Differences Between Pick Disease and Alzheimer Disease in Clinical Appearance and Rate of Cognitive Decline

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Objectives: To define the cognitive characteristics of Pick disease (PcD), and to determine which features distinguish PcD from Alzheimer disease (AD), in a cross-sectional and longitudinal study.

Methods: The participants were 44 patients with PcD (10 pathologically verified), 121 patients with AD (14 pathologically verified), and 60 normal control subjects. We obtained information regarding the initial symptom of dementia from each patient’s caregiver, estimated global dementia severity by the Blessed Dementia Scale and the Activities of Daily Living Scale, and assessed specific cognitive domains by administering 10 tests of memory, language, visuospatial, and reasoning abilities and selective attention.

Results: Among initial symptoms reported by caregivers, personality change and language impairment were significantly more common in PcD than AD; deficits in memory were common in both groups but more prevalent in AD (P<.001). At initial cognitive testing, the scores of patients with PcD were inferior to those of normal controls on all tests, except on a measure of visuospatial function; the scores of patients with AD were inferior to those of controls on all tests. Patients with PcD were superior to patients with AD on measures of explicit memory (P<.001) and visuospatial function (P=.001) but had greater impairments on the Activities of Daily Living Scale (P<.05). During the course of illness, patients with PcD declined significantly faster than those with AD on language tests and on global measures of dementia severity (P<.05), whereas measures of explicit memory and visuospatial and reasoning abilities worsened equally in both patient groups.

Conclusions: There is a characteristic cognitive profile and course of dementia in PcD. Nonetheless, cognitive test performance does not clearly distinguish PcD from AD.

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SUBJECTS AND METHODS

SUBJECTS

This study was based on data collected from 34 clinically diagnosed and an additional 10 neuropathologically diagnosed patients with PcD (Table 1), all of whom were examined between January 1, 1985, and December 31, 1996, in the Memory Disorders Unit (MDU) of the Massachusetts General Hospital, Boston. These 44 cases represented 2% of all patients with dementia examined in the MDU during this period. During the same time, the prevalence of AD was 63%. These percentages are comparable with those recorded in the MDU Brain Bank: of 605 autopsies conducted between 1985 and 1996, 54% had AD and 3% had PcD or other variants of lobar atrophy. The clinical diagnosis of PcD was made in individuals with progressive dementia, prominent language impairments, and subtle personality changes; these features meet current criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,10 and International Classification of Diseases, 10th Revision (ICD-10).17 Three of the 44 patients with PcD in the sample had an antemortem diagnosis of AD but a neuropathological diagnosis of PcD; their behavioral data are included in the PcD group. All patients with an antemortem diagnosis of PcD who underwent autopsy had PcD neuropathologically; none had AD. All of the patients with autopsy-confirmed AD had a clinical diagnosis of AD; none had a clinical diagnosis of PcD. The neuropathological examination in all 10 cases of PcD demonstrated lobar atrophy with ballooned neurons and numerous Pick bodies in the damaged brain regions.

METHODS

The course of dementia was assessed in all 44 patients with PcD by the Blessed Dementia Scale (BDS)18 and Activities of Daily Living Scale (ADL)19 scores. In addition to the BDS and ADL, 33 of the 44 completed, at least once, a set of standardized cognitive tests that examined memory, language capacities, visuospatial skills, abstract reasoning abilities, and selective attention.20-21, 19 (6 studied by autopsy and 13 living) had 2 or more examinations (with a mean of 1.1 years between the first 2 sessions), 7 had 3 or more, 2 had 4 or more, and 1 had 6. They were followed up for a mean of 1.8 years (SD, 1.1 years; range, 0.5 to 5.3 years).

The normal control subjects (NCSs) included 60 older subjects living in the community (Table 1). They were generally spouses or caregivers of the patients, and some were volunteers from the Geriatric Education Center of the Harvard Medical School Division on Aging, Boston, Mass. None had past or current histories of neurologic or psychiatric disorders. They underwent the same clinical and cognitive evaluations as did the patients with PcD and AD. Of the 60 NCSs, 11 had 2 or more testing sessions with an average of 2.5 years between the first 2 testings. The NCSs were followed up for a mean of 0.7 year (SD, 1.5 years; most had only 1 testing; otherwise, range was 0.5-6.3 years).

STATISTICAL ANALYSIS

The continuous demographic variables and the scores of the first cognitive assessment, including BDS and ADL scores, for the 3 groups were compared by means of analysis of variance, analysis of covariance, and Tukey post hoc test. The χ² and Fisher exact tests were used for qualitative variables (ie, sex and initial symptoms). The significance tests for the Fisher exact tests of initial symptoms were corrected for multiple testing with a resampling method.22 Tukey post hoc tests were corrected for multiple group comparisons on demographics.

To delineate differences between the PcD and AD groups, we modeled change in cognitive test performance, BDS, and ADL vs duration of illness and age. The change models were derived with the use of mixed random and fixed coefficient linear regression models.23 Maximum likelihood estimation techniques determined population models for which our data had the highest probability of occurrence. These methods had the advantage of including all available clinical data in the analyses, regardless of the varying numbers of test dates per subject and unequal test intervals. For all cognitive tests, higher scores indicated better performance; whereas, for the BDS and ADL, higher scores indicated greater disease severity. Age at onset of illness, education level, and sex were entered into the models as covariates to determine whether they were significantly related to the dependent variables. We determined whether relations between test performance and duration of illness (or age) were linear or curvilinear by testing quadratic terms for duration of illness (or age).
First symptoms of disease during a structured interview from a menu that included impairment in 11 domains (Table 2). Of the 11 symptoms queried, patients with Pcd and AD differed significantly on 3: memory (episodic memory), speech (word finding), and personality problems (defined by the presence of 1 or more of the following symptoms: apathy, agitation, depression, irritability, appetite change, disinhibition, and euphoria). Memory loss was the most common initial symptom in patients with Pcd and AD but was significantly more prevalent in AD than in Pcd (P < .001). In contrast, speech and personality change as the first symptom were more prevalent in Pcd than in AD (P = .03 and P = .07, respectively).

INITIAL BEHAVIORAL TESTING

For the cognitive tests administered at first clinical examination, analyses covaried age, educational level, and duration of illness. The mean scores for NCSs were significantly superior to those for the patients with AD on all tests and were significantly superior to those for the patients with Pcd on all tests except the Luria Mental Rotation Test (Table 3). As a group, patients with Pcd performed better than patients with AD on tests of explicit memory (New York University [NYU] Delayed Story Recall: F = 11.47, P < .001) and visuospatial skill (Luria Mental Rotation Test: F = 11.17, P = .001). Mean scores on all other cognitive tests did not differ between the Pcd and AD groups. The mean BDS scores at first evaluation for the Pcd and AD groups did not differ, whereas the Pcd group had a higher mean ADL score (P = .049) than the AD group, indicating greater functional impairment.
in PcD (Table 1). Although these differences were statistically significant, they were not large enough to provide discriminant utility. Using logistic regression analysis with jackknife classification, we examined initial test scores for NYU Delayed Story Recall, Luria Mental Rotation, and ADL in separate analyses. In each case, optimal cutoffs provided only 44% to 67% sensitivity for PcD, with 60% to 69% specificity.

**RATE OF PROGRESSION**

The rate of deterioration was significantly greater for patients with PcD than AD on the Boston Naming Test, Category Verbal Fluency Test, BDS, and ADL (Figure 1 and Figure 2). The rates of decline for the PcD and AD groups did not differ significantly on the Raven's Progressive Matrices Test, the Stroop Color Naming Test, Geometric (easy and hard) Copy Figure Copy and Recall, Benton Visual Retention Test, NYU Stories Immediate and Delayed Recall, Money Road Map Test, Luria Mental Rotation Test, and Picture Arrangement Test.

For all 3 groups, there was a slightly curvilinear decline in the Boston Naming Test score. The best-fitting model (Figure 1) showed that patients with PcD had a steeper curvilinear change over time than patients with AD (P = .04). Category Verbal Fluency Test scores declined linearly; the model showed a significant interaction (P < .001) between duration of disease and group in that the slope of decline was significantly greater for patients with PcD (Figure 1). Mean BDS and ADL scores for patients with PcD increased (ie, worsened) significantly faster than those for patients with AD. For both measures, there were significant group differences in curvilinear change (P = .03 and P = .02, respectively), but not in the level of performance (Figure 2). Patients with PcD had a higher level of performance than patients with AD on the NYU Delayed Story Recall Test (P = .004; for patients studied by autopsy only, P = .008), and the Luria Mental Rotation Test (P = .07), but the slope of decline for the 2 patient groups did not differ (Figure 1). For NYU Delayed Story Recall, the change was curvilinear, whereas for Luria Mental Rotation the effects were linear. Additional analyses indicated that these results on rate of cognitive progression that distinguish PcD from AD did not interact significantly with whether patients were living or dead. Even within the relatively small number of cases studied by autopsy, the rate of decline on the Category Verbal Fluency Test was significantly greater in PcD than in AD (Figure 3).

**COMMENT**

This report on PcD is the first, to our knowledge, in which the cognitive aspects of the disease were examined in a comprehensive cross-sectional and longitudinal study. The patients with PcD, patients with AD, and NCSs received the same systematic, standardized assessment, permitting a rigorous observation of the differences among the 3 groups. The majority of our patients with PcD and AD are still alive, and in some the clinical diagnosis may not be confirmed pathologically. To enhance confidence in our findings, we compared initial cognitive test scores and subsequent rates of progression for living and autopsy-studied patients with PcD and AD, and found no evidence in either patient group that the data for the pathologically confirmed cases differed from the clinically diagnosed and still-living cases. A separate analysis of cognitive test scores restricted only to autopsy-studied cases reinforced the conclusions derived from the entire subject sample: at first examination, patients with AD were significantly more impaired on NYU Delayed Story Recall than patients with PcD, whereas the rate of decline on Category Verbal Fluency was significantly greater in patients with PcD than in patients with AD.

Not all cases of dementia with frontal and temporal atrophy contain Pick bodies. It is controversial whether Pick bodies must be present for PcD to be diagnosed or, conversely, whether the absence of Pick bodies excludes a diagnosis of PcD. From a neuropathological point of view, the requirement for Pick bodies is seductive but probably too restrictive, in that it would preclude the ante-mortem diagnosis of PcD. In this regard, Pick's original observations were clinical and did not rely on microscopic examination of the brain. To minimize nosologic confusion, the broad diagnostic term FTD has been proposed to encompass PcD, and it contains other focal lobar atrophies including those that result in the syndromes of primary progressive aphasia, semantic dementia, frontal lobe dementia, frontal lobe dementia with amytrophic sclerosis, frontotemporal dementia with Parkinson disease linked to chromosome 17, and corticobasal degeneration.7,8,34 This classification scheme emphasizes the belief that the topography of the atrophy is more responsible for the clinical manifestations than is the underlying histopathologic condition. Although criteria have been proposed to diagnose FTD,7,35 these conditions are still difficult to distinguish from themselves.
and from other dementias. None of the 44 cases in the present series conformed to the phenomenological descriptions of these other FTD conditions. We use the specific term PCD when it seems diagnostically accurate rather than the broad generic term FTD because of the historical precedent for PCD, because we began collecting our series of patients many years before the FTD classification was proposed, and because all of our cases studied by autopsy did in fact have the gross and microscopic findings of PCD. The analyses of the demographic characteristics of the PCD cohort reinforce previous reports of an increased prevalence in men and an earlier disease onset than AD.

**FIRST SYMPTOMS**

To gain information regarding the nature of the initial symptom(s) and the estimated date of disease onset, we queried the patient’s caregiver. Memory, speech, and personality changes were the 3 reported symptoms that differentiated patients with PCD from those with AD. Our data confirm that memory impairment, specifically affecting explicit memory, is the chief hallmark of AD and is much more prevalent in AD than in PCD. This result is consistent with neuropathological findings that medial temporal-lobe structures are damaged early in the course of AD. Language disturbances, mainly word-finding difficulty, and personality changes are significantly more common in PCD than in AD. Personality changes may stem from diffuse damage to the amygdala, in contrast to the selective nuclear damage in AD. Anomia may reflect the underlying atrophy and neuronal death in the temporal and frontal lobes that characterize PCD pathologically. Although the differences in frequency of initial symptoms are statistically significant, overlaps preclude diagnostic specificity, and it remains a challenge to obtain reliable and diagnostically discriminant information regarding the onset of cognitive and behavioral symptoms in dementia.

**INITIAL EVALUATION**

On initial cognitive testing, the mean scores for patients with PCD were inferior to those of the NCs, except for the Luria Mental Rotation Test, whereas the mean scores for the patients with AD were inferior to those for the
ties and a relative but significant preservation of the ca-
cifically, patients with PcD had spared visuospatial abili-
to define a pathognomonic PcD cognitive profile. Spe-
found between the PcD and AD groups on individual tests,
both groups. Although some significant differences were
mata severity, as estimated by the BDS scores, was equal in
education, and age. At initial examination, mean demen-
tment of the 2 groups, adjusting for duration of disease,
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played a cognitive profile that distinguished them from
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ficientally more impaired in PcD than memory capacities, and
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inforce the diagnostic importance of aphasia in PcD and
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emphasize rapid deterioration in expressive language as
a marker of PcD. With the Boston Naming Test and Category Verbal Fluency Tests, we assessed only 2 aspects of language function. Inability to name objects and retrieve words from the lexicon is also common in

rate of progression

A longitudinal study contains more information than a cross-sectional one, so we analyzed and compared the progression of cognitive test, BDS, and ADL scores for patients with PcD and AD. Patients with PcD worsened over time significantly faster than patients with AD on measures of language, global cognitive impairment, and ADL. The 2 patient groups did not differ in rate of decline on all other cognitive tests. Because initial Boston Naming Test and Category Verbal Fluency Test scores were equivalent, the more rapid decline in scores in the PcD group compared with the AD group likely reflects the biological characteristics of the disease and not a diagnostic selection bias. The accelerated decline in PcD remained even after adjusting for education and age at disease onset. This finding was also evident in the cases studied by autopsy, where the rate of decline in verbal fluency was significantly greater in the PcD group than in the AD group. Progressive language deterioration is a common feature in single case reports of PcD; anoma, neologisms, phonemic paraphasias, echolalia, and verbal stereotypes have all been reported.13,14,52 Our data reinforce the diagnostic importance of aphasia in PcD and emphasize rapid deterioration in expressive language as a marker of PcD. With the Boston Naming and Category Verbal Fluency Tests, we assessed only 2 aspects of language function. Inability to name objects and retrieve words from the lexicon is also common in

NCSs in all cognitive domains. The Luria Mental Rotation Test requires the mental manipulation of spatial information. The processing of spatial information depends on parietal lobe and occipital lobe functioning, with the right hemisphere playing a predominant role. The preservation of these cognitive capacities may reflect the relative preservation of the posterior cortical areas in PcD. Damage to frontal lobes may account for the observation that executive functions are relatively more impaired in PcD than memory capacities, and the resultant suggestion that this pattern may aid in differentiating PcD from AD.31

Patients with PcD are often misdiagnosed as having AD. To determine whether patients with PcD displayed a cognitive profile that distinguished them from patients with AD, we compared the cognitive assessment of the 2 groups, adjusting for duration of disease, education, and age. At initial examination, mean dementia severity, as estimated by the BDS scores, was equal in both groups. Although some significant differences were found between the PcD and AD groups on individual tests, these differences were not sufficiently numerous or large to define a pathognomonic PcD cognitive profile. Specifically, patients with PcD had spared visuospatial abilities and a relative but significant preservation of the cogni-

Figure 2. Maximum-likelihood estimated models of change for the Blessed Dementia Scale and Activities of Daily Living Scale. PcD indicates Pick disease; AD, Alzheimer disease. Within each group, separate lines correspond to different educational levels and onset ages as explained for Figure 1, except that higher lines correspond to fewer years of education (because the Blessed Dementia Scale and Activities of Daily Living Scale scores measure severity of illness). On both measures, the patients with PcD worsened significantly faster than the patients with AD (P = .03 and P = .02, respectively).

Figure 3. Maximum-likelihood estimated models of change for the Category Verbal Fluency Test in cases of neuropathologically confirmed Pick disease (PcD; n = 10) and Alzheimer disease (AD; n = 14). The PcD group declined significantly (P = .01) more sharply than the AD group across duration of illness.
AD, and further research is needed to explore differences between these 2 groups of dementia. Patients with PcD showed less impairment than patients with AD on tests of explicit memory at initial examination and during the disease course, but the rate of progression was similar, both in the autopsy-studied cases and in the total sample including living patients. Explicit memory depends on a great extent on medial temporal-lobe structures, which participate in the initial encoding and storage of information. Medial temporal-lobe structures, including the entorhinal cortex and hippocampus, are damaged early in the course of AD, but these structures are also affected in PcD. Cortical pathologic changes may also contribute to the progressive memory deficits in both diseases. Memories are likely stored outside the hippocampal formation in cortical regions. Accumulation of neurofibrillary tangles, decreases in synapses, and loss of neurons in the cortex underlie disease progression in AD, while widespread cortical atrophy with frontal and temporal lobe accentuation are prominent features of PcD. In both diseases, ongoing neuronal degeneration in cortical regions could produce progressive deficits in explicit memory. The similar rate of decline for the 2 groups on delayed recall of the NYU Stories and Geometric Figures suggests that the specific nature of the histopathologic changes are less important determinants of progression rate than are the loci of the lesions.

In conclusion, the observations reported in this study document cognitive and ADL differences in the appearance and course of PcD compared with AD. These crosssectional and longitudinal cognitive test data provide a clinical index of the underlying pathologic changes in the brain. Despite distinctive differences, however, substantial overlaps between the test performance of patients with PcD and AD limit the diagnostic value of the cognitive testing. To enhance diagnostic precision for PcD, it will be necessary to couple cognitive abnormalities with distinctive biological markers, such as gene abnormalities or characteristic patterns of impaired cerebral metabolism.

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