

Dementia in the Oldest Old

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ABSTRACT

Purpose of Review: This article discusses some of the unique features of dementia in the oldest old, including some of the most common diagnostic challenges, and potential strategies to overcome them.

Recent Findings: Advances include new insight into the role of common risk factors and the effects of multiple underlying neuropathologic features for dementia in the oldest old. In addition, this article contains the latest age-specific normative data for commonly used neuropsychological tests for the oldest old.

Summary: The oldest old—people aged 90 years and older—are the fastest-growing segment of society and have the highest rates of dementia in the population. The risk factors, diagnostic challenges, and underlying neuropathologic features of dementia are strikingly different in the 90-years-and-older population compared to younger elderly. Special consideration of these unique features of dementia is necessary when evaluating oldest-old subjects with cognitive impairment.

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THE OLDEST OLD

In this article, *the oldest old* refers to people who are 90 years old or older. A report from the US Census Bureau published in 2011 concluded that the commonly used definition of “oldest old” as those 85 and older was no longer appropriate and argued for a new definition: those 90 and older.¹ The 90-and-older age group represents the fastest-growing segment of the US population² and is growing at a faster rate than the 85- to 89-year-old cohort. In 2010, the oldest old accounted for approximately 1.9 million people in the United States (0.6% of the US population). According to population projections by the US Census Bureau, this number is estimated to more than quadruple to over 8.7 million by 2050 (2% of the total US population) (Figure 10-1).^{2–6} The oldest-old population is also growing as a proportion of the US elderly population, defined as people aged 65

years and older. In 2010, the oldest old represented 4.7% of the elderly population, and that number is expected to increase to 9.9% by 2050.¹ Thus, the oldest-old cohort is increasing not only in number but also in its proportion within the population as a whole and within the elderly population. The projected expansion of this group is largely due to the continued increase in human life expectancy,⁷ declining birth rate, and the aging of the populous “baby boom” generation.

According to the US Census Bureau report, the current oldest-old population is surprisingly homogenous across the United States.¹ Most of the oldest old in the United States are well educated (over 60% have at least a high school education), white (88%), and female (women outnumber men 3 to 1 at this age). Nonetheless, the median annual personal income for the oldest old was only \$14,760 from 2006

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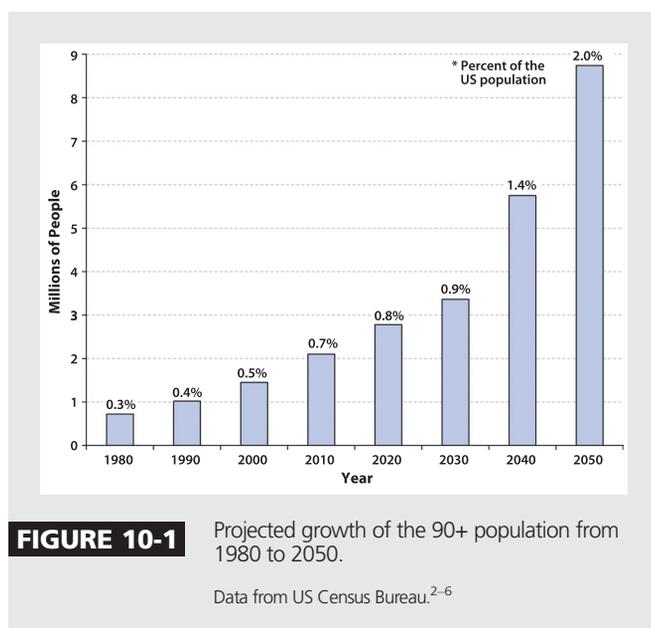
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**KEY POINTS**

- The oldest old—people aged 90 years and older—are the fastest-growing segment of the society. By 2050, the oldest old will account for 2% of the US population.
- The oldest old have the highest incidence and prevalence rates of dementia in the population. Women have a higher prevalence of dementia than men. The incidence of dementia is similar in men and women and doubles approximately every 5 years after the age of 90.

to 2008, and 14.5% of them lived in poverty.¹

The rapid growth of the oldest-old population will bring unprecedented challenges for clinicians and public health officials. With the oldest-old cohort maintaining the population's highest rates of disability^{1,8} and dementia,⁹ the social and financial challenges of caring for the very elderly in the coming decades will be enormous.¹⁰

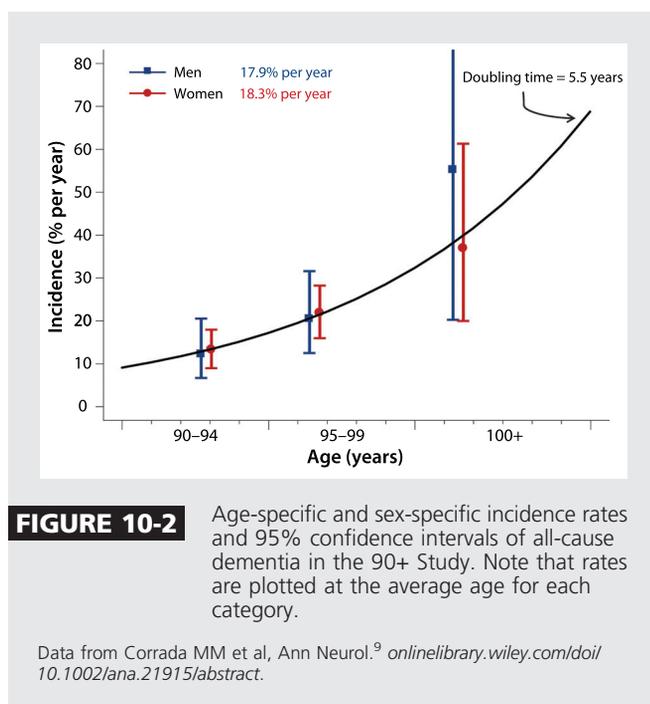
The 90+ Study, created to address important questions about this understudied age group, is a population-based study of dementia and aging in people aged 90 years and older,¹¹ with a subset of participants who agree to eventual postmortem examination. The study was established in 2003 and comprises the survivors of the Leisure World Cohort Study, an epidemiologic investigation of a retirement community in Orange County, California, established in the early 1980s.¹² Participants of the 90+ Study are mostly white, well educated, and female; thus, representative of the overall oldest-old population in the United States.¹ The main differences between the oldest old in general and participants of the 90+ Study are the

slightly higher educational attainment and socioeconomic status in the latter.

EPIDEMIOLOGY

The incidence of dementia, or the frequency with which new cases develop, doubles every 5 years after the age of 65.¹³ Although previous studies suggested that the incidence may plateau in nonagenarians, this does not appear to be the case. Based on findings from the 90+ Study, the incidence of dementia from all causes continues to increase exponentially and is very similar in both men and women, even in those of very advanced age: from 13% per year in the 90 to 94 age group, to 21% per year in the 95 to 99 age group, to 41% per year in centenarians; a doubling every 5.5 years (Figure 10-2).⁹ The overall incidence rate of dementia in the study was around 18% per year. Other studies report a wide range of dementia incidence rates for the oldest old (from 6% to 21% per year)^{14,15} most likely due to differences in methodologies as well as in characteristics and number of subjects studied.

Although incidence rates of dementia in the oldest old are similar between men and women, a significant sex difference exists in prevalence, or the proportion of men versus women with dementia. In the 90+ Study, the disorder is more common in women (45%) than in men (28%),¹⁶ similar to other studies.¹⁷ Moreover, after age 90, the doubling of prevalence was observed in women but not in men. The sex difference in dementia prevalence in the 90+ Study may be explained by longer survival of women after a diagnosis of dementia compared to men; just as women in general live longer than men, women with dementia may live longer than men with dementia. Longer survival in younger elderly women with dementia has been reported by other studies.^{18,19}



KEY POINT

■ Risk factors for cognitive decline and dementia appear to change with age. In the oldest old, some risk factors are no longer relevant (eg, the apolipoprotein E ε4 allele) and some may have a protective effect (eg, hypertension).

Age remains the most important risk factor for dementia even in the oldest old. However, the effect of common risk factors for all causes of dementia appears to change in late life, with some risk factors losing their effects or having opposite effects on the risk of dementia in the oldest old.

The *APOE*E4* allele has been shown to represent genetic susceptibility for Alzheimer disease (AD)²⁰ and other types of dementia in younger elderly²¹; however, its effect appears to diminish with age.²² As shown in several studies, including the 90+ Study,²³ *APOE*E4* is no longer a risk factor for dementia or AD in people who survive to very old age without dementia.

Midlife hypertension is a known risk factor for the development of dementia and AD later in life,²⁴⁻²⁶ but evidence indicates that hypertension is no longer a risk factor when present at very advanced ages. In several studies, increased blood pressure was associated with risk of dementia at ages under 74 years but was protective against de-

mentia at ages over 85 years.^{27,28} Thus, at older ages the highest risk of dementia and cognitive impairment appears to be in people with normal or low blood pressure.²⁷⁻²⁹ Possible mechanisms for this effect have been proposed. In late life, vessel stiffness due to atherosclerosis, loss of elasticity, and other age-related processes can lead to changes in blood vessels, resulting in cerebral hypoperfusion.³⁰ Moreover, factors such as aggressive treatment with antihypertensive medications and age-associated autonomic dysfunction can lead to hypotension and subsequent hypoperfusion. Sustained hypoperfusion can result in hypoxic and ischemic injuries, such as microinfarcts,³¹ which can directly result in dementia or affect its clinical expression. Maintaining a certain level of blood pressure may theoretically be necessary to sustain adequate blood perfusion and maintain cognitive health in the oldest old. Further research is needed to determine the exact role of blood pressure levels and dementia in the oldest old.

KEY POINT

■ Cognitive performance declines with age even in subjects who are cognitively intact. Using age-specific normative data is crucial to avoid overestimation of cognitive impairment in oldest-old subjects.

DIAGNOSIS OF DEMENTIA

Several diagnostic criteria are used in research and clinical settings to diagnose dementia. One of the most widely used criteria is from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.³² According to these criteria, the diagnosis of dementia (regardless of etiology) requires the presence of several conditions: (1) impairment in memory and one additional cognitive domain, (2) decline from a previous level of functioning due to cognitive impairment, and (3) presence of cognitive deficits not only during delirium.

In an ideal setting, to determine whether a person has cognitive impairment, the subject's cognition is compared

to his or her previous performance. In clinical practice, longitudinal data are generally not available, and performance is instead compared to standardized age-specific norms. In most investigations, the cognitive performance of oldest-old participants continues to decline with age even in the absence of dementia.³³ The availability of normative data for the oldest old is therefore imperative because using normative data from younger populations could lead to overestimating the degree of cognitive impairment in the oldest old.

Table 10-1 shows normative data for several commonly used neuropsychological tests to aid in the evaluation of oldest-old patients with cognitive difficulties. The norms derived from 655

TABLE 10-1 Age-Specific Norms for 10 Common Neuropsychological Tests: The 90+ Study^{a,b}

Test	Age	Number of Participants	Mean	SD	5%	10%	25%	Median	75%	90%	95%
Mini-Mental Status Examination	90–91	225	26.9	2.6	22	24	26	27	29	30	30
	92–94	229	26.5	2.5	21	23	25	27	28	29	30
	95+	132	25.4	2.8	20	22	24	26	27	28	29
	Overall	586	26.4	2.7	21	23	25	27	28	29	30
Modified Mini-Mental Status Examination	90–91	224	90.8	7.5	77	83	87	92	96	98	99
	92–94	228	89.8	7.2	77	79	87	91	95.5	97	99
	95+	131	85.3	9.3	68	74	81	87	92	96	96
	Overall	583	89.2	8.1	74	79	85	91	95	98	99
Boston Naming Test	90–91	181	12.7	2.3	8	10	12	13	14	15	15
	92–94	177	12.0	2.4	8	9	11	12	14	15	15
	95+	81	11.2	2.4	8	8	9	11	13	14	15
	Overall	439	12.1	2.4	8	9	11	13	14	15	15
Animal fluency	90–91	241	13.4	4.5	7	8	10	13	16	20	21
	92–94	248	13.2	3.8	7	8	10	13	16	19	20
	95+	160	11.4	3.8	6	7	9	11	13.5	16	18
	Overall	649	12.8	4.2	6	8	10	12	15	18	20
Letter F fluency	90–91	191	12.1	4.2	5	7	9	12	15	18	20
	92–94	176	11.7	4.1	5	6	8.5	12	15	17	18
	95+	108	10.7	3.8	5	6	8	10	13	16	18
	Overall	475	11.6	4.1	5	7	9	11	14	17	19

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TABLE 10-1 *Continued*

Test	Age	Number of Participants	Mean	SD	5%	10%	25%	Median	75%	90%	95%
California Verbal Learning Test trial 1	90–91	201	4.6	1.7	2	2	4	5	6	7	7
	92–94	212	4.3	1.6	2	2	3	4	5	6	7
	95+	106	3.8	1.6	1	2	3	4	5	6	6
	Overall	519	4.3	1.6	2	2	3	4	5	6	7
California Verbal Learning Test long delay	90–91	201	5.6	2.6	0	1	4	6	8	8	9
	92–94	209	4.9	2.7	0	1	3	5	7	8	9
	95+	105	4.1	2.5	0	0	2	4	6	7	8
	Overall	515	5.0	2.7	0	1	3	5	7	8	9
California Verbal Learning Test cued delay	90–91	200	6.2	2.3	1	2	5	7	8	9	9
	92–94	209	5.4	2.4	1	2	4	6	7	8	9
	95+	105	4.9	2.2	0	2	3	5	6	8	8
	Overall	514	5.6	2.4	1	2	4	6	8	8	9
Trails A	90–91	188	60.2	27.4	32	36	42	51	71	97	110
	92–94	175	65.1	28.8	30	35	48	59	78	90	129
	95+	85	91.0	45.1	41	44	53	81	117	176	180
	Overall	448	68.0	33.9	32	37	45	58	81	114	150
Trails B	90–91	186	183.6	80.1	72	89	112	166	273	300	300
	92–94	167	197.8	84.4	80	91	123	185	300	300	300
	95+	76	249.0	72.8	99	127	186	300	300	300	300
	Overall	429	200.7	83.7	80	92	127	188	300	300	300
Trails C	90–91	179	26.7	14.6	13	14	18	23	32	42	50
	92–94	163	29.2	17.7	14	15	20	25	34	47	55
	95+	65	32.7	16.0	14	16	21	29	40	50	65
	Overall	407	28.7	16.2	13	15	19	24	34	46	55
Clock drawing	90–91	205	5.7	1.8	3	3	4	6	7	8	8
	92–94	201	5.4	1.9	2	3	4	6	7	8	8
	95+	114	5.0	2.0	2	2	4	5	6	8	8
	Overall	520	5.4	1.9	2	3	4	6	7	8	8

SD = standard deviation.

^a Update to Whittle C, et al, *J Clin Exp Neuropsychol*.³⁴^b The Mini-Mental Status Examination and the Modified Mini-Mental Status Examination are tests of global cognition. The Boston Naming Test is a 15-item test of confrontational naming. Animal fluency and letter F fluency tests are administered for 60 seconds. The California Verbal Learning Test is a 9-word list to assess short-term memory with a 10-minute delay immediately followed by a cued recall. Trails A and B are tests of executive function. In Trails A, participants connect dots in numerical order (1-2-3, etc). In Trails B, participants connect dots by shifting sets 1-A-2-B-3-C etc. Trails C tests psychomotor speed by asking participants to trace a dotted line connecting 25 circles. The clock drawing test asks participants to place numbers and hands at “ten after eleven” on a predrawn circle and tests visuospatial abilities.

nondemented individuals from the 90+ Study are an update to previously published norms³⁴ and include almost twice as many subjects. Age-specific norms are presented as means, standard devia-

tions (SDs), and percentiles for three age categories. Impairment is often defined as performance below the 10th percentile or performance 1.5 SDs below the mean of people in the same age category.

KEY POINT

■ Vision and hearing impairment, frailty, and fatigue are common in oldest-old patients and can easily affect cognitive performance. Modifications to neuropsychological testing to accommodate these limitations are important to avoid misdiagnosis of dementia in oldest-old subjects.

Assessing the contribution of cognitive impairment due to loss of functional abilities in the oldest old can be challenging. The prevalence of sensory loss, medical comorbidities, disability, and frailty are extremely high in the 90-years-and-older population. These conditions can all contribute to loss of abilities in activities of daily living such as eating, bathing, and dressing, and in instrumental activities of daily living, such as shopping for food, cooking, and managing medications.

In the 90+ Study, over 70% of the participants have experienced some degree of visual loss, hearing loss, or both.³³ To overcome these challenges, modifications were implemented in the design of the neuropsychological testing forms and their administration to participants aged 90 years and older. Visual stimuli are presented in a large font to all subjects to maximize visibility, and sound amplifiers are given to participants with hearing difficulties. In addition, the administration of several common neuropsychological tests was modified. For example, for the Mini-Mental State Examination (MMSE) and the short form of the California Verbal Learning Test-II, the words for recall are spoken in a loud, clear voice and simultaneously shown to the participants on a card with a large typeface. This type of multimodal presentation promotes the participant's ability to register the appropriate word despite sensory limitations.

Frailty and fatigue are also common in the oldest old and can have a detrimental effect on the subjects' cognitive performance and functional abilities. To accommodate these limitations, examiners shorten the standard evaluations, provide frequent breaks, and divide the evaluations into multiple visits as necessary to reduce the burden of prolonged testing.

Another common diagnostic challenge is the evaluation of functional ca-

capacity. Functional disability due to physical impairment, cognitive impairment, or both is very common in the oldest old.³⁵ Because the diagnosis of dementia requires functional loss specifically due to cognitive impairment, it is essential to accurately determine the causes of the disability. To determine more accurately the reasons for the functional disability, information about function must be obtained from a variety of sources, including the patient and his or her family, friends, and care providers.

When gathering information from collateral sources, it is vital to factor in cultural and environmental expectations. Social, occupational, and functional expectations of individuals over 90 years old are traditionally modest at best and often further attenuated by physical limitations, medical illness, or sensory losses. The contribution of memory impairment to functional loss may also be minimized because of the presence of preserved long-term memory. Although collateral information is crucial for the diagnosis, the validity of such information is sometimes questionable because of reduced expectations toward oldest-old subjects. Therefore, to determine the contribution of cognitive loss to functional disability, clinical judgment is essential to evaluate and synthesize the gathered information, especially in light of the limited cultural and environmental expectations.³⁶ **Case 10-1** illustrates the typical diagnostic challenges clinicians face when evaluating oldest-old patients for cognitive impairment.

NEUROPATHOLOGY

AD remains the most common underlying pathology of dementia in the oldest old. In a recent clinicopathologic study, as many as 61% of participants met criteria for AD defined as intermediate or high likelihood according to National Institute on Aging and Reagan Institute

Case 10-1

A 94-year-old, right-handed woman with a medical history of severe osteoarthritis, macular degeneration, and paroxysmal atrial fibrillation was referred for a neurologic evaluation by her primary care physician of more than 15 years. The primary care physician was concerned that the patient's forgetfulness was beyond age-related changes and requested further evaluation and possible treatment for dementia.

The patient was a widowed homemaker who had lived in an assisted living facility since the death of her husband 20 years ago. At the time of the first visit, the patient was accompanied by her son, who lived nearby.

As part of the initial evaluation, the patient underwent a comprehensive neuropsychological evaluation and neurologic examination. Results of the general and neurologic examinations were unremarkable, but the neuropsychological evaluation revealed impairment in global cognition (in the Mini-Mental State Examination and the Modified Mini-Mental State Examination,³⁷ memory (in the California Verbal Learning Test short, long, and cued long delays), and visuospatial abilities (in a clock-drawing exercise). The patient scored below the 10th percentile on these tests compared to age-adjusted norms. When the patient was asked about her functional abilities, she denied any impairment or decline in her functional capacity. She stated that, although all of her instrumental activities of daily living are done for her, she could do them on her own if she wanted. When the patient's son was asked confidentially about his mother's functional abilities, he denied any functional limitation due to cognitive impairment. He stated that his mother had never handled the finances, so it was natural for him to take over after his father's death; he added that she had a history of osteoarthritis and macular degeneration, and these physical impairments were the sole reason she required help with shopping, cooking, dressing, and bathing. He stated that the patient was "sharp as a tack" and remembered every detail of his childhood. However, he admitted that she had a hard time remembering the grandchildren's names, "only because those names are too modern for her."

Comment. This patient had significant cognitive impairment in two domains. She was likely in the early stages of dementia; however, the diagnosis was difficult to establish because of insufficient evidence of functional loss due to decline in cognition. At this early stage of dementia, initiation of pharmacotherapy should be considered. This case illustrates some of the typical diagnostic difficulties in the oldest old. Physical limitations, such as visual loss or decreased mobility, often conceal the degree of functional loss due to cognitive impairment. In addition, although gathering reliable collateral information is crucial, diminished cultural and environmental expectations may limit the validity of collateral information in certain cases. The use of clinical judgment is critical.

criteria.³⁸ Similarly, in the 90+ Study, 54% of autopsied participants had intermediate or high likelihood of AD pathology.³⁹ Although the proportion of AD pathology is higher in demented (57%) versus nondemented (49%) participants, great overlap in AD pathology

exists between these two groups. The high prevalence of AD pathology found in nondemented participants in the 90+ Study suggests that the clinical expression of the neuropathologic features of AD changes in the oldest old. A population-based study by the Medical

KEY POINT

- Alzheimer disease remains the most common pathology underlying dementia. However, the relationship between Alzheimer disease pathology and cognitive impairment weakens in the oldest old. Alzheimer disease pathology is also common in nondemented oldest old; about half of nondemented subjects have high levels of Alzheimer disease pathology at death.

Research Council Cognitive Function and Ageing Study⁴⁰ showed that the association between AD pathology and dementia diminished significantly with age. The prevalence of moderate or severe AD neuropathology increased with age in nondemented subjects, whereas it remained stable or decreased slightly with age in subjects with dementia (Figure 10-3). These changes resulted in weaker associations between AD pathology and dementia with advancing age. When comparing the odds ratio (OR) for dementia between people who died at age 75 and those who died at age 95, the OR declined for hippocampal neuritic plaques (OR 10.19

versus 1.42), hippocampal neurofibrillary tangles (OR 8.61 versus 2.11), neocortical neuritic plaques (OR 8.63 versus 2.48), and neocortical neurofibrillary tangles (OR 35.2 versus 7.0).

Vascular pathology (which includes lacunar infarcts, large vessel infarcts, and microinfarcts) is the second most common pathologic feature found in the oldest old (Figure 10-4). As described in a recent review, between 75% and 90% of autopsied participants aged 90 years and older have some vascular pathology.⁴¹ Similarly, in the National Alzheimer's Coordinating Center neuropathologic dataset, which combines data from 25 Alzheimer Disease Research

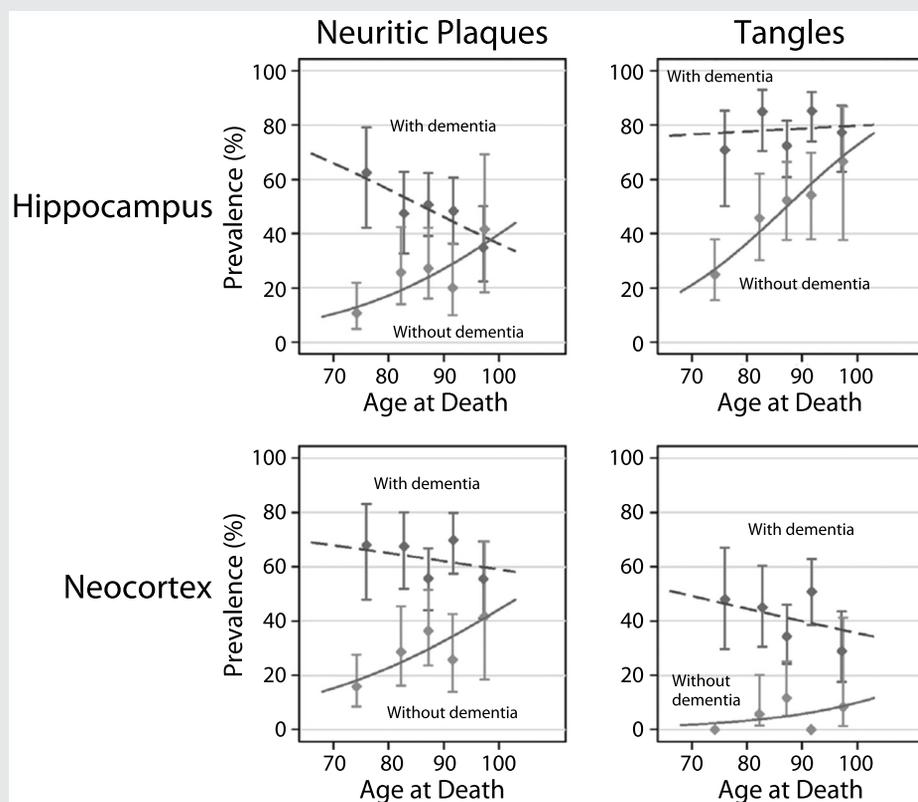
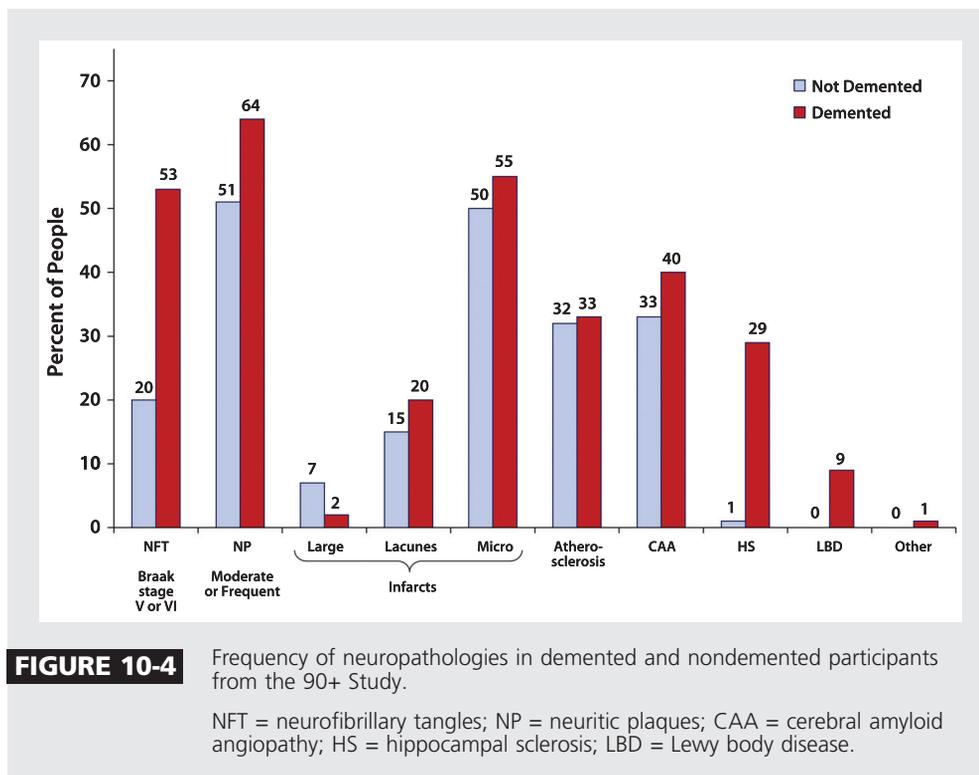


FIGURE 10-3 Modeled and observed prevalence of moderate or severe pathologic lesions according to age. *Solid lines* (people without dementia) and *dotted lines* (people with dementia) represent the modeled prevalence of moderate to severe pathologic lesions, whereas solid symbols represent the observed prevalence with 95% confidence intervals depicted by the I bars.

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KEY POINT

■ Vascular pathology is the second most common pathologic feature in the oldest old. Although the number of large-vessel infarcts decreases in the 90-years-and-older population, the prevalence of microinfarcts increases significantly in the oldest old.

Center sites in the United States, cerebrovascular pathology was found in more than 70% of autopsied participants over the age of 90 years.⁴²

Interestingly, there is a notable shift in the frequency of the morphologic subtypes of vascular lesions in the oldest old. At extreme ages, the frequency of large-vessel infarcts decreases, while smaller lacunar and microinfarcts become more common.⁴³ Microinfarcts were found in 64% of autopsy participants in the Honolulu-Asia Aging Study, an epidemiologic study of Japanese American men,⁴⁴ with a mean age at death of 85.5 years, and in 48% of autopsied participants in a community sample in the United Kingdom with a mean age at death of 90.7 years.⁴⁵ Microinfarcts are increasingly being investigated as an important cerebrovascular pathology in relation to cognition and may be as strong a predictor for dementia as AD.⁴⁶ Because these lesions cannot be detected through conventional imaging procedures, their

contribution to cognitive impairment is often underestimated.

Similar to vascular pathology, the frequency of hippocampal sclerosis increases with age. In the 90+ Study, hippocampal sclerosis was found in over one-quarter of participants with dementia but was rarely present in nondemented subjects (Figure 10-4).⁴⁷ In other cohorts, the frequency of hippocampal sclerosis increases noticeably after age 95 to about one-fifth of all autopsies.⁴²

Other neuropathologies, such as dementia with Lewy bodies (DLB) and frontotemporal dementia and related disorders, are relatively rare in the oldest old. The 90+ Study estimates the prevalence of DLB as less than 10% (Figure 10-4). Neuropathologic features of frontotemporal dementia and related disorders, including corticobasal degeneration and other Parkinson-plus syndromes, are rarely encountered in subjects aged 90 or older, with an estimated prevalence of each below 1%.⁴²

KEY POINTS

- Accumulation of multiple neuropathologic features is common in the oldest old. The odds of dementia increase with increasing number of pathologies.
- Approximately a quarter of oldest-old people develop dementia without obvious underlying pathology.

The accumulation of multiple pathologies is more common in the oldest old than in the younger elderly. Whereas the association between dementia and AD neuropathology weakens from age 75 to age 95,⁴⁰ the presence of multiple neuropathologic features increases the odds of dementia significantly in the oldest old. A community-based clinicopathologic cohort study of older persons (mean age at death 87.9 ± 5.6) concludes that having one versus more than one underlying neuropathology (AD, vascular dementia, or DLB) increases the odds of having dementia

by almost threefold (OR of 2.8, 95% CI of 1.2 to 6.7).⁴⁸ In a report from two community-based samples, mixed pathologies were more common than single pathologies in the oldest old. Furthermore, the presence of multiple pathologies was more strongly related to dementia than when AD was the only neuropathology present.³⁸

In spite of the multiple pathologies present in many participants aged 90 or older, a relatively high percentage of participants with dementia (22%) still have no obvious significant underlying pathology to explain their cognitive

Case 10-2

A woman was 99 years old at the time of her death in a nursing home after a 15-year history of slowly progressive cognitive decline. She was a retired veterinarian and had been widowed at the age of 75. Her symptoms were first noticed in her eighties, when she began getting lost while driving; her license was revoked after she caused an accident by driving against traffic on a one-way street. The visuospatial impairment was soon followed by mild memory impairment and executive dysfunction. The patient was no longer able to take care of her finances and required help to remember her appointments. These changes prompted her daughter to move in with her and seek formal neurologic evaluation when the patient was 91 years old. At the time of the first evaluation, the patient displayed significant impairment in memory (on the California Verbal Learning Test), executive function (on the Trail-Making Test Parts A and B), and praxis (performing learned skilled movements), scoring below the 10th percentile of her age-specific norms. Her score on the Mini-Mental State Examination (MMSE) was 22; results of the neurologic examination were otherwise normal. Noncontrast CT of the head revealed moderate diffuse central and cortical atrophy and moderate periventricular white matter disease. No additional acute or chronic intracranial pathologies were identified. The diagnosis of probable Alzheimer disease was made, and donepezil was initiated. The patient continued to decline gradually. Over 3 years her MMSE score dropped to 11, and she became dependent in all activities of daily living and instrumental activities of daily living. Memantine was added to her medications. A year later, her MMSE score was 10; she started wandering and required constant supervision. The patient was moved to a nursing home at the age of 96 when her daughter could no longer care for her even with additional help. By age 98 she was completely bedbound, incontinent, and mute. She died of aspiration pneumonia at the age of 99.

Despite the typical clinical course for Alzheimer disease, the autopsy revealed minimal pathologic changes in the brain. Although the brain was severely atrophic (brain weight 940 g), neurofibrillary degeneration was

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Braak and Braak stage III, and only sparse neuritic plaques were found (Consortium to Establish a Registry for Alzheimer's Disease plaque score A). Neuropathologic evaluation also revealed mild atherosclerosis and two microinfarcts. No Lewy bodies, Pick bodies, or achromatic neurons were noted. In addition, the examination failed to reveal any signs of large vessel or lacunar infarction, microhemorrhages, or hippocampal sclerosis.

Comment. This case, in which individual pathologies are insufficient to explain the patient's clinical presentation, occurs frequently in the oldest-old population. In the 90+ Study, 22% of participants with dementia did not have sufficient pathology to account for their cognitive loss. The association between common pathologic lesions and dementia in the oldest old is poor, but growing evidence suggests that low levels of multiple pathologies may be additive and may include some pathologies yet to be identified.

symptoms.³⁹ **Case 10-2** demonstrates a common scenario in which an oldest-old patient with dementia presents with a typical clinical manifestation and course of Alzheimer disease but is found to have insufficient pathology on autopsy to explain cognitive deficits. The high prevalence of these discordant cases (ie, cognitive impairment without significant underlying pathology) suggests that certain underlying pathomechanisms of dementia in the oldest old need better quantification or are yet to be identified.

As discussed in the sections above, several factors may be contributing to the weakened association between the neuropathologic features of AD and dementia. First, the higher prevalence of coexisting non-AD pathologies may weaken the association between the clinical and neuropathologic features. Second, the neuropathologic features of AD may develop at a slower rate in people who survive beyond age 90, allowing for compensatory mechanisms to take place.⁴⁰ Finally, because of the diagnostic challenges discussed earlier, the diagnosis of AD might be less accurate in the 90-years-and-older population. Some oldest-old subjects might be classified as nondemented when they are in the preclinical stages of de-

mentia, whereas others might be erroneously diagnosed with dementia due to frailty, sensory losses, or comorbidities that impair cognitive performance on neuropsychological testing. A misdiagnosis of dementia may decrease the strength of association between the clinical diagnosis and the neuropathologic features of AD.

TREATMENT

Although the treatment strategies are virtually the same for oldest-old subjects as they are for the younger elderly, the "start low, go slow" approach is particularly important in this patient population. Pharmacokinetics and pharmacodynamics change with aging. These age-related changes are particularly noticeable in the oldest old and associated with a higher incidence of adverse events.⁴⁹ Therefore, consideration of therapeutic alternatives (ie, nonpharmacologic interventions) should always be the first step. When pharmacologic management is initiated, close monitoring, careful evaluation of the duration of the therapy, and frequent reassessment of indications for discontinuation of medications are crucial in the medical management of dementia in oldest-old patients. In the current issue of **CONTINUUM**, Dr Lon Schneider and

KEY POINT

- The oldest old are particularly susceptible to the unwanted side effects of pharmacotherapy; therefore, the "start low, go slow" approach and nonpharmacologic alternatives are important in the treatment of dementia.

Dr Kristine Yaffe provide expert reviews of pharmacologic and nonpharmacologic treatment strategies for patients with cognitive impairment and dementia that could be applied to the oldest-old population.

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