Age at Onset and Rate of Progression of Alzheimer's Disease

F. Jacob Huff, MD,* John H. Growdon, MD,† Suzanne Corkin, PhD,‡ and T. John Rosen, PhD‡

Age at onset, duration, and severity of dementia were evaluated in 165 patients with a clinical diagnosis of Alzheimer's disease. Rate of progression of dementia was determined in 77 patients by repeated administration of the Blessed Dementia Scale (BDS). The distribution of age at onset among patients was bimodal, with a division at about age 65. Duration of dementia at the time of initial examination was shorter, and rate of progression on follow-up examination was more rapid in senile-onset (age 65 or greater) than in presenile-onset (before age 65) cases. Considerable overlap among values for the two patient groups was observed for both variables, indicating that age at onset is not a strong predictor of rate of progression of dementia in patients with Alzheimer's disease. J Am Geriatr Soc 35:27-30, 1987

The traditional distinction between presenile and senile dementia of the Alzheimer type has been questioned in recent years. It is now widely believed that presenile and senile dementia represent arbitrary divisions of a single disease entity. Differences between early- and late-onset cases of Alzheimer's disease have been observed, however, in biochemical and clinical studies. Clinical observations and mortality data have suggested that presenile cases may progress more rapidly. We examined the relations among age at onset, duration, severity, and progression of dementia, in an effort to establish whether rate of progression differs as a function of age at onset.

SUBJECTS AND METHODS

Data were collected over five years on 165 consecutive patients with a clinical diagnosis of Alzheimer's disease who attended a memory disorders clinic. The diagnosis was based upon a history of gradual deterioration of cognitive functions that impaired work performance or activities of daily living, and upon the results of physical examination. The diagnostic criteria have been published previously, and correspond to those adopted by a recent Health and Human Services Task Force. Computed tomography (CT) brain scan, electroencephalogram (EEG), and blood studies were done in order to exclude other causes of dementia. Patients with a Hachinski Ischemia Scale score of five or greater, and those with a history of alcoholism or primary affective disorder were excluded. Of these 165 patients, eight have died; six of these patients' brains were examined and all contained abundant senile plaques and neurofibrillary tangles characteristic of Alzheimer's disease. No clinical features differentiated these autopsy-confirmed cases from the remainder of the patients diagnosed by the same clinical procedures.

Estimates of age at onset of dementia and duration of dementia were obtained from a family member at the time of initial examination. Severity of dementia was determined using the BDS. It was readminis-
terred to 77 patients at follow-up intervals of three months or greater. Rate of progression of dementia was estimated for these patients by dividing the difference between the two Blessed Scale scores by the number of months between the two administrations. This method of determining "rate of progression" is based on the notion of "rate" as it is used in physiology, indicating change in a variable over time. The BDS has been shown to correlate with the number of senile plaques on postmortem examination, supporting its use in the present study to measure rate of progression of Alzheimer's disease.

RESULTS

The mean age at onset of dementia was 64.3 years (Table 1). The distribution of age at onset among patients was bimodal (Figure 1), with a division at about age 65. This distribution differed significantly in shape from the normal Gaussian function (Kolomogorov-Smirnov test, d = 0.11, P < .01).

The majority of cases (62%) were women, and this disproportion was significant statistically ($\chi^2 = 10.2$, df = 1, P < .01). Men and women did not differ in severity of dementia at initial examination.

The 77 patients to whom the BDS was administered on follow-up examination were younger (mean age, 65.8 years; standard deviation (SD), 8.7) than the total group of 165 patients (mean age, 68.3 years; SD, 8.8), and had lower initial BDS scores (mean, 20.7; SD, 11.7; mean, 24.3; SD, 13.5, respectively). The mean rate of progression was 0.63 BDS points per month (SD, 0.56). Pearson correlations were determined between rate of progression and severity at first examination (defined by the first BDS score), age at first examination, estimated duration of dementia at the time of first examination, and age at onset of dementia. Rate of progression of dementia correlated weakly with age of onset of dementia ($r = .20$, $P < .10$), age ($r = .17$, $P > .10$), and duration ($r = .15$, $P > .10$). Rate of progression did not correlate with severity at first examination ($r = .03$). Rates were essentially the same at all levels of severity.

The subset of patients with onset of dementia before age 65 was defined as the presenile-onset group, and those with onset at age 65 or thereafter as the senile-onset group (Table 2). The groups were equal in severity, as judged by the BDS, but patients in the senile-onset group had a significantly shorter duration of illness ($t = 163 = 3.65$, $P < .001$). For the 77 patients in whom a second BDS score was obtained on follow-up examination, a significantly faster rate of progression of dementia ($t = 75 = 2.10$, $P < .05$) was observed in senile-onset cases. The proportion of women to men was similar in the presenile- and senile-onset groups (Table 2).

DISCUSSION

The bimodality of the distribution of age at onset of dementia suggests the possible existence of two populations of patients, differing by age at onset of dementia. Mayeux et al. reported a bimodal distribution of patients by age at onset, with a division at age 65 in contrast to the division at age 65 that we observed. Both the present study and that of Mayeux et al. were based upon clinical series, in which patients were entered either by their choice or by referral. The emergence of a bimodal distribution of age at onset of dementia in these studies may have resulted from a bias in patient selection, although no systematic bias is apparent in the selection procedure for these studies that would produce a bimodal distribution. Population-based epidemiologic studies generally do not suggest a bimodal incidence of Alzheimer's disease, but a study performed in the eastern United States showed a lower incidence in the 65 to 69 age-range than in younger or older age groups.

### TABLE 1. PATIENT PROFILE AT FIRST EXAMINATION

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Mean (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first examination</td>
<td>68.3 (8.8)</td>
</tr>
<tr>
<td>Age at onset of dementia</td>
<td>64.3 (9.3)</td>
</tr>
<tr>
<td>Duration of dementia (years)</td>
<td>4.0 (2.8)</td>
</tr>
<tr>
<td>Blessed dementia scale score</td>
<td>24.3 (13.5)</td>
</tr>
</tbody>
</table>

*N = 165.
TABLE 2. CLINICAL FEATURES OF PATIENTS WITH PRESENILE-ONSET* AND SENILE-ONSET† ALZHEIMER’S DISEASE

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Presenile-Onset</td>
</tr>
<tr>
<td>Age at first examination</td>
<td>60.7(5.3)</td>
</tr>
<tr>
<td>Age at onset of dementia</td>
<td>55.9(4.8)</td>
</tr>
<tr>
<td>Duration of dementia (years)</td>
<td>4.8(3.3)</td>
</tr>
<tr>
<td>Blessed Dementia Scale score</td>
<td>24.9(14.5)</td>
</tr>
<tr>
<td>Rate of change in Blessed Scale score</td>
<td>0.32(0.54)</td>
</tr>
<tr>
<td>(points/month)</td>
<td></td>
</tr>
<tr>
<td>Number (percentage) women</td>
<td>51(64%)</td>
</tr>
</tbody>
</table>

*N = 80.
†N = 85.

Numbers indicate mean (standard deviation) or number (percentage) for group.
Significant differences between groups by t test: P < .05, ‡ P < .001.

The high proportion of women with Alzheimer’s disease in the present investigation is of the same magnitude as that reported in other clinical studies. This has been shown to be statistically significant, even when the relatively greater number of women of corresponding age in the general population is taken into account. Population-based studies have also suggested a disproportional prevalence among women.

The similar percentage of women among presenile- and senile-onset cases in the present study implies that sex is not a factor determining age at onset of Alzheimer’s disease.

Our patients with senile-onset of dementia had a shorter duration of dementia at initial examination than did presenile-onset cases, and because the groups were nearly identical in severity of dementia on first examination, it can be inferred that the rate of progression of dementia was more rapid in patients with senile-onset. Duration of dementia was estimated by patients’ relatives, and it is possible that onset of symptoms was evident earlier in the disease course in presenile-onset cases because these patients were employed or required to assume more responsibilities in the family than were senile-onset cases. Such factors, however, do not affect determinations of rate of progression of dementia based upon repeated administration of the BDS.

Rate of progression was also found to be more rapid for senile-onset cases using this more objective method. Repeated evaluation was done in 77 patients, who were slightly younger and less demented than the total group of 165 patients. It is possible that these 77 patients are not representative of the entire group, although no other difference among these patients relevant to age at onset or rate of progression of dementia is evident. Several reports suggesting that progression of disease is more rapid in presenile cases have been based only on estimates of duration or on mortality figures which reflect rate of progression less directly than do the longitudinal assessments of clinical severity used in the present study.

Although the differences in duration of dementia and rate of change in BDS scores between presenile- and senile-onset cases were significant statistically, there was considerable variance in these measures in both groups, and the distribution of values overlapped between the two patient groups. The degree of overlap indicates that age at onset of dementia is not a strong predictor of rate of progression. From a clinical perspective, age at onset cannot be viewed as a major determinant of malignancy of Alzheimer’s dementia.

Our results do not provide a clue to the reason that dementia progressed more rapidly in older patients. It is possible that age-associated factors unrelated to Alzheimer’s disease make older individuals more vulnerable than younger ones to the pathological changes of Alzheimer’s disease. Alternatively, a difference in pathophysiological mechanism between presenile and senile forms of Alzheimer’s disease may result in more rapid progression in senile-onset cases. Other studies suggest that there may be distinct early-onset and late-onset forms of Alzheimer’s disease. Sellzter and Sherwin observed a greater prevalence of language disturbance and left-handedness in patients with early-onset disease. Age-dependent differences in the pattern of brain neurotransmitter abnormalities have been found in postmortem studies.

All of these observations support the hypothesis of distinct presenile and senile forms of Alzheimer’s disease. This hypothesis implies that there is a difference in pathophysiological mechanism between the forms, but does not deny that many features of pathophysiology may be similar in the two forms.

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REFERENCES