;32:412-9.

55. Schott JM, Revesz T. Inflammation in Alzheimer's disease: insights from immunotherapy. Brain. 2013;136:2654-6.

56. Kling MA et al. Vascular disease and dementias: paradigm shifts to drive research in new directions. Alzheim Dement. 2013;9:76-92.

57. Hachinski V, Sposato LA. Dementia: from muddled diagnoses to treatable mechanisms. Brain. 2013;136:2652-4.

58. Bowler JV et al. Fallacies in the pathological confirmation of the diagnosis of Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1998;64:18-24.

59. Snowdon DA et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997;277:813-7.

60. Dubois B et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13:614-29.