Is there a neuropathology difference between mild cognitive impairment and dementia?

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Mild cognitive impairment (MCI) represents a clinical construct that identifies an intermediate state of cognitive function between that of healthy aging and memory and cognitive deficits associated with frank dementia. In most cases, the definition of MCI is intended to be applicable to those persons in the intermediate state of memory and cognitive impairment who are destined, if they live long enough, to meet criteria, at least clinically, for dementia or Alzheimer’s disease (AD). Although the causes of dementia and therefore MCI can vary widely, we will limit the discussion of the neuropathology of MCI to the role of postmortem neuropathological and neurobiological features that are commonly associated with AD. The criteria and definitions for MCI as initially described by the Canadian Study of Health and Aging,1,2 Reisberg et al,3-7 and Flicker8 in the late 1980s were relatively broad and permissive.

The number of studies that have investigated the neuropathology of mild cognitive impairment (MCI) is small, but growing. In this paper we have restricted our focus to the consideration of the presence and extent of postmortem findings relevant to the neuropathology of Alzheimer’s disease. We have drawn from studies that have investigated the postmortem neurobiology of the brains of persons with cognitive function at the interface between unimpaired normal function and mild but definite dementia. The data derived from these studies suggest that i) the brains of persons with MCI evidence significant neuropathological and neurobiological changes relative to those without cognitive impairment; ii) in general, the neuropathological and neurobiological changes are qualitatively similar to those observed in the brains of persons with frank AD-like dementia; and iii) the neuropathological and neurobiological brain changes associated with MCI are quantitatively less than those of persons who meet criteria for dementia. Thus, the available, albeit limited, data suggests that MCI is associated with the early stages of the neurobiological and neuropathological changes that culminate in the florid lesions of AD, including the accumulation of neuritic plaques, neurofibrillary tangles, synaptic and neurotransmitter associated deficits, and significant neuronal cell death.

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Subsequent clinical studies suggested that some individuals with MCI remain in this intermediate stage of cognitive function for longer periods of time than expected. The criteria/definitions were then further refined to include amnestic MCI (i.e., predominantly memory impairment cases expected to be predisposed to progress to dementia) and nonamnestic MCI (i.e., non-memory-impairment cases expected to be predisposed to progress to dementia before they die and come to autopsy. The neuroimaging literature of pathological changes, such as atrophy and sclerosis, in the hippocampus and entorhinal cortex, and the likely development of amyloid plaques based on molecular neuroimaging, by positron emission tomography (PET) using an amyloid-β-peptide (Aβ) ligand known as Pittsburgh Compound B (PiB). The validity of PET studies with PiB has been bolstered by a limited number of in vivo imaging and postmortem neuropathology studies, and one recent study that combined PiB-PET with neuropathological study of brain biopsy specimens. The neuroimaging literature in MCI has been reviewed recently. An issue that influences how we interpret postmortem neurobiological studies of MCI and dementia is the way that neuropathological criteria are applied and the way that experiments are designed. It is important to recognize that neuropathological criteria such as the CERAD or NIA/Reagan criteria are probabilistic constructs designed to distinguish between persons with significant AD neuropathology and those without. The probabilistic nature of these criteria stems from the recognition that there are significant instances of persons with no cognitive impairment who nevertheless evidence unusually high levels of AD-associated neuropathology, and instances of persons with clinically diagnosed AD-like dementia who present with little or no discernable neuropathology. In addition, age, the most significant risk factor for dementia, also plays a role in the extent of AD-associated neuropathology observed in the brain, irrespective of the presence or absence of dementia symptoms. Thus, if questions regarding the presence, absence, or extent of neuropathologic lesions or neurobiological changes are framed in the context of whether persons with MCI meet neuropathological criteria for AD, the results may lead to very different conclusions than if the questions are framed within the context of whether persons with MCI present with lesion densities or neurobiological changes that are different from those without cognitive impairments. In general, the brains of persons with MCI do not meet neuropathological criteria for AD, but they nevertheless evidence pathological features that are qualitatively, but not quantitatively, AD-like (please see below). An illustrative example is a study of the association of neuritic plaques with cognitive compromise as defined by the CDR. Persons with no cognitive impairment were compared with those with different levels of impairment. Persons with CDRs of 0.5 (i.e., MCI), had cortical neuritic plaque densities that were significantly higher than that of persons with intact cognition. Yet, the
majority of the studied sample with CDR scores of 0.5 and even those with CDR scores of 1 did not meet accepted neuropathological criteria for AD. Similar results have been reported using different MCI classification schemes and different metrics of AD-associated lesion densities (eg, ref 37).

**General neuropathology**

The majority of the studies of the neuropathology of MCI, especially degenerative/amnestic MCI, suggest that in most instances MCI is associated with a less fervent manifestation of the neuropathologies that are generally associated with dementia. Unselected MCI samples derived from memory clinic or general geriatric populations evidence a variety of neuropathologic lesions such as those associated with diffuse Lewy body disease, cerebrovascular disease, ischemic changes and hippocampal sclerosis, argyrophilic grain disease, Parkinson’s disease, and, of course, AD (eg, refs 37-40). Nearly invariably, the extent of these lesions is considerably less than those observed in persons with frank dementia. In general, relative to persons with intact cognition, the frequency of AD-associated neuropathology in persons with MCI, especially those with amnestic MCI, is significantly greater than other neuropathologic lesions associated with dementia.

**Hallmark lesions of AD**

Alzheimer’s disease is characterized by extracellular neuritic plaques (NP) and intracellular neurofibrillary tangles (NFT). Early studies by Morris et al suggested that in MCI there is less involvement in MCI than in persons with frank dementia (ie, CDR>1). Similar changes were noted recently in a study where the definition of MCI was restricted to those persons with amnestic MCI as defined by Petersen et al. In that study, the numbers of neocortical diffuse plaques were not significantly elevated in MCI, but the numbers of NPs were significantly higher than those in persons with intact cognition. Since the pathogenic constituent of NPs is the Aβ peptide, it is not surprising that Aβ levels in the brains of persons with MCI are also significantly elevated. Just as diffuse plaques may represent premature NPs, oligomeric forms of Aβ may precede the diffuse aggregates and represent an even earlier neurotoxic form of Aβ. The question of the association of oligomeric forms of Aβ in MCI is an area of current investigation by many laboratories (see below). As mentioned previously, these observations of plaque involvement in MCI are consistent with neuroimaging/PET studies of MCI using PiB.

Generally similar conclusions can be drawn regarding the involvement of NFTs in MCI. However, the precise distribution of NFTs within neocortical and medial temporal lobe structures and the phosphorylation or conformational state of the tau protein constituent of NFTs may be critical factors. Several studies have found that the density of NFTs in the hippocampus and the parahippocampal gyrus as well as the amygdala increase significantly in persons with MCI (eg, refs 39,49). Most studies find that the NFT involvement in neocortical regions is associated with more advanced cognitive impairment, supporting the staged development of NFT pathology as a function of AD progression. The development of early NFT pathology and its progression is further supported by cellular studies. Stereological analyses have shown that, at least in the neocortex, MCI or early AD-associated NFTs develop first in degeneration-susceptible large neurons of layers III and V of the frontal cortex, implicating long-track association circuits of the brain. Multivariate analyses of NFTs with an emphasis on early conformational changes of tau in the frontal cortex support these observations. On the other hand, other studies (eg, refs 44,63) have noted an age-dependent increase in NFTs, like those cited above, but they have found NFT association with cognitive function relatively late in the course of disease. A possible explanation of these apparently discrepant results may lie in the...
way that NFTs develop. Just as NPs are thought to evolve (from diffuse to cored to neuritic), NFTs develop gradually through changes in protein structure. NFTs are comprised of paired-helical filaments that are aggregates of the microtubule-associated protein tau that have undergone abnormal conformation and phosphorylation. Several studies suggest that even when an association between MCI and histopathological indices of NFTs is not identified, changes in the phosphorylation or conformation state of tau are associated with MCI (eg, refs 76,77). In addition, recent studies suggest that the neurofilament protein tau within the AD-vulnerable cholinergic neurons of the nucleus basalis of Meynert (NBM) and noradrenergic neurons within the brainstem locus ceruleus become conformationally altered or hyperphosphorylated in MCI.

**Neuronal and synaptic loss**

Although NPs and NFTs are hallmark and diagnostic lesions for AD, their net effect on cognitive function may be expressed through cell death and/or loss of synapses. Only a few studies have examined neuronal or synaptic loss in MCI directly, eg, refs 76-80. Several of these studies used stereological techniques and found significant loss of neurons in the frontal cortex, the entorhinal cortex and the CA1 field of the hippocampus. An interesting feature of one of these studies was that the neuronal loss exceeded the number of NFT-bearing neurons. This observation could suggest that in addition to NFTs, other factors influence neuronal loss in MCI and AD; but it can also be argued that the greater neuronal loss reflects the death and elimination of NFT-bearing neurons, and the survival of other NFT-bearing neurons that have not yet been eliminated from the neuronal pool. On the other hand, other studies have noted that detectable cell loss does not occur in the brains of persons with MCI, but is evident in the brain of more cognitively impaired early AD persons. Credence for this hypothesis can be derived by the observation that in at least one of the studies reporting MCI-associated cell loss, the subjects included in the MCI group evidenced sufficient NP and NFT lesions to meet diagnostic criteria for AD. This observation raises the possibility that persons classified as MCI in this study were in a more advanced stage of cognitive impairment than those assessed in some of the other studies (eg, ref 79). Clearly, the number of studies that have investigated the question of neuronal loss in MCI, and the number of cases of MCI samples in each of these studies is too small to justify firm conclusions. However, the cited studies all suggest that neuronal loss is a feature of cognitive compromise that can be observed early in the dementing process, even if absent at the very earliest stages of impairment.

That more subtle cellular changes occur also in MCI is supported by recent studies that suggest that, while some neurons are lost in MCI, others, especially those in the cerebral cortex, hippocampus, and NBM, undergo hypertrophy of their nuclear volumes. It has been hypothesized that these cellular changes may reflect a compensatory state that forestalls cell death in MCI. Although the numbers of studies are still very limited, there is growing emphasis on exposing the neurobiological mechanisms responsible for cell death in MCI. The toxicity of Aβ and Aβ oligomers mentioned above is one example, as is the susceptibility of some neurons to oxidative stress and the expression and response to neurotrophic factors. One recently emergent concept that is consistent with neuronal loss in MCI and AD is the abnormal re-execution of cell division/cycle programs in neurons and the abnormal expression of cell-cycle related genes and proteins. Unquestionably, these divergent mechanisms may not be mutually exclusive and many other cellular processes are likely to play important roles in MCI-associated cell loss. These and other similar studies underscore the clear imperative for future research to more fully describe the mechanistic processes that contribute to neuronal death.

Early studies (eg, ref 74), that have since been replicated multiple times, showed that the cholinergic neurons of the NBM were especially vulnerable to degeneration in AD. This finding was highly consistent with even earlier observations that the activities of cholinergic enzymes are significantly reduced in AD. Several studies (eg, refs 95,96) indicated that although the cholinergic deficits in AD were profound, they became manifest only in the late stages of cognitive impairment. More recent reports have suggested that MCI is associated with more subtle cholinergic abnormalities that may be indicative of compensatory changes. These detailed studies of MCI found that the activities of cholinergic marker enzymes rose in multiple cortical regions and in the hippocampus of persons with MCI, but then returned to levels comparable to that of nondemented individuals in early AD and early dementia cases before decreasing to below normal in advanced AD. That the MCI-associated
Neuropathology of MCI in the oldest old

Until recently, most studies of the neurobiological substrates of dementia and AD have focused on persons in the 65 to 85 years of age range or have not specifically differentiated between different age groups within the elderly population. However, US Census Bureau data and projections\(^{105,106}\) show that the number of Americans over the age of 85 (4.4 million in 2001) will rise significantly by 2010 to 5.8 million and will quadruple to 19.3 million by 2050 (http://www.census.gov/population/www/projections/natdet-D1A.html). Of these 19.3 million, 8 million are predicted to develop dementia\(^{107}\) with the prevalence of dementia increasing from 13% in 77- to 84-year-olds to 48% in persons 95 years old and older.\(^{108,109}\) Similarly, the incidence of dementia increases from 1% at age 65 to 21% to 47% at ages 85 and older.\(^{109-111}\) Only recently have studies begun to distinguish between “young-old,” often defined as those younger than 85 or 90, and oldest-old individuals (persons over the age of 85 or 90). That understanding the neurobiological substrates of dementia and MCI in this age group is important is highlighted by a recent study\(^{112}\) suggesting that even after controlling for physical disorders, 5-year mortality in persons 95 years and older is significantly higher in demented individuals than in those who are cognitively intact (96% vs 73%, respectively). In fact, dementia was a stronger predictor of mortality in this population than cardiovascular disease, cancer or male sex. The importance of this distinction has become even more apparent from recent evidence suggesting that the neuropathological substrates of dementia may be different in these two broad age categories. Accumulating evidence suggests that nonagenarians and centenarians display different patterns of cortical vulnerability to the neurodegenerative process compared with younger elderly, and it is not known whether correlations between clinical severity and neuropathological stages remain valid in this age group. Several investigations have noted that oldest-old participants who die with dementia frequently do not have the high amounts of the hallmark NP and NFT neuropathological lesions generally associated with dementia and/or AD\(^{113-121}\) (but see ref 43). One of these studies directly compared the density of neocortical and hippocampal NPs and NFTs in the brains of young-old individuals with CDR scores of 0.5, to similarly impaired oldest-old persons.\(^{121}\) As expected from the foregoing, a relatively high number of NPs and NFTs were associated with CDR 0.5 in young-old individuals, but the density of NPs and NFTs was not significantly higher in the brains of CDR 0.5 oldest-old persons. The failure of NFT-based neuropathological staging to distinguish between persons without cognitive impairment and those with MCI has also been reported in nonagenarians.\(^{122}\) Interestingly, the association of synaptic abnormalities and dementia appear to be relatively constant between young-old and oldest-old persons with frank dementia\(^{123}\) raising the possibility that the association of synaptic proteins with MCI noted in young old persons (see above) will also be true of oldest-old persons with MCI. Even when evidence of MCI associated neuropathology is found in the oldest-old, the neuroanatomical distribution of the lesions appears to vary from that of young-old persons. One quantitative study\(^{48}\) that investigated the distribution of NPs and NFTs within the different fields of the hippocampus in mild AD cases found modest associations...
of NFTs in the CA2 field of the hippocampus in the oldest-old, whereas NFTs in the CA1 field, which is more closely associated with dementia in younger persons, appeared to be relatively spared.

**Concluding remarks**

Given the clinical relevance of MCI and its importance and implications for the development of treatment approaches for dementia in the elderly, it is disappointing that direct postmortem and neurobiological studies of MCI are insufficient for firm conclusions. Many of the existing studies are marred by small sample sizes, insufficient clinical characterization, and experimental and practical constraints on consideration of crucial variables such as age, symptom duration, and sex. Despite these limitations, the available data suggests that similar to the continuum of cognitive impairment, the AD-associated neurobiology and neuropathology of MCI are typified by prediagnostic mild changes that are qualitatively similar to those associated with the pathophysiology of AD dementia. Neuropathological, anatomical, and neurobiological studies of MCI in the oldest-old are even more sparse than age-indiscriminate studies or studies in young-old persons.

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REFERENCES

1. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet. 1997;349:1793-1796.

2. Fisk JD, Merry HR, Rockwood K. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. Neurology. 2003;61:1179-1184.

3. Reisberg B, Ferris SH, DeLeon MJ, Crook T. The Global Deterioration Scale for Assessment of Primary Degenerative Dementia. Am J Psychiatry. 1982;139:1136-1139.

4. Flicker C, Ferris SH, Reisberg B. A 2-year longitudinal-study of cognitive function in normal aging and Alzheimer's-disease. J Genet Psychiatry Neurol. 1993;8:84-96.

5. Kluger A, Ferris SH, Golomb J, Mittelman MS, Reisberg B. Neuropsychological prediction of decline to dementia in nondemented elderly. J Genet Psychiatry Neurol. 1999;12:168-179.

6. Kluger A, Gianutsos JG, Golomb J, et al. Patterns of motor impairment in normal aging, mild cognitive decline, and early Alzheimer's disease. J Gerontol Series B-Psychological Sciences and Social Sciences. 1997;52:28-39.

7. Kluger A, Gianutsos JG, Golomb J, Ferris SH, Reisberg B. Motor/psychomotor dysfunction in normal aging, mild cognitive decline, and early Alzheimer's disease: diagnostic and differential diagnostic features. Int Psychogeriatr. 1997;9:307-316.

8. Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. Neurology. 1991;41:1006-1009.

9. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment - beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256:240-246.

10. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256:183-194.

11. Petersen RC. Mild cognitive impairment: current research and clinical implications. Semin Neurol. 2007;27:22-31.

12. Petersen RC, Negash S. Mild cognitive impairment: an overview. CNS Spectr. 2008;13:45-53.

13. Mariani E, Monastero R, Mecocci P. Mild cognitive impairment: a systematic review. J Alzheimers Dis. 2007;12:23-35.

14. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. Neurology. 1993;43:2412-2414.

15. Piaggiopsi PP, Berardi D, Ferrari B, Quartesan R, De Ronchi D. Use concept models for clinical and research use. Brain Res Bull. 2006;68:227-232.

16. Fox NC, Crum WR, Scalfill RI, Stevens JM, Janssen JC, Rossor MN. Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. Lancet. 2001;358:201-205.

17. Killiany RJ, Gomez-Isla T, Moss M, et al. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol. 2000;47:430-439.

18. Jack CR, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology. 1999;52:1397-1403.

19. Jack CR, Petersen RC, Xu Y, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology. 2000;55:484-489.

20. Jack CR, Shiung MM, Weigand SD, et al. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. Neurology. 2005;65:1227-1231.

21. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. N Engl J Med. 1996;334:752-758.

22. Small GW, Mazzotti JC, Collins MT, et al. Apolipoprotein-e type-4 allele and cerebral glucose-metabolism in relatives at risk for familial Alzheimer-disease. JAMA. 1995;273:942-947.

23. Drzezga A, Grimmer T, Riemenschneider M, et al. Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. J Nucl Med. 2005;46:1625-1632.

24. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004;55:306-319.

25. Small GW, Kepe V, Ercoli LM, Siddarth P, Vinters HV, Satyamurthy N, Huang SC, Phelps ME, Barrio JR. FDDNP-PET binding differentiates MCI from dementia and increases with clinical progression. Alzheimer's Dementia. 2006;2:5318-5319.

26. Alzhenstein HJ, Nebes RD, Saxton JA, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol. 2008;65:1509-1517.

27. Tolboom N, Yaqub M, van der Flier WM, et al. Detection of Alzheimer Pathology In Vivo Using Both 11C-PIB and 18F-FDDNP PET. J Nucl Med. 2009;50:191-197.

28. Klunk WE. Biopsy support for the validity of Pittsburgh compound B positron emission tomography with a twist. Arch Neurol. 2008;65:1281-1283.

29. Leinonen V, Alafuzoff I, Aalto S, et al. Assessment of beta-amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B. Arch Neurol. 2008;65:1304-1309.

30. Matsuda H. The role of neuroimaging in mild cognitive impairment. Neuropsychology. 2007;27:570-577.

31. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991;41:479-486.

32. NIA-Reagan. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease: The National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Neurobiol Aging. 1997;18:51-52.

33. Crystal H, Dickson D, Fuld P, et al. Clinico-pathologic studies in dementia: nondemented subjects with pathologically confirmed Alzheimer's disease. Neurology. 1988;38:1682-1687.

34. Katzman R, Terry R, DeTeresa R, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol. 1988;23:138-144.

35. Haroutunian V, Perl DP, Purohit DP, et al. Regional distribution of neuritic plaques in the nondemented elderly and subjects with very mild Alzheimer disease. Arch Neurol. 1998;55:1185-91.

36. Khachaturian ZS. Diagnosis of Alzheimer's disease. Arch Neurol. 1985;42:1097-1105.

37. Petersen RC, Parisi JE, Dickson DW, et al. Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol. 2006;63:665-672.

38. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006;66:1837-1844.

39. Markesbery WR, Schmitt FA, Kryscio RJ, Davis DG, Smith CD, Wekstein DR. Neuropathologic substrate of mild cognitive impairment. Arch Neurol. 2006;63:36-48.

40. Saito Y, Murayama S. Neuropathology of mild cognitive impairment. Neurology. 2007;27:578-584.

41. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol. 2001;58:397-405.

42. Haroutunian V, Davies P, Vianna C, Buxbaum JD, Purohit DP. Tau protein abnormalities associated with the progression of Alzheimer disease type dementia. Neurobiol Aging. 2007;28:1-7.

43. Nelson PT, Jicha GA, Schmitt FA, et al. Clinico-pathologic correlations in a large elderly disease center autopsy cohort: neuritic plaques and neurofibrillary tangles “do count” when staging disease severity. J Neuropathol Exp Neurol. 2007;66:1136-1146.

44. Haroutunian V, Purohit DP, Perl DP, et al. Neurofibrillary tangles in nondemented elderly subjects and mild Alzheimer disease. Arch Neurol. 1999;56:713-8.

45. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging. 1997;18:351-357.

46. Von Gunten A, Kovaari E, Rivara CB, Bouras C, Hof PR, Giannakopoulos P. Stereologic analysis of hippocampal Alzheimer's disease pathology in the oldest-old: Evidence for sparing of the entorhinal cortex and CA1 field. Exp Neurol. 2005;193:198-206.
Bussiere T, Gold G, Kovari E, et al. Stereologic analysis of neurofibrillary tangle formation in prefrontal cortex area 9 in aging and Alzheimer’s disease.

Neuroscience. 2003;117:577-592.

Morris JC, Storandt M, McKeel DW, Jr, et al. Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and preclinical Alzheimer’s disease.

Neuropsychology. 1996;46:707-719.

Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer’s disease.

Neurobiol Aging. 1991;12:295-312.

Morris JC, McKeel DW, Jr, Storandt M, et al. Very mild Alzheimer’s disease: informant-based clinical, psychometric, and pathologic distinction from normal aging (comments).

Neurology. 1991;41:469-478.

Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome.

Arch Neurol. 1999;56:303-308.

Cataldo AM, Petanceska S, Terio NB, et al. Abeta localization in abnormal endosomes: association with earliest abeta elevations in AD and Down syndrome.

Neurobiol Aging. 2004;25:1263-1272.

Parvathy S, Davies P, Haroutunian V, et al. Correlation between Abeta-40, Abeta-42, and Abeta-43-containing amyloid plaques and cognitive decline.

Arch Neurol. 2001;58:2025-2032.

Naslund J, Haroutunian V, Mohs R, et al. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline.

JAMA. 2000;283:1571-1577.

Walsh DM, Selkoe DJ. A beta oligomer: a decade of discovery.

J Neurochem. 2007;101:1172-1184.

Hof PR, Blerer LM, Perl DP, et al. Evidence for early vulnerability of the medial and inferior aspects of the temporal lobe in an 82-year-old patient with preclinical signs of dementia. Regional and laminar distribution of neurofibrillary tangles and senile plaques.

Arch Neurol. 1992;49:946-953.

Bouras C, Hof PR, Morrison JH. Neurofibrillary tangle densities in the hippocampal-formation in a nondemented population define subgroups of patients with differential early pathological changes.

Neurosci Lett. 1993;153:131-135.

Giannakopoulos P, Hermann FR, Bussiere T, et al. Tangle and neuron number loss at 6-month amyloid load, predict cognitive status in Alzheimer’s disease.

Neurology. 2003;60:1495-1500.

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer’s disease.

Neurology. 1992;42:631-639.

Mesulam M, Shaw P, Mash D, Weintraub S. Cholinergic nuclear basalis tautopathy emerges early in the aging-MCI-AD continuum.

Ann Neurol. 2004;55:815-822.

Braak H, Braak E. Evolution of the neuropathology of Alzheimer’s disease.

Acta Neurol Scand Suppl. 1996;165:3-12:3-12.

Braak H, Braak E. Staging of Alzheimer’s disease-related neurofibrillary changes.

Neurobiol Aging. 1995;16:271-278.

Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. The importance of neuritic plaques and tangles to the development and evolution of AD.

Neurology. 2006;67:578-589.

Von Gunten A, Kovari E, Bussiere T, et al. Cognitive impact of neuronal pathology in the entorhinal cortex and CA1 field in Alzheimer’s disease.

Neurobiol Aging. 2006;27:270-277.

Iacono D, O’Brien R, Resnick SM, et al. Neuronal hypertrophy in asymptomatic Alzheimer disease.

J Neuropath Exp Neurol. 2008;67:578-589.

Riidavets MA, Iacono D, Resnick SM, et al. Resistance to Alzheimer’s pathology is associated with nuclear hypertrophy in neurons.

Neurobiol Aging. 2007;28:1484-1492.

Lovell MA, Markesbery WR. Oxidative damage in mild cognitive impairment and early Alzheimer’s disease.

J Neurosci Res. 2007;85:3036-3040.

Lovell MA, Markesbery WR. Oxidatively modified RNA in mild cognitive impairment.

Neurobiol Dis. 2008;29:169-175.

Cuello AC, Bruno MA, Bell KF. NGF-cholinergic dependency in brain aging, MCI and Alzheimer’s disease.

Curr Alzheimer Res. 2007;4:351-358.

Mufson EJ, Counts SE, Fahnstock M, Ginsburg SD. Cholinotrophic molecular substrates of mild cognitive impairment in the elderly.

Curr Alzheimer Res. 2007;4:340-350.

Mufson EJ, Ikonomovic MD, Styren SD, et al. Preservation of brain nerve growth factor in mild cognitive impairment and Alzheimer disease.

Arch Neurol. 2003;60:1143-1148.

Sultana R, Butterfield DA. Regional expression of key cell cycle proteins in brains from subjects with amnestic mild cognitive impairment.

Neurochem Res. 2007;32:655-662.

Yang Y, Geldmacher DS, Herrup K. DNA replication precedes neuronal cell death in Alzheimer’s disease.

J Neurosci. 2001;21:2661-2668.

Yang Y, Mufson EJ, Herrup K. Neuronal cell death is preceded by cell cycle events at all stages of Alzheimer’s disease.

J Neurosci. 2003;23:2557-2563.

Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer’s disease.

Lancet. 1976;2:1403.

Perry RK, Perry RH, Blessed G, Tomlinson BE. Necropsy evidence of central cholinergic deficits in senile dementia.

Lancet. 1977;1:189.

Davies P. Loss of choline acetyltransferase activity in normal aging and in senile dementia.

Adv Exp Med Biol. 1978;113:251-256.

Davis KL, Mohs RC, Marin D, et al. Cholinergic markers in elderly patients with early signs of Alzheimer disease.

JAMA. 1999;281:1401-6.
96. Tiraboschi P, Hansen LA, Alford M, Masliah E, Thal LJ, Corey-Bloom J. The decline in synapses and cholinergic activity is asynchronous in Alzheimer’s disease. Neurology. 2000;55:1278-1283.
97. DeKosky ST, Ikonomovic MD, Styren SD, et al. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann Neurol. 2002;51:145-155.
98. Ikonomovic MD, Mufson EJ, Wu J, Cochran EJ, Bennett DA, DeKosky ST. Cholinergic plasticity in hippocampus of individuals with mild cognitive impairment: correlation with Alzheimer’s neuropathology. J Alzheimers Dis. 2003;5:39-48.
99. Masliah E, Miller A, Terry RD. The synaptic organization of the neocortex in Alzheimer’s disease. Med Hypotheses. 1993;41:334-340.
100. Terry RD, Masliah E, Salmon DP, 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.
101. Masliah E, Terry RD, DeTeresa RM, Hansen LA. Immunohistochemical quantification of the synapse-related protein synaptophysin in Alzheimer disease. Neurosci Lett. 1989;103:234-239.
102. Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer’s disease and mild cognitive impairment. Neurobiol Aging. 2006;27:1372-1384.
103. Selkoe DJ. Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav Brain Res. 2008;192:106-113.
104. Counts SE, Nadeem M, Lad SP, Wu J, Mufson EJ. Differential expression of synaptic proteins in the frontal and temporal cortex of elderly subjects with mild cognitive impairment. J Neuropathol Exp Neurol. 2006;65:592-601.
105. Population Projections (middle series). US Census Bureau. 2002.
106. National Vital Statistics Report. Centers for Disease Control. 2004;53.
107. Hebert LE, Scherr PA, Lad SP, Wu J, Mufson EJ. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003;60:1119-1122.
108. von Strauss E, Viitanen M, De Ronchi D, Winblad B, Fratiglioni L. Aging and the occurrence of dementia: findings from a population-based cohort with a large sample of nonagenarians. Arch Neurol. 1999;56:587-592.
109. Eby EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. Neurology. 1994;44:1593-1600.
110. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer’s disease in a community population of older persons. Higher than previously reported. JAMA. 1989;262:2551-2556.
111. Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svansborg A. A population-based study of dementia in 85-year-olds. N Engl J Med. 1993;328:153-158.
112. Borjesson-Hanson A, Gustafson D, Skoog I. Five-year mortality in relation to dementia and cognitive function in 95-year-olds. Neurology. 2007;69:2069-2075.
113. Polvikoski T, Sulkava R, Myllykangas L, et al. Prevalence of Alzheimer’s disease in very elderly people: a prospective neuropathological study. Neurology. 2001;56:1690-1696.
114. Prohovnik I, Perl DP, Davis KL, Libow L, Lesser G, Haroutunian V. Dissociations of neuropathology with severity of dementia in late-onset Alzheimer’s disease. Neurology. 2006;66:49-55.
115. Crystal HA, Dickson D, Davies P, Masur D, Grober E, Lipton RB. The relative frequency of “dementia of unknown etiology” increases with age and is nearly 50% in nonagenarians. Arch Neurol. 2000;57:713-719.
116. Silver MH, Newell K, Brady C, Hedley-White ET, Perls TT. Distinguishing between neurodegenerative disease and disease-free aging: correlating neuropsychological evaluations and neuropathological studies in centenarians. Psychosom Med. 2002;64:493-501.
117. Giannakopoulos P, Pof, Hof PR, Surini M, Michel JP, Bouras C. Quantitative immunohistochemical analysis of the distribution of neurofibrillary tangles and senile plaques in the cerebral-cortex of nonagenarians and centenarians. Acta Neuropathologica. 1993;85:602-610.
118. Delaere P, He Y, Fayet G, Duycyaerts C, Hauw JJ. Beta-A4 deposits are constant in the brain of the oldest old - an immunocytochemical study of 20 French centenarians. Neurobiol Aging. 1993;14:191-194.
119. Mizutani T, Shimada H. Neuropathological background of 27 centenarian brains. J Neurol Sci. 1992;108:168-177.
120. Head E, Corrada MM, Kahle-Wrobleski K, et al. Synaptic proteins, neuropathology and cognitive status in the oldest-old. Neurobiol Aging. 2009;30:1125-1134.
121. Haroutunian V, Schnider-Beeri M, Schmeidler J, et al. Role of the neuropathology of Alzheimer disease in dementia in the oldest-old. Arch Neurol. 2008;65:1211-1217.
122. Gold G, Bouras C, Kovari E, et al. Clinical validity of Braak neuropathological staging in the oldest-old. Acta Neuropathologica. 2000;99:579-582.