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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In 1892, Arnold Pick, a professor of psychiatry at the University of Prague, provided the first description of the clinical and gross pathological features of a demen-
ting illness that now bears his name. Pick observed a 71-year-old man with a history of dementia lasting 3 years. The associated features included prominent aphasia with many paraphasic errors. The autopsy disclosed prominent atrophy of the frontal and temporal lobes. Pick subsequently described other cases of dementia with cerebral atrophy localized to the temporal lobes and to the parietal and frontal lobes. Neither Pick nor his pathologist collaborator Chiari commented on the histological nature of the atrophy they observed, but several years later, Alz-heimer described the histological characteristics of the disease as “spongy cortical wasting, ballooned cells, and argentophilic globes in neuronal cytoplasm.” Neurofibrillary tangles and senile plaques were notably absent. Gans and Onari and Spatz proposed the name Pick disease (Pcd) for this neuropathological entity. According to a new proposed classification of focal cortical atrophies, PcD is now considered a subtype of a broad category of frontotemporal degeneration (FTD).

From a clinical point of view, PcD is difficult to differentiate from other forms of progressive dementia and is often confused with Alzheimer disease (AD). There are relatively few comprehensive studies that report the clinical and behavioral features of PcD. What studies exist report either single cases or small numbers of cases or, when based on a large sample, rely on analyses of data collected retrospectively. In taking a fresh look at PcD, we based our study on a relatively large number of patients with PcD who were examined longitudinally over time with the same comprehensive set of cognitive tests. The goals of the study were

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SUBJECTS AND METHODS

SUBJECTS

This study was based on data collected from 34 clinically 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,16 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.20-31, 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 1.6 years (SD, 1.0 year; range, 0.5-4.4 years). The demographic characteristics of this subgroup of 33 did not differ significantly from those of the total group of 44 (10 studied by autopsy; 23 living; 21 men, 12 women; mean age, 66.2 ± 9.1 years; education, 14.3 ± 3.3 years; age at onset of disease, 63.4 ± 9.4 years; unless otherwise indicated, data are given as mean ± SD). The remaining 11 patients with PCD were unable to complete the full set of cognitive tests.

We compared the patients with PCD with a pool of 123 patients with AD20 (Table 1). These 123 were all of the patients examined in the MDU at Massachusetts General Hospital between 1985 and 1993 who met these criteria: a clinical diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association guidelines10 and completion of the same cognitive tests as those administered to the patients with PCD.20 Of the 123 patients with AD, 34 died and an autopsy was performed in 16. The clinical diagnosis of AD was confirmed neuropathologically in 14 patients; 2 patients had a neuropathological diagnosis of PCD, and their clinical data were removed from the AD group and incorporated into the PCD group for this study. Another patient with an antemortem diagnosis of AD had autopsy-proved PCD. This subject had been examined in the MDU but was not part of the original cohort of 123 patients with AD. All 121 of the remaining patients with AD had at least 2 testing sessions (with a mean of 1 year between the first 2 sessions); 49 had 3 or more testings, 19 had 4 or more, 5 had 5 or more, and 3 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 tests. 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.32 Tukey post hoc tests 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.33 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).
Table 1. Demographic Features of PcD, AD, and NCS Groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Subjects (M/F)</th>
<th>Age at Disease Onset, y†</th>
<th>Age at First Evaluation, y</th>
<th>Score on Activity of Daily Living Scale‡</th>
<th>Blessed Dementia Scale Score: Information, Memory, and Orientation Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>PcD</td>
<td>44 (26:18)</td>
<td>63.6 ± 9.4</td>
<td>66.9 ± 9.2</td>
<td>14.1 ± 3.5</td>
<td>34.8 ± 19.8</td>
</tr>
<tr>
<td>AD</td>
<td>121 (46:75)</td>
<td>67.3 ± 8.8</td>
<td>70.6 ± 8.5</td>
<td>13.1 ± 3.5</td>
<td>29.2 ± 16.1</td>
</tr>
<tr>
<td>NCS</td>
<td>60 (25:35)</td>
<td>NA</td>
<td>69.7 ± 11.1</td>
<td>15.1 ± 3.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SD. PcD indicates Pick disease; AD, Alzheimer disease; NCS, normal control subjects; and NA, not applicable.
†P < .05.
‡P = .03.
§P = .07.

RESULTS

DEMOGRAPHIC FINDINGS

The PcD, AD, and NCS groups did not differ significantly in mean age at first evaluation (Table 1). The patients with PcD did not differ significantly from either of the other groups in mean education, but the NCS group had a higher mean education level than the AD group (P = .02). The proportion of men in the PcD group was significantly greater than in the AD group (P = .02). The reported age at disease onset was significantly lower in the PcD than in the AD group (P = .02), but the 2 groups did not differ in mean interval from disease onset to the initial clinical examination in the MDU. To ensure that the total PcD sample represented a homogeneous group of patients, we compared the demographic variables and cognitive test scores at initial evaluation of the 10 patients with PcD who underwent autopsy with those of the 34 living patients with PcD. The 2 groups of patients with PcD did not differ significantly on any demographic variable (respective values for the autopsy vs living groups: sex, 6 men and 4 women vs 20 men and 14 women; mean age at disease onset, 64.1 ± 7.9 vs 63.5 ± 10.0 years; education, 13.8 ± 3.5 vs 14.3 ± 3.6 years; mean age at first evaluation, 66.8 ± 6.4 vs 67.0 ± 10.0 years), mean duration of the illness at first testing (2.7 ± 1.9 vs 2.9 ± 1.6 years), or cognitive test score at initial examination.

FIRST SYMPTOMS OF DISEASE

As part of the initial neurologic examination, the caregiver of each patient with PcD and AD was asked, “When did the illness begin?” and “What were the first symptoms of the illness?” Caregivers selected the initial symptoms 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 (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: P = .001; §P = .07) 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.
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) 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 ($F = .004$; for patients studied by autopsy only, $P = .008$), and the Luria Mental Rotation Test ($F = .07$), 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
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cifically, patients with PcD had spared visuospatial abili-
to define a pathognomonic PcD cognitive profile. Spe-
theses differences were not sufficiently numerous or large 
found between the PcD and AD groups on individual tests, 
both groups. Although some significant differences were 
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played a cognitive profile that distinguished them from 
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flect the relative preservation of the posterior cortical ar-
formation. The processing of spatial information de-
NCSs in all cognitive domains. The Luria Mental Rota-
tion Test requires the mental manipulation of spatial in-
formation. The processing of spatial information de-
pends on parietal lobe and occipital lobe functioning,45 
with the right hemisphere playing a predominant role.46 
The preservation of these cognitive capacities may re-
fect the relative preservation of the posterior cortical ar-
eas in PcD.3,4,47-50 Damage to frontal lobes may account 
for the observation that executive functions are re-
latively more impaired in PcD than memory capacities, and 
the resultant suggestion that this pattern may aid in dif-
ferentiating PcD from AD.51

Patients with PcD are often misdiagnosed as hav-
ing AD. To determine whether patients with PcD dis-
played 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 demen-
tia 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. Spe-
cifically, patients with PcD had spared visuospatial abili-
ties and a relative but significant preservation of the ca-
pacity to recall verbal material compared with patients 
with AD. Among the cases studied by autopsy, patients 
with AD were significantly (P = .008) impaired in ver-
bal recall compared with patients with PcD. Surpris-
ingly, the PcD and AD groups did not differ at initial ex-
amination on 2 tests of language abilities, the Boston 
Naming Test and Category Verbal Fluency Test, or on a 
measure of selective attention, the Stroop Color Naming 
Test. Overall, we conclude that the cross-sectional 
analysis of a single set of cognitive and ADL measures is 
not sufficient to disclose all of the potential differences 
between patients with PcD and those with AD.

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 de-
cline 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 di-
agnostic 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 ver-
bal stereotypy have all been reported.13,14,52 Our data re-
force the diagnostic importance of aphasia in PcD and 
emphasize rapid deterioration in expressive language as 
a marker of PcD. With the Boston Naming and Cat-
egory Verbal Fluency Tests, we assessed only 2 aspects 
of language function. Inability to name objects and re-
trieve words from the lexicon is also common in
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 cross-sectional 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 biologic markers, such as gene abnormalities or characteristic patterns of impaired cerebral metabolism.

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