

ORIGINAL ARTICLE

Age, Neuropathology, and Dementia

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ABSTRACT

BACKGROUND

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Research in Alzheimer's disease is focused mainly on younger old persons, whereas studies involving very old persons report attenuated relationships between the pathological features of Alzheimer's disease and dementia.

METHODS

We assessed 456 brains donated to the population-based Medical Research Council Cognitive Function and Ageing Study from persons 69 to 103 years of age at death. We used a standard neuropathological protocol that included measures of the pathological features of Alzheimer's disease, cerebral atrophy, and cerebrovascular disease. Neuropathological variables were dichotomized to represent no burden or a mild burden of pathological lesions as compared with a moderate or severe burden. Logistic regression was used to estimate the effect of age on the relationship between neuropathological features and dementia.

RESULTS

The difference in the prevalence of moderate and severe Alzheimer's-type pathological changes between persons with and those without dementia decreased with increasing age. The association between neocortical neuritic plaques and dementia was strong at 75 years of age (odds ratio, 8.63; 95% confidence interval [CI], 3.81 to 19.60) and reduced at 95 years of age (odds ratio, 2.48; 95% CI, 0.92 to 4.14), and similar attenuations with advancing age were observed in the association between other pathological changes related to Alzheimer's disease and dementia in all brain areas. In contrast, neocortical cerebral atrophy maintained a relationship with age in persons with dementia at both 75 years of age (odds ratio, 5.11; 95% CI, 1.94 to 13.46) and 95 years of age (odds ratio, 6.10; 95% CI, 2.80 to 13.28) and thus distinguished the cohort with dementia from the cohort without dementia.

CONCLUSIONS

The association between the pathological features of Alzheimer's disease and dementia is stronger in younger old persons than in older old persons. Age must be taken into account when assessing the likely effect of interventions against dementia on the population.

DURING THE 20TH CENTURY, INTEREST in the dementias focused on specific disorders defined by criteria that were developed for patients who had onset of dementia before the age of 65 years, which had come to be considered by many as pathologically distinct from late-onset dementia.¹ In the second half of that century, the distinction between early-onset and late-onset dementias was challenged by the realization that the hallmarks of Alzheimer's disease in older persons were indistinguishable from those in younger persons with Alzheimer's disease.² Population epidemiologic studies of dementia have revealed a relentless rise in the incidence of dementia into old age,³ and clinically diagnosed Alzheimer's disease is considered to be the major subtype of dementia.⁴ The role of Alzheimer's disease in very old persons has become less clear since the contribution of vascular and other pathological changes has been recognized.^{5,6}

Research in dementia is driven by the expectation that understanding the genetic and molecular findings underlying clinical subtypes of dementia will result in major prevention strategies for the whole population.⁷ The greatest demographic change is the increasing number of persons over 85 years of age, in whom most cases of dementia will occur.⁸ It is therefore important to know whether research findings in younger old persons, often in tertiary research settings, are relevant to older old persons in the population. Only a small number of brain-donation programs are linked to longitudinal, population-based studies of aging.⁹ Programs that have included persons in the oldest age groups consistently show that these persons have mixed neuropathological features^{10,11} and that those who die in their 80s and 90s may have pathological features of Alzheimer's disease without a diagnosis of dementia during life.¹² Current diagnostic criteria that seek to define Alzheimer's disease, vascular dementia, and Lewy body dementia may not apply as well to the oldest old as to the younger old, in whom they were generated.

The relationship between underlying biology and clinical phenotype in the oldest old merits further examination, because current diagnosis, treatment, and management are predominantly shaped by research based on the younger old.¹³ Here we explore the effect of age on the relationship between the classic neuropathological fea-

tures of dementia and the clinical manifestation of dementia in a population-based cohort of the elderly.

METHODS

POPULATION SELECTION AND INTERVIEW PHASES

The Medical Research Council Cognitive Function and Ageing Study (CFAS) is a multicenter, prospective, population-based study of older people in the United Kingdom. The study design and data on the prevalence and incidence of dementia have been previously reported and have been used in the development of international and national policies on dementia.^{5,8,10,14,15} The population base used was derived from lists of primary care physicians in specific geographic areas that included institutions that cared for elderly people. In five urban and rural centers in England and Wales, random samples of approximately 2500 persons aged 64 years or older underwent a screening interview that included the Mini-Mental State Examination (MMSE)¹⁶ and the Geriatric Mental State–Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT)¹⁷ items related to organic disorders. The response rate was 82%. Detailed assessment was conducted in a subsample of approximately 20% of subjects stratified according to the MMSE and the AGECAT organicity scores. The screening and assessment process was repeated after 2 years, and a further 20% of those not previously included were added to the assessment group. This assessment group was followed up again 6 years after baseline, and the entire remaining cohort was assessed 10 years after baseline. Additional interviews at 1, 3, and 8 years were conducted in samples of the assessment group. In a sixth center, 5200 people underwent similar assessments at baseline, 1 or 2 years, 3 or 4 years, 5 or 6 years, 8 years, and 10 years.

Those who took part in assessment interviews were asked whether they and their families were willing to consider brain donation after the respondent's death. The analysis presented here was based on 456 brains donated up to July 2004 (data set version 3.1).

DIAGNOSIS OF DEMENTIA

Dementia status at death was determined on the basis of all information available for each respondent. This information was based on interviews

during the last years of life, including the full GMS-AGECAT diagnostic algorithm¹⁷ that was equivalent to that in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R), interviews with informants after the respondent's death when this was possible, and death certification. Dementia was diagnosed before death in 243 of the 456 respondents, and 183 were determined not to have dementia. Sufficient information for a diagnosis of dementia was not available for an additional 30 respondents, who were excluded from the analysis. The approach to the diagnosis of dementia in the CFAS is described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

NEUROPATHOLOGICAL ASSESSMENT

Assessment by neuropathologists who were unaware of all clinical data was conducted according to a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol (www.cfas.ac.uk).^{10,18} Neuropathological lesions of Alzheimer's disease, diffuse plaques, neuritic plaques, and neurofibrillary tangles in the entorhinal, hippocampal, frontal, temporal, parietal, and occipital cortexes were classified into four categories (none, mild, moderate, and severe). Cortical atrophy was assessed macroscopically in each brain area, without knowledge of microscopical findings, and classified as absent, mild, moderate, or severe. Lewy bodies and hemorrhages, regional infarcts (>1 cm in diameter), and small-vessel disease (severe arteriosclerosis, lacunes, microinfarcts, or severe white-matter attenuation) were scored according to the CERAD protocol. Some subjects had more than one of the vascular pathological changes that were assessed. Inter-rater reliability for cerebral atrophy, tangles, plaques, Lewy bodies, and amyloid angiopathy was validated among contributing pathologists at the beginning of the study by circulating photographs of macroscopic findings and slides of microscopical findings.¹⁰

STATISTICAL ANALYSIS

Variables were dichotomized so that moderate and severe scores were considered to represent a significant burden of pathological lesions, as compared with no score and mild scores, which represented no burden or a low burden. In accordance with the CERAD protocol, maximum neocortical scores for each lesion and for atrophy were used.

Logistic regression was used to model the effect of age on the relationship between neuropathological lesions and dementia. Each dichotomized pathological indicator was considered as an outcome, and the effects of age and dementia and their interaction were included in the model. Age at death was modeled as a continuous variable to estimate the association between pathology and dementia at different ages and to test for interactions. For analysis of the relationship between the prevalence of lesions and dementia at death, the subjects were divided into five age groups: under 80, 80 to 84, 85 to 89, 90 to 94, and over 94 years of age.

Sensitivity analyses were conducted for the effects of potential confounders. These analyses included sex, level of education, social class, time since last interview, and center, as well as the interaction of each of these with dementia. Further analyses included only those participants who received an assessment 1 year before death and excluded all those with prevalent dementia at baseline.

RESULTS

SAMPLE CHARACTERISTICS

The sex, age, and dementia status of the members of the cohort at death are given in Table 1. More than 63% of donors were 85 years of age or older at death; 59% were women. Among those who had not received a diagnosis of dementia, there was no significant association between age and MMSE score at the most recent assessment before death. Among those who died with dementia, the MMSE score was lower (indicating poorer function) in the older groups. The time since the last interview was similar in all age groups. Among those who died without dementia, the causes of death were similar in those who had an autopsy and those who did not (the cause of death was cancer in 23% and 24% of respondents, respectively, and cardiovascular disease in 45% and 44%).

AGE AND ALZHEIMER'S DISEASE—TYPE PATHOLOGICAL LESIONS

The distribution of each pathological lesion according to age group and dementia status is shown in Table 1 in the Supplementary Appendix. The modeled and observed prevalence rates of pathological changes are shown in Figure 1. Among persons without dementia, the prevalence of moderate or

Table 1. Characteristics of the Respondents According to Age at Death.

Characteristic	<80 Yr (N=89)	80–84 Yr (N=79)	85–89 Yr (N=125)	90–94 Yr (N=104)	≥95 Yr (N=59)	Total (N=456)
Sex (no.)						
Male	48	35	57	34	14	188
Female	41	44	68	70	45	268
Dementia status (no.)						
Dementia	25	40	70	63	45	243
No dementia	57	35	44	35	12	183
Unknown	7	4	11	6	2	30
Median MMSE score at last interview*						
Dementia	9	11	5	4	9	7
No dementia	26	26	23	24	24	25
Mean interval between last interview and death (yr)						
Dementia	1.4	2.0	1.7	1.5	1.4	1.4
No dementia	1.4	1.4	1.4	1.5	1.6	1.6

* Mini-Mental State Examination (MMSE) scores range from 0 to 30, with higher scores indicating better cognitive function.

severe neuritic plaques and of neurofibrillary tangles in each area increased with increasing age at death. The prevalence of these pathological changes in those who died with dementia either remained constant or tended to decline with age. Consequently, the difference in the burden of pathological lesions between persons who died with and those who died without dementia was less in those who died at older ages. In contrast, the prevalence of cortical atrophy was higher at all ages among those who died with dementia than among those who died without dementia.

The association between pathological lesions and dementia, as estimated by our regression model, was compared in persons who died at 75 years of age and in those who died at 95 years of age (Table 2). These ages were selected in the model for comparison between younger and older persons. Atrophy of the hippocampus and the neocortex was strongly associated with dementia at all ages. Neuritic plaques and neurofibrillary tangles were strongly associated with dementia at 75 years of age, but the association was less strong at 95 years. This difference between the younger old and the older old was observed for both the hippocampus and the neocortex, although the effect was less striking for neocortical neurofibrillary tangles. Diffuse plaques were

less strongly associated with dementia than were neuritic plaques at the age of 75 years, but by the age of 95 years these two neuropathological changes showed a similar association with dementia. Adjustment for demographic factors and inclusion only of participants who received a diagnosis of dementia close to death did not alter our findings (see Table 2 in the Supplementary Appendix).

VASCULAR PATHOLOGICAL FEATURES AND LEWY BODIES

Small-vessel disease, infarcts, and the presence of more than one vascular pathological change were associated with dementia in the younger old. These associations were less pronounced in the older old, but the effect of age on the association was not significant. Lewy bodies were identified in 24 persons, 21 of whom were diagnosed with dementia, with no evidence of an association with age.

DISCUSSION

This cohort-based study has sufficient power to model the pathological changes associated with dementia across the age range from 70 to 100 years. Using a careful definition of dementia status before death, we found that the relationship between the clinical manifestations of dementia and un-

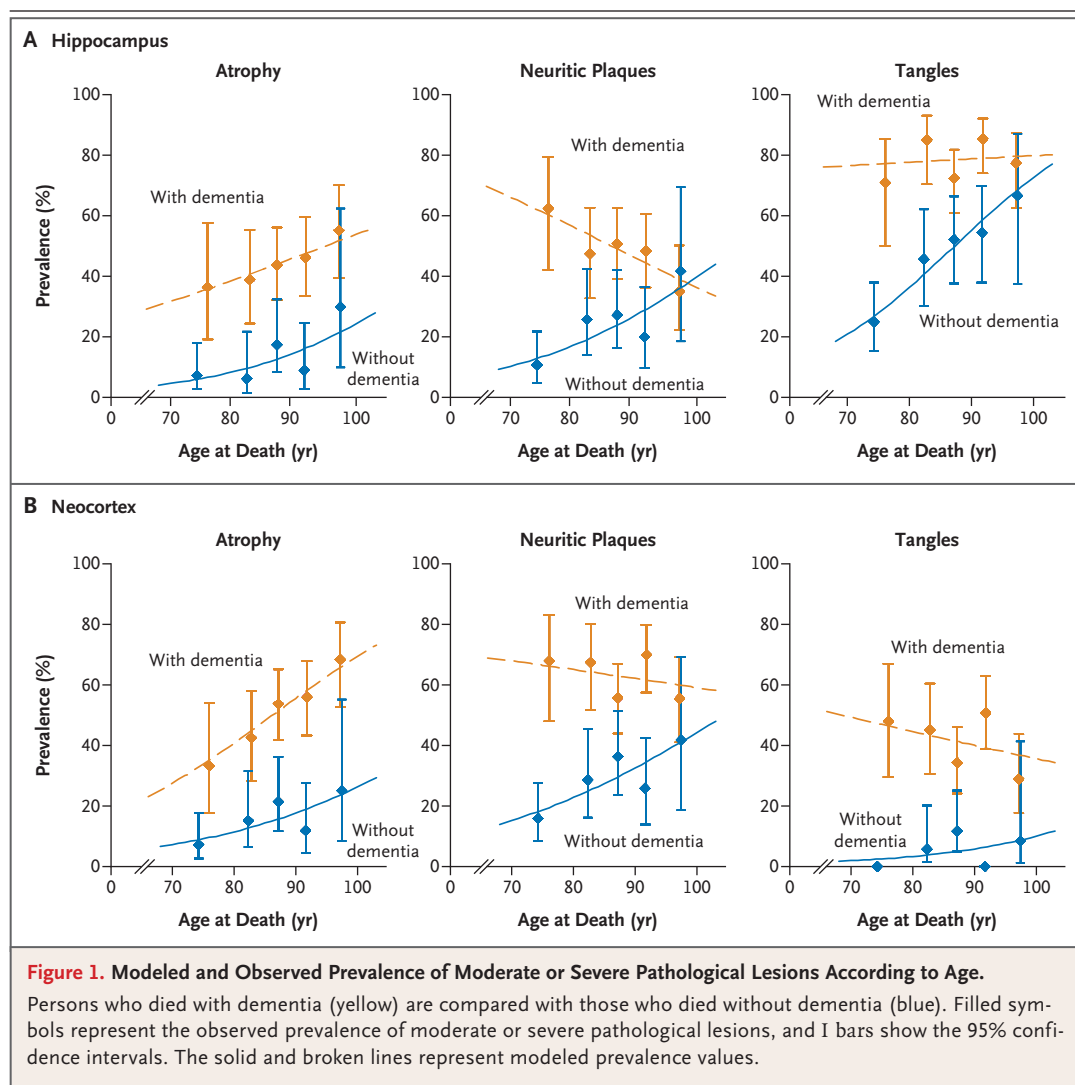


Figure 1. Modeled and Observed Prevalence of Moderate or Severe Pathological Lesions According to Age. Persons who died with dementia (yellow) are compared with those who died without dementia (blue). Filled symbols represent the observed prevalence of moderate or severe pathological lesions, and I bars show the 95% confidence intervals. The solid and broken lines represent modeled prevalence values.

derlying neuropathological findings varies with age within this population-based cohort of brain donors. Our study confirms earlier reports of considerable overlap in the burden of neuropathological features of Alzheimer's disease between groups of the oldest old persons with dementia and those without dementia.^{10,19,20} In those dying without dementia, we confirm that the burden of Alzheimer's-type disease in the population increases with increasing age at death.^{12,21} In contrast, cortical atrophy remains strongly associated with dementia in all age groups.

The use of the primary care system registry of the United Kingdom ensured that the entire population in the areas chosen, including persons living in institutions, served as the basis for selection of the sample. The response rate at baseline

was high, and all follow-up activity was assessed for potential bias due to attrition.²² The response rate among those who agreed to brain donation was high, considering the sensitive nature of this work, and has been scrutinized to exclude bias.¹⁰ The selection of persons to be interviewed for assessment of dementia, from whom the donor cohort was derived, was weighted toward the cognitively impaired, but no further bias in the donation process has been detected. Abrupt terminal decline could potentially affect our findings, but the diagnostic method makes it unlikely that this would have led to an inaccurate diagnosis of dementia. The 30 respondents for whom the diagnosis of dementia was doubtful were excluded from the analysis. The method for diagnosing dementia has been validated and is used widely in

Table 2. Odds Ratios for the Association between Neuropathological Features and Dementia at Death, Modeled at the Ages of 75 and 95 Years.*

Variable	75 Yr of Age	95 Yr of Age	P Value†
	<i>odds ratio (95% CI)</i>		
Tangles			
Hippocampus	8.61 (3.66–20.27)	2.11 (1.05–4.25)	0.03
Neocortex	35.16 (8.16–153.31)	7.04 (2.40–22.87)	0.14
Entorhinal cortex	4.72 (1.97–11.30)	2.94 (1.37–6.29)	0.48
Neuritic plaques			
Hippocampus	10.19 (4.28–24.25)	1.42 (0.71–2.82)	0.002
Neocortex	8.63 (3.81–19.60)	2.48 (0.92–4.14)	0.04
Entorhinal cortex	7.18 (2.99–17.25)	2.28 (1.11–4.67)	0.08
Diffuse plaques			
Hippocampus	2.36 (1.10–5.10)	2.12 (1.08–4.16)	0.86
Neocortex	2.67 (1.24–5.74)	1.83 (0.95–3.48)	0.42
Entorhinal cortex	2.91 (1.14–7.45)	1.19 (0.56–2.53)	0.20
Cortical atrophy			
Hippocampus	7.96 (2.67–23.68)	4.22 (1.80–9.91)	0.43
Neocortex	5.11 (1.94–13.46)	6.10 (2.80–13.28)	0.81
Vascular pathology			
More than one vascular pathological change	2.36 (1.09–5.11)	1.56 (0.80–3.04)	0.48
Infarcts	2.87 (1.29–6.40)	1.09 (0.53–2.26)	0.12
Hemorrhage	0.87 (0.15–4.93)	0.73 (0.15–3.57)	0.90
Lacunae	1.41 (0.58–3.46)	1.99 (0.88–4.51)	0.62
Small-vessel disease	2.69 (1.15–6.31)	1.79 (0.89–3.61)	0.52

* All pathological measures were recorded in accordance with the protocol of the Consortium to Establish a Registry for Alzheimer's Disease. The model is based on the presence of moderate or severe neurofibrillary tangles, neuritic plaques, diffuse plaques, and cortical atrophy. Vascular lesions are classified as present or absent rather than graded according to severity. The odds ratios were generated from a series of logistic-regression models; the dependent (outcome) variable for each model was a neuropathological variable, and the independent variables were dementia, age, and the interaction between age and dementia.

† P values represent the significance of the effect of age at death on the association between neuropathological features and dementia in the model.

different settings.^{23,24} The assessment of dementia from informant reports was based on the DSM-III-R, an approach supported by the previous validation studies performed with the use of the GMS-AGECAT instrument.

If our findings were artifacts due to misclassification of persons with regard to dementia status, such misclassification would have to be differentially associated with age. It could be argued that extremely old persons might receive a diagnosis of dementia because of a greater prevalence of impairments, including vision and hearing, but the interviews take these possibilities into account. The severity of dementia also does not explain the

convergence of neuropathological profiles at older ages in persons with and those without dementia, since the MMSE scores of those who died with and those who died without dementia appear to diverge slightly with increasing age. None of the sensitivity analyses led to different conclusions, a result suggesting that neither demographic factors nor the study design can explain our findings.

The neuropathological assessment was based on a modified CERAD protocol. We retained this basic assessment during the whole study to generate consistent data. The CERAD assessment relied on hematoxylin and eosin or ubiquitin stain-

ing to identify Lewy bodies; therefore, although our findings are robust, they need further confirmation with current techniques of staining.

Among those persons who died with dementia, the distribution of Alzheimer's-type pathological features remained roughly constant with increasing age, and consequently there was a decline in the association between the burden of Alzheimer's-type pathological features and dementia. With increasing age, there is a decrease in the ability to predict dementia on the basis of the burden of neuritic plaques in the hippocampus and neocortex and of neurofibrillary tangles in the hippocampus. Neuropathological validation of the diagnosis of Alzheimer's disease, based on confirmation of the presence of these changes, has a different meaning in the oldest old, because that same burden of pathological features may frequently be found in persons of the same age who do not have dementia. The association between neocortical neurofibrillary tangles and dementia during life remains strong at all ages, although the association is somewhat attenuated at increased ages. Previous studies support the idea of a convergence of Alzheimer's-type pathological features in people with and in those without dementia at very advanced ages: older persons with dementia have fewer Alzheimer's-type pathological features at death than do younger persons with dementia,²⁵ indexes of cholinergic innervations converge between persons with and those without dementia at advanced ages,^{26,27} and the relationship between Alzheimer's-type pathological features and dementia is clearest in the younger old.^{28,29}

These results suggest that additional factors determine the clinical expression of dementia in the oldest old. Hypothetically, these might include varying tolerance to neuropathological lesions; varying speed of lesion development, allowing compensatory processes; and interaction with coexisting illnesses. Neuronal and synaptic loss may represent an integral final common pathway mediating the effects of such factors. We found that cortical atrophy increases with age and continues to differentiate persons with dementia from those without dementia in all age groups, a finding echoing much earlier observations.³⁰ Atrophy, a feature commonly seen on neuroimaging, emerges as a robust marker of the accumulation of pathological lesions and the failure of compensatory mechanisms, both of which lead to dementia.

Atrophy reflects both Alzheimer's-type pathological changes and other factors, such as loss of neurons, axodendritic pruning, and reduced synaptic density, that occur in the course of normal aging and are a correlate of dementia.³¹ Perhaps if life span were sufficiently prolonged in some persons, aging changes in the brain, such as synaptic loss, could result in dementia without substantial Alzheimer's-type pathological changes.³²

Mixed pathologic factors are common in the older brain and contribute to dementia and cognitive impairment.^{11,33,34} Coexisting pathological changes, often vascular, may lower the burden of Alzheimer's-type pathological features that are required to produce dementia and thus are potential confounders in an analysis of interactions between Alzheimer's-type pathological changes and age. However, a recent analysis of a smaller cohort, which was not representative of a population and which excluded those with any vascular disease in the brain, also showed an attenuated association between Alzheimer's-type pathological features and dementia in the oldest persons.³⁵ To date, there is no protocol that has been widely validated and made operational that can score the diversity of vascular pathology encountered in the aging brain. Without such a protocol, analysis of the interaction between Alzheimer's-type and vascular pathological features remains limited.

The exponential relationship between age and the prevalence of dementia, combined with the increasing number of people surviving into old age, is driving the prevalence of dementia upward in the oldest old age groups. The CFAS, as a population-based study, can examine the implications of this increase. The study shows that the relationship between neuropathological indexes and dementia changes with age and that this change needs to be taken into account in models of dementia. Current disease-based classifications are based on discrete entities, such as Alzheimer's disease, vascular dementia, or mixed dementia. Our and other findings suggest this is a simplification and that the pathological basis of dementia should be considered as an interaction among pathological changes, compensatory mechanisms, and underlying synaptic dysfunction. Cognitive dysfunction in later life is a life-span issue and is affected by genetic, developmental, and lifestyle factors, accumulated neural insults, innate and acquired cerebral reserve and compensatory mechanisms, and age-related decline. The diverse in-

terplay of these factors must account for the variation in cognitive outcome that is observed among individual persons for particular pathological changes in the brain that are associated with age. This holistic view offers the opportunity to explore diverse factors that underlie dementia and suggests that therapeutic interventions based solely on studies in younger cohorts in the context of the classic view of Alzheimer's disease will be less

effective in the oldest old. Age cannot be neglected if the effect of dementia on the population is to be addressed and the most effective strategies are to be developed.

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