Clinicopathological concordance of dementia diagnoses by community versus tertiary care clinicians

W. Mok, MD
T. W. Chow, MD
L. Zheng, MS
W. J. Mack, PhD
C. Miller, MD

Abstract

Subjects enrolled in the Autopsy Program at the University of Southern California Alzheimer's Disease Research Center may receive clinical diagnoses from primary care providers in the community or from specialists in neurology. We reviewed the autopsy concordance rates for 463 subjects for diagnoses made by both groups of clinicians. Seventy-seven percent of the sample met neuropathological criteria for Alzheimer's disease (AD). The overall diagnostic accuracy for this sample was 81 percent. Neurologists assessed 200 of the subjects (43 percent). The diagnostic accuracy for any clinical diagnosis among the non-neurologists was 84 percent, and 78 percent (p = 0.07) among neurologists. For AD, non-neurologists had a diagnostic concordance rate of 91 percent and neurologists 87 percent. Where neuropathological AD was missed, non-neurologists had failed to detect any cognitive impairment; neurologists had diagnosed Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Erroneous clinical diagnoses of AD missed dementia with Lewy bodies (DLB) or AD concurrent with Parkinson's disease (PD). Our findings identify specific foci for improving clinical diagnosis of dementia among all physicians managing dementia.

Key words: Alzheimer's disease, autopsy, cerebrovascular disease, clinical audit, dementia, diagnostic accuracy

W. Mok, MD, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China.

T.W. Chow, MD, The Rotman Research Institute, University of Toronto, Toronto, Canada.

L. Zheng, MS, University of Southern California Alzheimer's Disease Research Center, Los Angeles, California.

W.J. Mack, PhD, University of Southern California Alzheimer's Disease Research Center, Los Angeles, California.

C. Miller, MD, University of Southern California Alzheimer's Disease Research Center, Los Angeles, California.

Introduction

The heterogeneous clinical presentations of dementia impose difficulties in clinical diagnosis and variation in diagnostic accuracy. Definitive diagnosis of dementia currently requires neuropathological examination. Previous studies show neuropathological confirmation of the clinical diagnosis of Alzheimer's disease (AD) in 70-92 percent of cases,[1-6] which is a wide range of clinical accuracy.

The majority of clinical audits assess accuracy at tertiary care clinics specializing in dementia. Data on clinicopathological correlation for community physicians and for non-AD dementia cases are less readily available and may vary even more in diagnostic accuracy. Subjects enrolled in the Autopsy Program at the University of Southern California (USC) Alzheimer's Disease Research Center (ADRC) receive clinical diagnoses from community physicians and neurologists. Almost a fourth of the neuropathology database includes patients with non-AD dementia. We audited the autopsy confirmation rates for clinical diagnoses made by community non-neurologist primary care physicians versus neurologists.

Methods

The USC ADRC clinical and autopsy programs have been approved by the USC Institutional Review Board. Subjects in this study or their legal representatives gave informed consent for postmortem autopsy examination between 1984 and 2002. Inclusion criteria were: premortem clinical diagnosis by a physician, consent for autopsy, and neuropathologic diagnosis confirming a dementing illness. Laboratory tests such as vitamin B12, folate, thyroid function test, syphilis serology, and neuroimaging studies (computerized tomography of head or magnetic resonance imaging of brain) were performed at the discretion of the diagnosing physician.

The community clinician group consisted of primary care physicians and other non-neurologists. There are few records available to reflect the diagnostic criteria used by these clinicians. ADRC clinicians used National Institute for Neurological and Communicative Disorders and Stroke, the Alzheimer's Diseases and Related Disorders Association criteria for probable or possible AD,[7] and the State of California Alzheimer's Disease Diagnosis and Treatment Centers criteria for probable or possible vascular dementia.[8] ADRC clinicians screened nondemented, elderly comparison subjects for history of or evidence on physical examination of a central nervous system abnormality, organic or nonorganic psychosis, or dementia. USC ADRC neuropathologists used modified Consotium to Establish a Registry for Alzheimer's Diseases criteria for all subjects.[9]

Table 1. Primary neuropathological diagnoses in the sample

Neuropathological diagnosis	Number of patients (percent) (N = 463)
Alzheimer's disease	339 (73)
Nondemented elderly	23 (5)
Amyotrophic lateral sclerosis	23 (5)
Dementia with Lewy bodies	15 (3)
Parkinson's disease	11 (2)
Combined Alzheimer's disease and Parkinson's disease	19 (4)
Frontotemporal dementia	11 (2)
Vascular dementia	5 (1)
Progressive supranuclear palsy	7 (2)
Cerebrovascular disease	8 (2)
Creutzfeldt-Jakob disease	1 (<1)
Acquired immunodeficiency syndrome	1 (<1)

Table 2. Concordance rate for each clinical diagnosis

Clinical diagnosis	Primary care physicians number confirmed at autopsy (clinical diagnosis percent)	Neurologists number confirmed at autopsy (clinical diagnosis percent)
Alzheimer's disease	205/225 (91)	112/129 (87)
Amyotrophic lateral sclerosis	0	19/31 (61)
Progressive supranuclear palsy	0	5/6 (83)
Parkinson's disease	0	8/13 (62)
Nondemented elderly	15/29 (52)	4/8 (50)
Frontotemporal dementia	0/1 (0)	7/9 (78)
Cerebrovascular disease	1/2 (50)	0/1 (0)
Vascular dementia	0/1 (0)	0/2 (0)
Combined Alzheimer's disease and Parkinson's disease	0	0/1 (0)

Table 3. Clinical diagnoses for discordant cases with autopsy diagnosis of AD		
Clinical diagnosis	**Primary care physicians number of patients (percent) (N = 17)**	**Neurologists number of patients (percent) (N = 14)**
Nondemented elderly	11 (64.7)	1 (7)
Vascular dementia	4 (23.5)	1 (7)
Frontotemporal dementia	1 (5.9)	1 (7)
Parkinson's disease	0 (0)	4 (29)
Cerebrovascular disease	1 (5.9)	1 (7)
Progressive supranuclear palsy	0 (0)	1 (7)
Amyotrophic lateral sclerosis	0 (0)	5 (36)

We calculated the concordance of autopsy confirmations for each group of clinicians for each dementia etiology. We then compared the concordance rates using chi-square tests.

Results

Upon review of the ADRC database, we identified 463 eligible subjects, with slightly more women (55.7 percent) than men. Mean age at death was 79.8 years (range from 40-104 years). Non-neurologists in the community assessed 263 subjects (56.8 percent), and neurologists assessed 200 subjects (43.2 percent). The overall diagnostic accuracy for the sample was 81.2 percent. The accuracy for clinical diagnosis by non-neurologists was 84 percent, while for neurologists it was 77.5 percent ($p = 0.125$). Table 1 lists the neuropathological diagnoses for the sample. In addition, there were two autopsy-diagnosed cases of corticobasal ganglionic degeneration (CBD): one of the CBD cases had been clinically diagnosed as frontotemporal dementia; the other had been diagnosed nonspecifically as "dementia."

Table 2 lists the concordance rates for each clinical dementia diagnosis. There was no statistically significant difference in the clinical diagnostic concordance rate between the two groups of physicians ($p = 0.07$). Tables 3 and 4 detail the nonconcordant diagnoses. Discordance among non-neurologists was mostly due to missing cognitive impairment altogether or mistaking vascular dementia for AD, whereas the neurologists contributing to this sample had difficulty distinguishing Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) from AD. It is unknown whether the one case with AIDS had HIV testing on file (Table 1). The one case of Creutzfeld Jakob disease had been diagnosed clinically as AD; otherwise, the USC ADRC Neuropathology Core does not accept clinically diagnosed Creutzfeldt-Jakob disease cases.

Discussion

The overall diagnostic accuracy for the sample, as well as for both groups of physicians, was high, which is consistent with other audits.[1-6] We were expecting the neurologists to have higher concordance rates than the community-based non-neurologists, but there was no significant difference between them. Primary care physicians manage numerous health problems presented by patients on a limited time schedule. A routine primary care physician office visit is much shorter than the standard 4-5-hour, multidisciplinary ADRC evaluation. The time difference might allow for more data collection in dementia symptoms and course of illness. In addition, neuroimaging technology such as functional MRI, PET, and SPECT scans of the brain are often more readily available to the specialist in a tertiary center that is funded specifically to complete these studies than to the community care physician. Nevertheless, these features did not improve diagnostic accuracy in a statistically significant way. There were clinically significant differences, however.

The types of clinical diagnostic errors made in this sample indicate that non-neurologists have the most difficulty differentiating between cognitive changes of normal aging and AD. This may be due to the indistinct

Table 4. Cases misdiagnosed clinically as AD		
Neuropathological diagnosis	**Primary care physicians number of patients (percent) (N = 20)**	**Neurologists number of patients (percent) (N = 17)**
Dementia with Lewy bodies	2 (10)	10 (59)
Vascular dementia	4 (20)	1 (6)
Both Alzheimer's disease and Parkinson's disease	7 (35)	2 (12)
Frontotemporal dementia	1 (5)	1 (6)
Parkinson's disease	0 (0)	2 (12)
Amyotrophic lateral sclerosis	0 (0)	1 (6)
Acquired Immunodeficiency Syndrome	1 (5)	0 (0)
Creutzfeldt-Jakob disease	1 (5)	0 (0)
Neuropathologically normal	2 (10)	0 (0)

boundary between normal aging and the earliest stage of dementia. Amnestic mild cognitive impairment (MCI)[10] as a predementia stage is difficult to diagnose consistently without neuropsychological testing at this time. In neuropathological evaluation, the USC ADRC now applies Braak scoring for stages of progression in AD. These stages correlate best with the clinical progression of MCI to AD.[11] Therefore, some cases of neuropathological AD may not have met clinical criteria for dementia by the time of death. Because our study included no subjects with an MCI diagnosis at the time of death, we cannot comment on non-neurologist versus neurologist diagnostic accuracy for MCI.

The neurologists tended to miss features of dementia with Lewy bodies (DLB) or presence of Lewy bodies or PD while detecting elements of AD. Clinical features common to AD and DLB might contribute to the problem. Both dementias are progressive in nature, with psychotic and extrapyramidal symptoms emerging in different stages of the dementia. Our results for this diagnosis resemble Hohl et al.'s[12] report of 50 percent clinical diagnostic accuracy. Careful clinical survey for fluctuations in consciousness and the presence of well-structured, detailed visual hallucinations might be useful to differentiate DLB from AD and improve the diagnostic accuracy. Ferman et al.[13] recently reported specific types of fluctuations in level of consciousness that reliably distinguish between the two. Use of α-synuclein immunohistochemistry has resulted in detection of Lewy bodies at autopsy in over 60 percent of sporadic AD cases diagnosed clinically.[14] Until the distinction between the clinical syndrome of DLB and the neuropathological findings of the Lewy body variant of AD is clear, diagnostic concordance may continue to be a moving target.

In addition, neurologists in this analysis mistook AD for PD and ALS, which was surprising. Clinical records on these cases were not available for review of whether patients presented with atypical AD symptoms.

Major limitations to this study include variable availability of criteria used to make the clinical diagnoses and variable time intervals between the time of clinical assessment and the time of death. The data available do not allow us to distinguish among: 1) patients without cognitive impairment at the clinician's office but with later progression to AD before death; 2) patients with the diagnosis of MCI missed in the clinician's assessment, which later progressed to AD; and 3) patients with a diagnosis of dementia missed altogether. Cognitive changes from normal should have been detected in those subjects who started as normal, elderly controls and

showed changes on serial neuropsychometric tests administered under the ADRC Longitudinal Study protocol, but not all subjects in this sample participated in the Longitudinal Study.

Findings from this study indicate an opportunity to educate community care physicians to better detect cognitive impairment among seemingly normal elderly patients. Early diagnosis affects patient management significantly because symptomatic treatment is most likely to help in early stages of dementia, and families often benefit from early referrals to ancillary services. Improved diagnostic accuracy in the community could also more appropriately determine resource allocation.

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References

1. Lim A, Tsuang D, Kukull W, et al.: Clinico-neuropathological correlation of Alzheimer's disease in a community-based case. *J Am Geriatr Soc*. 1999; 47(5): 564-569.
2. Rasmusson DX, Brandt J, Steele C, et al.: Accuracy of clinical diagnosis of Alzheimer's disease and clinical features of patients with non-Alzheimer's disease neuropathology. *Alzheimer Dis Assoc Disord*. 1996; 10(4): 180-188.
3. Larson EB, Edwards JK, Meara EO, et al.: Neuropathologic diagnostic outcomes from a cohort of outpatients with suspected dementia. *J Gerontol Med Sci.* 1996; 51A(6): M313-318.
4. Petrovitch H, White LR, Ross GW, et al.: Accuracy of clinical criteria for AD in the Honolulu-Asia Aging Study, a population-based study. *Neurology*. 2001; 57(2): 226-234.
5. Pearl GS: Diagnosis of Alzheimer's disease in a community hospital-based brain bank program. *South Med J*. 1997; 90(7): 720-722.
6. Nagy Z, Esiri MM, Hindley NJ, et al.: Accuracy of clinical operational diagnostic criteria for Alzheimer's disease in relation to different pathological diagnostic protocols. *Dement Geriatr Cogn Disord*. 1998; 9(4): 219-226.
7. McKhann G, Drachman D, Folstein M, et al.: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. *Neurology*. 1984; 34(7): 939-944.
8. Chui HC, Victoroff JI, Margolin D, et al.: Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology*. 1992; 42(3 Pt 1): 473-480.
9. 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(4): 479-486.
10. Petersen RC, Smith GE, Waring SC, et al.: Aging, memory and mild cognitive impairment. *Int Psychogeriatr*. 1997; 9(Suppl 1): 65-69.
11. Newell KL, Hyman BT, Growdon JH, et al.: Application of the National Institute on Aging (NIA)-Reagan Institute criteria for the neuropathological diagnosis of Alzheimer disease. *J Neuropathol Exp Neurol.* 1999; 58(11): 1147-1155.
12. Hohl U, Tiraboschi P, Hansen LA, et al.: Diagnostic accuracy of Dementia with Lewy bodies. *Arch Neurol*. 2000; 57(12): 347-351.
13. Ferman TJ, Smith GE, Boeve BF, et al.: DLB fluctuations: Specific features that reliably differentiate DLB from AD and normal aging. *Neurology*. 2004; 62(2): 181-187.
14. Hamilton RL: Lewy bodies in Alzheimer's disease: A neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol.* 2000; 10(3): 378-384.