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Diagnostic Validity of the Dementia Questionnaire for Alzheimer Disease

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Objective: To determine the sensitivity and specificity of postmortem dementia diagnoses based on a retrospective informant interview by comparison with criterion standard neuropathological diagnoses and the results of previous clinical examinations.

Setting: Three university-based academic research centers.

Subjects: Fifty-four deceased elderly persons with Alzheimer disease, another dementing disorder, a neurologic disease resulting in functional impairment but no dementia, or no neurologic disorder.

Methods: Blinded nonclinician interviewers administered the Dementia Questionnaire (DQ) by telephone to informants, typically close relatives, who were familiar with the intellectual and functional status of the subjects before death. Two senior clinicians (L.J.T. and C.K.) rated each DQ for the presence or absence of a dementia syndrome during life and for the specific disorders causing the dementia, if present. Raters were blinded to the neuropathological findings and based their assessments only on data provided by responses to the DQ. Comparison was made with diagnoses based on neuropathological assessment. In most cases, the results of antemortem clinical examinations were also available as a check on the clinical diagnosis of the dementia syndrome. Sensitivity and specificity of the DQ diagnoses were computed, and chance-corrected

agreement measures were calculated for the 2 independent DQ raters (L.J.T. and C.K.).

Results: Compared with antemortem clinical diagnosis, the average sensitivity of the DQ for the clinical syndrome of dementia was 92.8%, the specificity was 89.5%, and the interrater agreement was 98% ($\kappa=0.96$). Among 7 subjects with mild dementia (Mini-Mental State Examination score ≥ 24 at the last clinical examination), 5 (71%) were correctly identified using the DQ. The DQ correctly indicated the absence of dementia in 8 (80%) of 10 subjects with other neurologic disorders causing functional impairment. Compared with the neuropathological diagnoses, the DQ differentiated Alzheimer disease from other primary causes of dementia with a sensitivity of 89% and a specificity of 72%. The interrater agreement was 93.8% ($\kappa=0.85$).

Conclusions: Compared with the results of the antemortem clinical examinations, the DQ was sensitive to the presence of dementia, detected most cases of mild dementia, and discriminated dementia from other neurologic disorders causing functional impairment. Compared with the neuropathological diagnoses, the ability of the DQ to differentiate Alzheimer disease from other dementing disorders indicates that it may be useful as a research tool.

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NUMEROUS GENETIC determinants and susceptibility factors for Alzheimer disease (AD) and other dementias have been described.^{1,2} Linkage studies have contributed substantially to this increased knowledge.^{3,4} Such studies depend on the availability, accuracy, and completeness of clinical diagnoses for multiple members of a family, some of whom may be unavailable for clinical examination. To facilitate the ascertainment of more complete pedigrees, several instruments have been developed to help generate "remote" neurologic diagnoses, that is, to as-

sign specific diagnoses when the subjects are unavailable for examination.

Previous studies of the usefulness of these instruments have encountered numerous limitations. Kukull and Larson⁵ used a retrospective mailed questionnaire to discriminate AD from non-AD dementia in 36 patients with neuropathological diagnoses. While the sensitivity of the instrument was excellent (93%), the specificity was only fair (43%). Davis and colleagues⁶ compared diagnoses based on the Retrospective Collateral Dementia Interview, with diagnoses based on the results of comprehensive clinical and neuropathological examinations. Of the 21

SUBJECTS AND METHODS

SUBJECTS

The subjects were 54 deceased persons for whom complete neuropathological assessments were available. They represented 4 groups comprising persons in the following diagnostic categories: (1) AD, (2) dementia due to other causes, (3) neurologic impairment other than dementia, and (4) elderly control subjects without neurologic disorders. A breakdown of the subjects included is shown in **Table 1**. The subjects were selected from 3 university-based sites in the United States: The Alzheimer's Disease Research Center at the University of California, San Diego; the Baltimore Longitudinal Aging study at The Johns Hopkins University, Baltimore, Md; and the Alzheimer's Disease Center at the University of Kansas, Kansas City. The following inclusion criteria were used: (1) age at first clinical diagnosis, 50 to 85 years; (2) an interval of 3 years or less between the last clinical examination and death; and (3) an interval of 5 years or less between DQ administration and death. For all cases, a knowledgeable relative or friend who could serve as the informant was required for the DQ interview. The presence of mild cognitive impairment or difficulties in a single cognitive domain (ie, the subject did not meet criteria for dementia) did not exclude a subject from the study.

PROCEDURES

The DQ is a semistructured interview comprising 6 sections: (1) memory and cognition, (2) expression (language), (3) daily functioning, (4) recognition of problems (insight), (5) other medical and psychiatric difficulties, and (6) education and demographic data. Details of the instrument have been published.¹⁰ The DQ was administered by telephone to informants who were knowledgeable about the medical history and antemortem functional status of the subjects. Before the interviews, informants were contacted by one of the investigators (R.J.E.), who instructed the informants to answer the DQ items as completely as possible without revealing the specific diagnosis, if they knew it. While most DQ questions are answered in a multiple-choice format, marginal notes are permitted to assist raters in the interpretation of responses. Two interviewers administered the DQ; one (K.J.) was a third-year medical student, and the other was an administrative assistant. The 2 interviewers jointly reviewed 10 consecutive DQs to reach a consensus on administration of the instrument. Each interview lasted approximately 45 minutes. Before ratings were performed, the DQ forms were stripped of identifiers, and all marginal notes revealing the results of the neuropathological assessment were eliminated.

The DQs were scored independently by 2 raters at different institutions (L.J.T. and C.K.). The raters were provided only with answers from the DQ to make their diagnoses. First, the raters were asked to judge whether the subject had dementia and then to indicate whether AD was the primary cause of the dementing illness or if another disorder principally accounted for the dementia. In the cases in which a gradually progressive dementia preceded the onset of

parkinsonism by several years, AD was chosen as the primary cause of dementia. In the cases in which parkinsonian features (eg, unilateral tremor, shuffling gait, or postural instability) were the first and most prominent symptoms of the disease but dementia followed, Parkinson disease (PD) was chosen as the likely diagnosis. When the onset of dementia and parkinsonian features occurred in proximity, the diagnosis of AD with concomitant Lewy body disease was given. If progressive dementia and stroke or a transient ischemic attack occurred, raters chose 1 of the following diagnostic classifications based on the results of the overall clinical examination: (1) AD as the primary cause of dementia with stroke as an incidental feature, (2) vascular dementia (ie, cerebrovascular disease as the primary cause of dementia), or (3) mixed dementia (ie, cerebrovascular disease and AD as commensurate contributors to the clinical syndrome).

CLINICAL EXAMINATION

The results of complete antemortem clinical examinations, including mental status and physical and neurologic examinations, were available for 46 of the 54 subjects. Of these, 45 included scores on the Mini-Mental State Examination (MMSE¹²), performed a mean±SD of 1.0±0.89 years before death. The examinations also included a medical and neurologic history obtained from an informant and the results of a physical examination and laboratory studies. In the remaining 8 subjects (including 3 subjects with AD, 1 subject with vascular dementia, 2 neurologically healthy control subjects, and 2 control subjects without dementia but with another neurologic disorder), the clinical diagnosis was based on informant interview and review of the medical records. Clinical dementia was defined according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*.¹³ Published clinical research criteria for AD¹⁴ were used.

NEUROPATHOLOGICAL EXAMINATION

Neuropathologically, AD was defined according to the criteria of the Consortium to Establish a Registry for Alzheimer's Disease, Durham, NC.¹⁵ The Consortium criteria for *definite* and *probable* AD require a clinical diagnosis of dementia, which was omitted for the purpose of this study. The standard neuropathological diagnostic research criteria for PD¹⁶ were used. The designation *PD with dementia* indicated that a history of movement disorder preceded (by several years) the onset of cognitive difficulties, if any, and that neuropathological changes of PD, including nigral Lewy bodies, were present. Cortical Lewy bodies were identified by antiubiquitin immunostaining, and cases with neuropathological AD and concomitant cortical and subcortical Lewy bodies were designated as AD with Lewy body disease.¹⁷ Subjects were designated as having vascular dementia if at least 1 infarct greater than 10 mL was identified¹¹ and no other findings were present that could account for the presence of dementia. If criteria for AD and vascular dementia were met, a diagnosis of *mixed* dementia was assigned.

Continued on next page

STATISTICAL ANALYSES

Sensitivity was calculated as the number of test-positive cases (eg, subjects with a DQ diagnosis of AD) divided by the number of true-positive cases (ie, subjects with a neuropathological diagnosis of AD) and specificity, as the number of test-negative cases divided by the number of true-negative cases. The positive predictive value was the proportion of true-positive cases among the cases classified as positive by the DQ. The group means for continuous variables were compared by using analysis of variance or the Student *t* test as appropriate. The proportions were compared by using the χ^2 test. Analyses were performed using statistical calculation software (SPSS 6.1 for Macintosh, SPSS Inc, Cary, NC). Data are given as mean \pm SD unless otherwise indicated.

subjects in their study for whom clinical and neuropathological confirmation were available, 18 had severe dementia (clinical dementia rating, ≥ 3) before death. Furthermore, AD was documented neuropathologically in all dementia cases studied. Thus, no conclusions could be drawn about the sensitivity of the Retrospective Collateral Dementia Interview for the detection of mild or moderate dementia or about its specificity for the discrimination of AD from other dementing illnesses. Barber et al⁷ compared the ability of a retrospective post-mortem interview of informants to discriminate AD from frontotemporal dementia in 37 cases in which the neuropathological diagnoses were available. No control subjects were included in this study, so the ability of the interview to detect dementia cannot be assessed. Moreover, the prevalence of frontotemporal dementia is somewhat lower than that of other dementing illnesses such as AD, vascular dementia, and dementia associated with Lewy bodies.⁸

The Dementia Questionnaire (DQ)⁹ was designed not only to provide information pertinent to the diagnosis of the dementia syndrome but also to ascertain a specific cause of the cognitive and functional impairments. A previous report described the reliability, sensitivity, and specificity of the DQ for diagnoses based on clinical examination.¹⁰ The present study extends that assessment of the accuracy of DQ diagnoses by including patients with dementia from causes other than AD and by validating the clinical diagnoses from the DQ against the neuropathological diagnoses. This is important because although advances have been made in the clinical diagnosis of AD, the standard remains the neuropathological diagnosis.¹¹

RESULTS

Clinical and demographic characteristics of the 54 study subjects are provided in **Table 2**. The sample included 39 men and 15 women; the preponderance of men in the study is consistent with the previously

reported demographics of the Baltimore Longitudinal Aging Study cohort¹⁸ and with the inclusion of subjects with PD, which has a male predominance. The overall age at death was 79.3 \pm 8.5 years, and educational attainment was 16.1 \pm 3.4 years. For subjects with dementia, the age at onset of dementia symptoms was 73.3 \pm 10.8 years. For the 46 subjects for whom complete data from the antemortem clinical examination were available, the interval between the last clinical examination and death was 1.0 \pm 0.9 years. The AD and non-AD dementia groups were similar in age at onset and in the interval between clinical evaluation and death. Compared with the non-AD group, the AD group included a higher proportion of women and had a lower mean level of education, but these differences were not statistically significant. There was a trend for subjects with a neuropathological diagnosis of AD to have lower MMSE scores than subjects with non-AD dementing disorders at the last clinical examination ($P=.06$, 2-tailed test). Of the informants, 35 were spouses of the deceased subjects, 16 were sons or daughters, 2 were other family relatives, and 1 was a close friend.

DIAGNOSIS OF THE DEMENTIA SYNDROME BY USING THE DQ

Two independent raters (L.J.T. and C.K.) scored each of the DQ interviews. Interrater agreement on the diagnosis of dementia vs no dementia was high (53/54 subjects [98.1%]; $\kappa=0.96$). In the case for which there was a disagreement, the DQ diagnoses assigned were AD and PD with cognitive impairment. Compared with the results of the antemortem clinical examination, the sensitivity of the DQ for the diagnosis of dementia averaged 92.8% (91.4% for 1 rater and 94.3% for the other). The specificity of the DQ was 89.5% for both raters. Among 7 subjects with mild dementia at the last antemortem clinical examination (MMSE score, ≥ 24 ; mean time of administration, 1½ years before death), the postmortem DQ correctly diagnosed dementia in 5 subjects (71%). Of the 10 subjects with no dementia but with other neurologic disorders, 8 (80%) were correctly designated as not having dementia by using the DQ responses. In both cases in which the responses of the DQ resulted in false-positive errors (ie, indicated dementia in a subject who did not have clinically evident dementia), the clinical diagnosis was PD without dementia, and the neuropathological diagnosis was PD; the last MMSE scores of these 2 subjects were 25 and 29.

False-negative DQ errors (ie, failure to diagnose dementia when it was present at the antemortem clinical examination) were made in 2 subjects by 1 rater and in 3 subjects by the other. Two of these subjects were the same for both raters; the last recorded MMSE scores in these subjects were 26 and 28. Thus, 2 of the false-negative errors were in subjects who had mild dementia at the last clinical examination. For the remaining subject, 1 rater attributed the functional impairment evident on the DQ to motor disability and, thus, did not diagnose dementia in a subject with a final clinical-neuropathological diagnosis of AD.

DIAGNOSIS OF SPECIFIC DEMENTING ILLNESSES BY USING THE DQ

To evaluate the capacity of the DQ to distinguish AD from other dementing disorders, we compared the final diagnoses made by the 2 raters based on the DQ responses with the neuropathological diagnoses. There were 32 subjects with a DQ diagnosis of dementia. In 22 (69%) of these subjects, both raters designated AD as the primary cause of dementia; in another 8 subjects (25%), the raters agreed that a disorder other than AD was the primary cause or a commensurate contributor to the dementia syndrome; and in 2 cases (6%), they disagreed.

Table 1. Diagnoses of Study Subjects

Diagnosis	No. of Subjects
Dementia	35
Primary cause of dementia	
Alzheimer disease	25
Isolated	20
With cortical Lewy body disease	3
With incidental stroke	2
Not Alzheimer disease	10
Parkinson disease and dementia	5
Mixed vascular dementia and Alzheimer changes	3
Vascular dementia	2
No dementia	19
Neurologically healthy	9
Disease present	10
Stroke	6
Parkinson disease	4

Overall agreement as to whether AD was the primary cause of dementia was 93.8% ($\kappa=0.85$). In the 2 subjects in which the raters disagreed, both indicated that AD contributed to the dementia, but they differed about whether AD was the principal or contributing cause. The sensitivity of the postmortem DQ for the diagnosis of AD as the primary cause of dementia averaged 89% (91% for 1 rater and 87% for the other), and the specificity averaged 72% (67% and 78%). The positive predictive value for the specific diagnosis of AD as the primary cause of dementia was 89.2%; the negative predictive value, 72.5%; and the efficiency, 84.4%.

The cases of dementia studied included 3 subjects with combined AD changes and cortical Lewy bodies, and 5 subjects in whom cerebrovascular lesions and neuropathological features of AD were present. The diagnostic accuracy in this group averaged 62% (5/8 subjects) for the 2 raters. All but 1 of the erroneous DQ diagnoses consisted of misidentification of the primary cause of dementia, eg, designating vascular disease as the primary cause of dementia when the neuropathological diagnosis was AD with incidental stroke. By comparison, the diagnostic accuracy of the DQ among subjects with dementia and a single neuropathological diagnosis was 81%.

For all neuropathological diagnoses and all subjects (including subjects without dementia), the overall diagnostic accuracy of the DQ was 80% (43/54 subjects). The results of the antemortem neurologic and neuropsychological examinations were unavailable for 8 subjects; the diagnostic accuracy of the DQ in these subjects was 100%.

Table 2. Subject Characteristics*

	Subjects With Dementia		Control Subjects		P†
	AD Dementia (n=25)	Non-AD Dementia (n=10)	OND Without Dementia (n=10)	Neurologically Healthy Elderly (n=9)	
Age, y					
At onset of symptoms	73.3±11.3	72.3±12.283
At death	80.9±9.92	79.0±8.4	75.6±7.5	78.3±7.4	.42
Sex, F/M	10/15	2/8	2/8	1/8	.28
Education, y‡	14.9±3.9	17.4±2.4	16.0±2.9	18.1±2.0	.05
Interval to death, y					
From last clinical examination§	0.9±0.8	0.7±0.8	1.2±1.0	1.6±0.9	.19
From DQ interview	2.1±1.4	1.8±1.6	2.1±1.5	1.8±1.6	.93
Last MMSE					
Score	9.0±10.2	17.1±9.3	27.8±2.1	28.9±1.1	<.001
Range, raw score	0-26	0-28	24-30	27-30	...
Study site, No. of subjects					
UCSD	18	1	1	1	...
JHU	7	4	6	8	...
UK	0	5	3	0	...

*AD Dementia indicates that Alzheimer disease was considered the primary cause of dementia; non-AD dementia (NAD), a process other than Alzheimer disease was the sole or a major contributing cause of the dementia; OND, other neurologic disease; ellipses, not applicable; DQ, Dementia Questionnaire; MMSE, Mini-Mental State Examination; UCSD, the Alzheimer's Disease Research Center, University of California, San Diego; JHU, the Baltimore Longitudinal Aging Study, The Johns Hopkins University; and UK, the Alzheimer's Disease Center, University of Kansas. Data are given as mean±SD unless otherwise indicated.

†P by analysis of variance.

‡No 2 groups were significantly different (Tukey-Kramer Honestly Significant Difference test).

§Antemortem clinical examinations were unavailable for 8 subjects, including 3 with AD, 1 with NAD, 2 control subjects with dementia and OND, and 1 NL.

||Alzheimer disease dementia different from OND and NL, $P<.001$. Non-AD dementia different from NL, $P<.05$. The last MMSE score was missing for 9 subjects, including 3 with AD, 2 with NAD dementia, 2 with dementia and OND, and 2 NLS (see "Clinical Examination" Subsection in the "Subjects and Methods" section).

Despite the limitations of informant-based diagnosis, in most cases, the DQ detected clinical dementia (sensitivity, 91%) and discriminated dementia from other neurologic disorders that cause functional impairment. Two independent DQ raters agreed on the presence or absence of clinical dementia in all but 1 subject. The DQ discriminated AD from other causes of dementia with acceptable sensitivity (89%) and specificity (72%), achieving concordance rates comparable to those reported in traditional clinicopathologic correlation studies.^{11,19} Because multiple centers contributed cases to this study, and because interrater agreement was good, the findings may be considered generalizable.

Informants may be unable to differentiate disability due to dementia from disability due to motor, sensory, or psychiatric impairment, leading to potential false-positive diagnoses. The inclusion of a group of subjects without dementia but with other neurologic disorders therefore provided an important test of validity of the DQ. Ten of our subjects had PD or stroke but did not meet the criteria for dementia. In 2 of the subjects with PD, motor impairment led to false-positive diagnoses of dementia based on the DQ responses. In the remaining 8 subjects, however, the DQ correctly indicated the absence of dementia. Most of the false-negative errors associated with the DQ were for subjects with mild dementia at the last clinical examination. Furthermore, the 2 raters made the same errors in most cases, suggesting that the information provided by the DQ informant was inaccurate or that the DQ did not adequately capture important clinical information in these particular cases.

Because the design of our study required that all subjects undergo brain autopsy, and because most autopsied subjects have previously participated in clinical research, we were limited in our choice of subjects and informants. Because many informants were involved in the subjects' previous antemortem clinical examinations, they may have been more sophisticated in their ability to discriminate dementia from other disorders. We noted also that the educational attainment of our subjects, and likely their informants, was relatively high. It is possible that administration of the DQ to less sophisticated informants might result in poorer accuracy of diagnoses based on DQ responses. Nevertheless, even in the 8 subjects in which no antemortem neurologic or neuropsychological examination results were available, the diagnostic accuracy of the DQ was 100%.

The familiarity of informants with the subjects' neuropathological diagnoses was not systematically assessed. It is the policy of each of the research centers to release such information to family members on request. Several informants asked to be provided autopsy reports at the time of the DQ interview, suggesting that they had not seen this information. For the informants who were aware of the neuropathological diagnosis, this knowledge may have biased their responses.

The mean interval between the DQ interview and death in this study was 2 years. Because informant-based interviews may become less reliable as the post-

mortem interval lengthens, and because knowledgeable informants may die, the DQ is most useful when administered within a few years after death.

Severe dementia and normal cognitive function can be differentiated easily; however, the history given by an informant may not accurately identify subjects in the early stages of a dementing process. Because most previous studies of retrospective informant-based diagnosis have included only subjects with severe dementia before death,⁶ their utility in the presence of mild or moderate dementia is uncertain. We studied 7 subjects (4 with isolated AD, 1 with AD and incidental stroke, 1 with mixed AD and vascular dementia, and 1 with PD) who had mild dementia (MMSE score, ≥ 24) when tested a mean of 1½ years before death. The diagnostic accuracy remained acceptable (5/7 [71%]) in this group. A recent study comparing dementia diagnoses based on DQ responses with neuropathological diagnoses²⁰ reported sensitivity and specificity values comparable to those found in our study. Most of the subjects in that study, however, had severe dementia (mean clinical dementia rating, 3.8) before death, and most subjects did not undergo a formal antemortem clinical examination to confirm the presence of dementia and exclude other neurologic disorders.

Of particular difficulty for clinicians is the differentiation of dementias due to mixed causes from dementias with a sole predominant cause. In most cases of mixed dementia, AD changes coexist with cerebrovascular disease or Lewy body disease (with or without suggestive clinical features). The diagnostic accuracy for AD plus cerebrovascular disease is about 50% in most clinicopathologic case series.^{11,19,21-23} When AD and cortical Lewy body disease coexist, nomenclature and the cause of clinical dementia remain the subjects of controversy.²⁴ Our study included 8 subjects with multiple contributing causes. While the average diagnostic accuracy among these subjects was somewhat lower (62%) than among subjects with a single neuropathological diagnosis (81%), such figures are comparable to those reported in previous series in which clinicopathologic correlation was performed.^{11,19,23}

We conclude that the DQ is a standardized instrument that can be used to reliably diagnose dementia and, specifically, AD in deceased persons. Perhaps the DQ also could be applied to the study of living subjects who are unavailable for clinical examination. The strengths of the DQ may facilitate the study of large pedigrees with inherited dementing disorders such as AD. The DQ may also show promise as an instrument for use in epidemiologic studies by retrospectively determining the prevalence of dementia before death in elderly persons.

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