

## Heterogeneity and Prognosis in Dementia of the Alzheimer Type

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The diagnosis of dementia of the Alzheimer type (DAT) depends on the clinician's ability to document intellectual impairment in the patient and to exclude other causes of dementia. About 50% of all demented patients entering a hospital are ultimately found at postmortem examination to have Alzheimer's disease. However, using the most rigorous criteria the accuracy of correct clinical diagnosis at autopsy approaches only 80-90% and this excludes some unusual patients. Most investigators use the Diagnostic and Statistical Manual of Mental Disorder—third ed. (DSM-III) criteria for dementia, a rating of performance in activities of daily living, and an assessment of personality and intellectual function for diagnosis. Two clinical rating scales: the Blessed Dementia Rating Scale (parts 1 and 2) and the Clinical Dementia Rating Scale, are used frequently and seem to identify patients with DAT with greater accuracy than other scales.

Our assessment protocol for dementia includes a quantitative neurological examination because certain motor manifestations have been observed in DAT: myoclonus, rigidity, stooped posture, and bradykinesia. We found these clinical features to be useful in predicting the course in some patients. Our data indicate clinical heterogeneity in DAT and may suggest the presence of unique subgroups.

### METHODS

We reviewed the records of 138 patients who met our research criteria for DAT. These included: history of intellectual impairment for at least 6 months, objective neuropsychological evidence of dementia, and DMS-III criteria for primary degenerative dementia. We accepted only those patients whose laboratory studies were compatible with a diagnosis of DAT. We excluded patients with a history of affective disorder, Parkinson's disease, stroke, cancer, anoxia, or seizures.

Every patient was interviewed with a family member present to verify all historical information. The neurological examination included a modified version of the Columbia University Parkinson's Disease rating scale and dyskinesia rating scale. Activities of daily life were assessed by the Blessed Dementia Rating Scale (BDRS) (part 1). A brief neuropsychological test, a modified version of the Mini-Mental State Examination (mMMS), and a semistructured interview to derive symptoms for depression and psychosis were completed.

A subset of the original cohort was identified and included in a longitudinal analysis. This group consisted of 62 individuals who received primary treatment at our

medical center; each had been evaluated on at least two occasions separated by a minimum of 6 months.

A database from the original 138 patients was used to isolate clinical factors, such as family history, age-at-onset, or motor manifestations, that were related to mMMS performance and BDRS. We then examined the utility of these factors in predicting the decline in intellectual skills and functional capacity in the 62 patients from the longitudinal study.

#### RESULTS

The mean age of the large patient group was 68.9 ( $\pm$  9.7). Modified MMS and BDRS scores varied widely but correlated ( $r = -0.54$ ,  $P < 0.001$ ). BDRS increased and mMMS decreased significantly with duration of symptoms ( $r = -0.2$ ,  $P < 0.01$ ). Neither age at the first examination or age-at-onset of dementia correlated with mMMS or BDRS.

In the 138 patients, 25.9% (36) had extrapyramidal signs consisting of rigidity, bradykinesia, and stooped posture unrelated to medication. BDRS and mMMS were significantly worse in this group compared to the others, but there was no difference in age, age-at-onset or duration of symptoms. Twelve (11.5%) had myoclonus and were younger at the onset of their dementia. Myoclonus and extrapyramidal signs coexisted in five patients. BDRS was significantly higher and mMMS lower in the group with myoclonus compared to all patients in other groups. Another 12 patients had extrapyramidal signs which we considered drug induced; mMMS and BDRS scores were significantly worse in these patients compared to all groups except those with myoclonus.

The 62 patients in the longitudinal component of this study were slightly younger at their initial examination ( $66.7 \pm 9.3$ ) and had lower BDRS scores. Each patient had been examined at least twice over a 6-month interval. The majority had been examined a number of times over a period of 4 years.

The 62 patients were separated into four groups: typical DAT ( $n = 16$  only dementia), DAT with extrapyramidal signs ( $n = 30$ ; sporadic = 14 and drug-induced = 16), DAT with myoclonus ( $n = 9$ ), and DAT-benign ( $n = 7$  slow progression). Myoclonus and extrapyramidal signs coexisted in three patients.

Two groups, those with extrapyramidal signs and those with myoclonus initially, had significantly higher BDRS scores and lower mMMS scores at the last examination ( $P < 0.01$  for both measures) than the typical or benign patient groups. They also experienced a more rapid change in these measures over time than the other groups. Patients with drug-induced extrapyramidal signs deteriorated even more rapidly than the other groups. The seven benign patients, by contrast, progressed very little over the study period in comparison to the typical patient group.

Family history of dementia or age-at-onset were not distinguishing features. However, we found that patients with evidence of thought disorder, defined by the presence of persistent delusions or hallucinations, also deteriorated more rapidly than those without these manifestations (BDRS,  $P < 0.05$  and mMMS,  $P < 0.01$ ). Thought disorder occurred most frequently in patients with extrapyramidal signs and myoclonus, but it was also present in a few typical patients and precipitated a rapid decline in a single benign patient.

## COMMENT

The demonstration of heterogeneity in our patients has both practical and theoretical importance. The presence of myoclonus or extrapyramidal signs at the initial examination was strongly predictive of a more rapid progression of illness, imparting a poor prognosis for these patients since the motor manifestations do not resolve. More importantly these observations may indicate biological heterogeneity. The presence of myoclonus in patients with Alzheimer's disease has been found to be the best predictor of low choline acetyltransferase activity in postmortem brain. Patients with autopsy confirmed Alzheimer's disease may also have degeneration in substantia nigra and Lewy bodies suggesting a possible overlap with Parkinson's disease (PD), and loss of cells in the basal forebrain can occur in both DAT and PD. However, the biochemical changes of Alzheimer's disease can be observed in demented parkinsonians, but the converse is not always found.

The benign group is unusual because of the slow progression, but this may also identify a biological subgroup. "Simple dementia" is a term used to describe a milder form of the disease that is characterized by less striking cell loss, neuritic plaques, and tangles. The biochemical changes are also less pronounced. Postmortem confirmation of diagnoses in this group will be essential to determine its relationship to Alzheimer's disease.

Psychosis was also associated with a poor prognosis, and could also define a subgroup. However, psychosis occurred in a few patients in every subgroup we defined suggesting that it is a malignant but nonspecific manifestation of DAT. Longitudinal study of this phenomenon will determine if it represents a unique subgroup.

Our data suggest the existence of four unique subgroups of DAT: extrapyramidal, myoclonic, typical, and benign. Although there is some overlap in these groups their course and prognosis are distinctly different. Four of our 62 patients have died and Alzheimer's disease was confirmed in all, but we expect our diagnostic accuracy to remain around 90%.

DAT may be a heterogeneous disorder even when restrictive criteria are used for research diagnosis. Certain motor manifestations and psychiatric features have remarkable prognostic implications. The pathological and biochemical issues raised by these observations need careful consideration in longitudinal studies of DAT.

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