noted hoarseness as the initial manifestation in 3.9% of 441 patients with ALS being seen by an otolaryngologist. It may be that systematic screening for vocal cord dysfunction by an otolaryngologist, and not only in case of clinical manifestations, would reveal early involvement more frequently than we are now aware of.

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1. Puls I, Jonnakuty C, LaMonte BH, et al. Mutant dynactin in motor neuron disease. *Nat Genet*. 2003;33(4):455-456.
2. van der Graaff MM, Grolman W, Westermann EJ, et al. Vocal cord dysfunction in amyotrophic lateral sclerosis: four cases and a review of the literature. *Arch Neurol*. 2009;66(11):1329-1333.
3. Salameh JS, Atassi N, David WS. SOD1 (A4V)-mediated ALS presenting with lower motor neuron facial diplegia and unilateral vocal cord paralysis. *Muscle Nerve*. 2009;40(5):880-882.
4. Vilariño-Güell C, Wider C, Soto-Ortolaza AI, et al. Characterization of DCTN1 genetic variability in neurodegeneration. *Neurology*. 2009;72(23):2024-2028.
5. Carpenter RJ III, McDonald TJ, Howard FM Jr. The otolaryngologic presentation of amyotrophic lateral sclerosis. *Otolaryngology*. 1978;86(3 pt 1): ORL479-ORL484.

The Challenge and Public Health Implications of Alzheimer Overdiagnosis in the Oldest Old

The recent article by Cairns and colleagues[1] describes a patient who developed episodic memory loss at 88 years of age and was diagnosed with dementia of Alzheimer type (DAT) at 90 years. At the time of his diagnosis, his Mini-Mental State Examination score was 26 of a possible 30. On subsequent evaluation, it was 28 of 30. This case report reflects the problem of an overt overdiagnosis of Alzheimer disease (AD) in patients aged 85 years or older.

With such a liberal and broad definition of DAT, most elderly persons older than 85 years may be considered to have a disease. At least 9 recent neuropathologic studies have demonstrated the heterogeneity of brain pathologies in this patient population.[2] In fact, the correlation between plaque density and dementia diminishes with advancing age, and the load of plaques and tangles may not differ significantly between those with and without dementia.[3] These new findings suggest that neuropathologic criteria for AD are a poor reflection of the link between pathology and functional status in the oldest old persons.[4]

The biochemical markers and imaging studies for AD also demonstrate the dissociation between Alzheimer pathology and dementia; cerebrospinal fluid and Pittsburgh compound B imaging data correlate with each other but not with the cognitive decline or progression of dementia in patients.[5] Moreover, the cerebrospinal fluid testing findings for Alzheimer disease of a high tau and low β-amyloid 1-42 have only 72% specificity; therefore, these values cannot be considered indicative of Alzheimer disease.[6] Could we diagnose a patient with human immunodeficiency virus if the blood assay had a similar 72% specificity?

A danger of overdiagnosis of AD among the oldest old—including individuals in clinical trials—is the loss of potential therapies for those who have "pure" Alzheimer disease. Most elderly persons older than 85 years have a mixture of pathologies, and the increasing number of pathologies, not the mere presence or absence of Alzheimer pathology, is the strong determinant of dementia.[7] Combining patients who have a predominant Alzheimer pathology with elderly persons who have mixed pathologies may be a key factor in accounting for the failure of all drugs tested for AD to date, including trials that have tested omega-3 fatty acids.[8]

Experts and leaders in the field of dementia should consider establishing an age beyond which mild cognitive decline and some loss of functional ability (such as driving) is not synonymous with Alzheimer disease. If the patient in this case report was aged 110 years, would the authors have considered giving him a diagnosis of DAT? In summary, we need to seriously rethink the accuracy of Alzheimer diagnosis among the oldest old persons.[9,10]

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1. Cairns NJ, Ikonomovic MD, Benzinger T, et al. Absence of PIttsburgh compound B detection of cerebralamyloid beta in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer disease. *Arch Neurol*. 2009; 66(12):1557-1562.
2. Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. *Nat Rev Neurol*. 2009;5(12):649-658.
3. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C; Medical Research Council Cognitive Function and Ageing Study. Age, neuropathology, and dementia. *N Engl J Med*. 2009;360(22):2302-2309.
4. Prohovnik I, Perl DP, Davis KL, Libow L, Lesser G, Haroutunian V. Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. *Neurology*. 2006;66(1):49-55.
5. Jagust WJ, Landau SM, Shaw LM, et al; Alzheimer's Disease Neuroimaging Initiative. Relationships between biomarkers in aging and dementia. *Neurology*. 2009;73(15):1193-1199.
6. Mattsson N, Blennow K, Zetterberg H. CSF biomarkers: pinpointing Alzheimer pathogenesis. *Ann N Y Acad Sci*. 2009;1180:28-35.
7. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol*. 2009;66(2):200-208.
8. Fotuhi M, Mohassel P, Yaffe K. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. *Nat Clin Pract Neurol*. 2009;5(3):140-152.
9. Aguero-Torres H, Kivipelto M, von Strauss E. Rethinking the dementia diagnoses in a population-based study: what is Alzheimer's disease and what is vascular dementia? a study from the Kungsholmen project. *Dement Geriatr Cogn Disord*. 2006;22(3):244-249.
10. Fotuhi M. How accurate is Alzheimer's diagnosis among patients over 80? *Practical Neurol*. 2009;8(8):42-45.

In reply

We appreciate Dr Fotuhi's interest in our article.[1] He raises important issues about a long-standing problem in the field, the accuracy of dementia diagnosis in the oldest old persons. Performance of daily activities often is compromised in very old individuals, and it can be difficult to determine whether the functional losses are owing to cognitive vs physical impairments (or both). Even when the losses are caused by cognitive changes, many possible disorders may be responsible. In this context, Dr Fotuhi suggests that the individual described in our recent article in the Archives of Neurology *represents a case of overdiagnosing DAT. For the reasons enumerated below, we respectfully disagree with this suggestion and with several of his comments.*

1. "Liberal and broad definition of DAT . . . " Criteria for the clinical diagnosis of DAT[2] do not restrict the diagnosis on the basis of age. They require a decline from previously attained levels of cognitive function for an individual such that daily function is impaired. The individual in our article entered our research program at 85 years of age without any history of cognitive or functional decline, and his objective cognitive performance was stable for the next 2 years. After his third assessment, there was a sharp inflection point in his episodic memory performance, with persistent decline. This decline of more than 2 standard deviations was a clear change from his previously attained cognitive function and was accompanied subsequently by newly impaired conduct of his usual activities, resulting in the diagnosis of DAT at a very mild stage (Clinical Dementia Rating=0.5). Persons who fulfill standard criteria for DAT should not be exempted from that diagnosis on the basis of age alone.

2. "Most elderly persons older than 85 years may be considered to have a disease." We would argue otherwise, at least regarding AD. Although increasing age is strongly associated with risk for AD, by no means do all older adults experience the disorder. In our sample of 80 individuals enrolled when cognitively normal at a mean age of 81 years and followed up until autopsy at a mean age of 88 years, 41 (51%) remained cognitively normal at the time of death and 27 (34%) did not have neuropathologic AD.[3] It thus is possible for very old individuals to remain cognitively intact and without neuropathologic AD, indicating that the disorder may not be inevitable with age. This premise is supported by the remarkable example of a woman who died at 115 years of age without cognitive deterioration or brain disease.[4]

3. "Poor . . . link between pathology and functional status in the oldest old persons." Age, again, is not the issue; dissociation between the presence of AD lesions in the brain and clinical status is observed in individuals in midlife.[5]

4. "Cerebrospinal fluid and Pittsburgh compound B . . . data [do not] correlate with the cognitive decline or progression of dementia." A growing number of studies have demonstrated that cerebrospinal fluid levels of β-amyloid 42 and tau not only correlate with cognitive decline in individuals with mild cognitive impairment[6] or very mild DAT,[7] they also predict the development of cognitive impairment and dementia in previously cognitively healthy older adults.[8-11] Moreover, we reported in the same issue of the Archives *in which our case report was published that Pittsburgh compound B imaging data in cognitively normal individuals predict who will develop DAT within a few years.[12] These data suggest that the "dissociation between Alzheimer pathology and dementia" noted by Dr Fotuhi may be, at least for some individuals, a reflection of a preclinical stage of AD that ultimately will culminate in DAT if the individual continues to live.[13]*

5. "Increasing number of pathologies . . . is the strong determinant of dementia." We agree that the frequency of mixed demented increases with age. What Dr Fotuhi does not state, however, is that even among the oldest old persons, "pure" AD still is present in about half of individuals with DAT.[14] Moreover, the determination that the coexistent pathologies contribute to the dementia often is based on inference. In our case series of 80 individuals initially without dementia followed up until autopsy, 12 of the 27 persons (44%) without neuropathologic AD had cerebral infarcts vs 19 of the 53 persons (36%) with neuropathologic AD. Because the frequency of infarcts in older adults does not differ in those with or without DAT,[3] it is not apparent that the mere presence of infarcts is sufficient reason to assume that they contribute to dementia. In any event, the discussion of mixed pathologies in reference to our case report is moot, as there was no cerebral pathology other than AD.

6. "[Establish] an age beyond which mild cognitive decline and some loss of functional ability is not synonymous with AD." We agree that many age-associated disorders, alone or in combination, can cause cognitive and functional decline. It would be inappropriate to simply attribute AD as the etiology for decline in all elderly persons. It also would be inappropriate not to diagnose AD as responsible for cognitive decline when careful assessment indicates it is the etiologic disorder, regardless of the individual's age. Dr Fotuhi seems to indicate that cognitive and functional losses should be accepted as part of normal aging. However, much of the cognitive decline that has been attributed to normal aging instead may be caused by preclinical AD[15] or reflect ascertainment bias.[16] When these factors are taken into account, there may be little or no decrement in cognitive performance with age.[3,17]

In summary, by adhering to the principle of intraindividual decline in cognitive and functional performance in diagnosing DAT, appreciating that AD appears not to be inevitable with age, exploring the prognostic value of cerebrospinal fluid and imaging biomarkers, and avoiding the confounds of preclinical AD and ascertainment bias when making assumptions about cognitive and functional loss in truly healthy aging, we can make substantial progress toward Fotuhi and colleagues' goal of improved accuracy of DAT diagnosis in the oldest old persons.

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1. Cairns NJ, Ikonomovic MD, Benziger T, et al. Absence of Pittsburgh Compound B detection of cerebral amyloid B in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer disease. *Arch Neurol*. 2009; 66:1557-1562.
2. American Psychiatric Association. *DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2000.
3. Galvin JE, Powlishta KK, Wilkins K, et al. Predictors of preclinical Alzheimer's disease and dementia: A clinicopathologic study. *Arch Neurol*. 2005; 62(5):758-765.
4. den Dunnen WFA, Brouwer WH, Bijlard E, et al. No disease in the brain of a 115 year old woman. *Neurobiol Aging*. 2008;29(8):1127-1132.
5. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging*. 1997;18(4):351-357.
6. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol*. 2006;5(3):228-234.
7. Snider BJ, Fagan AM, Roe CM, et al. Cerebrospinal fluid biomarkers and rate of cognitive decline in very mild dementia of the Alzheimer type. *Arch Neurol*. 2009;66(5):638-645.
8. Skoog I, Davidsson P, Aevarsson O, Vanderstichele H, Vanmechelen E, Blennow K. Cerebrospinal fluid beta-amyloid 42 is reduced before the onset of sporadic dementia: a population-based study in 85-year-olds. *Dement Geriatr Cogn Disord*. 2003;15(3):169-176.
9. Gustafson DR, Skoog I, Rosengren L, Zetterberg H, Blennow K. Cerebrospinal fluid b-amyloid 1-42 concentration may predict cognitive decline in older women. *J Neurol Neurosurg Psychiatry*. 2007;78(5):461-464.
10. Li G, Sokal I, Quinn JF, et al. CSF tau/Abeta42 ratio for increased risk of mild cognitive impairment: a follow-up study. *Neurology*. 2007;69(7):631-639.
11. Fagan AM, Roe CM, Xiong C, Morris JC, Holtzman DM. Cerebrospinal fluid tau/β-amyloid$_{42}$ ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol*. 2007;64(3):343-349.
12. Morris JC, Roe CM, Grant EA, et al. Pittsburgh Compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer's disease. *Arch Neurol*. 2009;66(12):1469-1475.
13. Morris JC, Price JL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early stage Alzheimer's disease. *J Mol Neurosci*. 2001; 17(2):101-118.
14. Schneider JA, Arvanitakis Z, Leurgans S, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol*. 2009;66(2):200-208.
15. Sliwinski M, Lipton RB, Buschke H, Stewart W. The effects of preclinical dementia on estimates of normal cognitive functioning in aging. *J Gerontol*. 1996;51(4):P217-P225.
16. Tuokko H, Garrett DD, McDowell I, Silverberg N, Kristjansson B. Cognitive decline in high-functioning older adults: reserve or ascertainment bias? *Aging Ment Health*. 2003;7(4):259-270.
17. Johnson DK, Storandt M, Morris J, Galvin JE. Longitudinal study of the transition from healthy aging to Alzheimer disease. *Arch Neurol*. 2009;66(10): 1254-1259.