Clinical Characterization of Alzheimer's Disease: Reliability of 'Age at Onset' and a New Descriptor, 'Age at Shift'

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Abstract

To determine the interrater reliability of clinical descriptors for Alzheimer's disease (AD), we assessed the degree of agreement among four clinicians who rated 21 patients during a longitudinal study. Despite variability in response patterns, degree of agreement for determining age at onset of dementia was statistically significant ($P < 0.005$). We also found significant agreement ($P < 0.0001$) among three clinicians for the clinical descriptor, "age at shift" from questionable to probable AD, according to the National Institutes of Health Consensus Criteria. These data demonstrate that both retrospective and prospective descriptors can be reliably determined in the clinical assessment of AD. (*J Geriatr Psychiatry Neurol* 1988;1:207–211).

Although the clinical characterization of Alzheimer's disease (AD) is an essential aspect of current research efforts into etiology and treatment, few data are available on the reliability of assessment. Age at onset of dementia has been a widely used measure since the disease's first description in 1907 as a presenile dementia.[1] Throughout the century, however, there has been controversy regarding the etiological and clinical significance of age at onset. How accurate are retrospective reports of relatives in determining age at onset? Are there different subtypes of the illness according to age at onset? If so, what age should subdivide these subtypes? Even more fundamentally, how should investigators operationally define age at onset? And, once defined, how consistent is this clinical measure? Despite considerable research on early-onset and late-onset AD, the controversy behind such questions remains unresolved.

In this report, we assess the interrater reliability of age at onset of Alzheimer-type dementia as well as a new clinical descriptor that may be useful in longitudinal studies of AD: the "age at shift" from questionable to probable AD, according to the National Institutes of Health (NIH) Consensus Criteria.[2]

Subjects and Methods

The study was performed on 21 patients (10 women and 11 men) from a larger ongoing project investigating positron emission tomography of local cerebral functions in patients with early-onset AD.[3] Diagnosis was made following psychiatric, neurological, and neuropsychological examination. Several standardized rating scales used to characterize the degree, nature, and rate of decline of these patients included the Mini-Mental State Examination (MMSE),[4] the Blessed-Tomlinson-Roth Dementia Scale (Blessed Scale),[5] the Clinical Dementia Rating Scale (CDR),[6] the Hamilton Rating Scale for Depression (HRSD),[7] and the Ischemic Scale.[8]

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To determine age at onset, family members, surrogates, or friends were asked when they first noted any mental or behavioral changes in the patient. This question was posed to the same informant by each of the health care professionals performing the initial patient evaluations, ie, a geriatric psychiatrist, a neurologist, a psychologist, and a nurse. The earliest age at onset from these four sources was used for comparisons with other variables. Age at shift was defined as the age during the follow-up period when the patient was first diagnosed as having probable AD.

Probable AD was diagnosed when the following criteria were satisfied: (1) presence of dementia was established by clinical examination, documented by standardized rating scales (eg, Mini-Mental State Examination), and confirmed by neuropsychological testing (Wechsler Adult Intelligence Scale—Revised [prorated version], Benton Visual Retention Test, Number Cancellation Protocol, Symbol Digit Modalities Test, Ravens Color Progressive Matrices Test, Hooper Visual Organization Test, Rey Auditory-Verbal Test, and Trial Making Test [Part A and Part B]); (2) deficits were present in two or more areas of cognitive functioning; (3) loss of memory and other cognitive functions was progressive; (4) level of consciousness was not disturbed; (5) onset was between ages 40 and 75 years; and (6) no other systemic disorder or brain disease could account for the deficits.[2]

Routinely recommended laboratory studies used to exclude other diseases that could cause dementia included complete blood count with sedimentation rate; analysis of urine; determinations of serum creatinine, urea nitrogen, glucose, electrolytes, bilirubin, vitamin B_{12}, and folic acid levels; serological test for syphilis; tests for thyroid function (T_4, T_3, and TSH); tests for liver function (SGOT, SGPT); electrocardiogram; electroencephalogram; and computerized tomographic (CT) scan of the head.[9] Patients with multi-infarct dementia were excluded by clinical examination and a score of 4 or more on the Ischemic Scale.[8] A score of 23 or less on the MMSE[4] as well as 4 or more on the Blessed Scale[5] was used as documentation of dementia. All patients scored a 0.5 or 1 on the CDR[6] on entry into the study. The MMSE, Blessed Scale, and CDR were also used to document progessive cognitive decline, and patients were followed at 6- to 12-month intervals, which increased our confidence in clinical diagnosis. A geriatric psychiatrist (GWS, JWA) and neurologist (DGF) examined patients at each interval and independently determined diagnostic categories. Another diagnostic determination was then made by a third clinician (DEK) following review of the medical record.

To assess the degree of association between age at onset and age at shift as well as associations with other clinical and demographic variables, we calculated Pearson's product-moment. The Kendall coefficient of concordance was used to calculate the degree of agreement for age at onset. Agreement for age at shift was determined by the Lawlis and Lu approach.[10]

Results

Clinical and demographic characteristics of the patients are listed in Table 1. Age at onset of the patients ranged from 45 to 75 years with a mean of 61.32 ± 6.90 (SD). Age at shift ranged from 54 to 77 years with

TABLE 1
Characteristics of Patients (Mean ± SD)

Characteristics*	Men (N = 11)	Women (N = 10)	Total (N = 21)
Age at examination (I)	65.27 ± 5.85	65.50 ± 6.24	65.38 ± 5.89
Years of education	14.91 ± 3.02	14.10 ± 2.13	14.52 ± 2.59
Age at onset	60.55 ± 6.67	62.10 ± 7.17	61.32 ± 6.90
Age at shift	66.45 ± 5.75	66.40 ± 6.26	66.43 ± 5.99
Duration of illness (I)	4.59 ± 1.74	4.08 ± 3.24	4.34 ± 2.45
Duration of illness (S)	5.49 ± 1.51	4.32 ± 3.47	4.94 ± 2.44
MMSE (I)	24.73 ± 1.35	24.80 ± 1.69	24.76 ± 1.52
MMSE (S)	21.55 ± 3.39	21.00 ± 3.40	21.29 ± 3.40
Blessed score (I)	7.68 ± 2.59	5.95 ± 1.88	6.85 ± 2.26
Blessed score (S)	9.23 ± 2.88	7.60 ± 2.23	8.46 ± 2.57
Rate of decline†			
MMSE	0.46 ± 0.35	0.58 ± 0.38	0.52 ± 0.36
Blessed	0.18 ± 0.12	0.29 ± 0.14	0.23 ± 0.14
HRSD score (I)	4.00 ± 2.72	6.00 ± 6.15	4.96 ± 4.36

* (I) = time of initial examination, (S) = time of shift from questionable to probable AD.
† = change in rating scale divided by number of months between first and last examination.

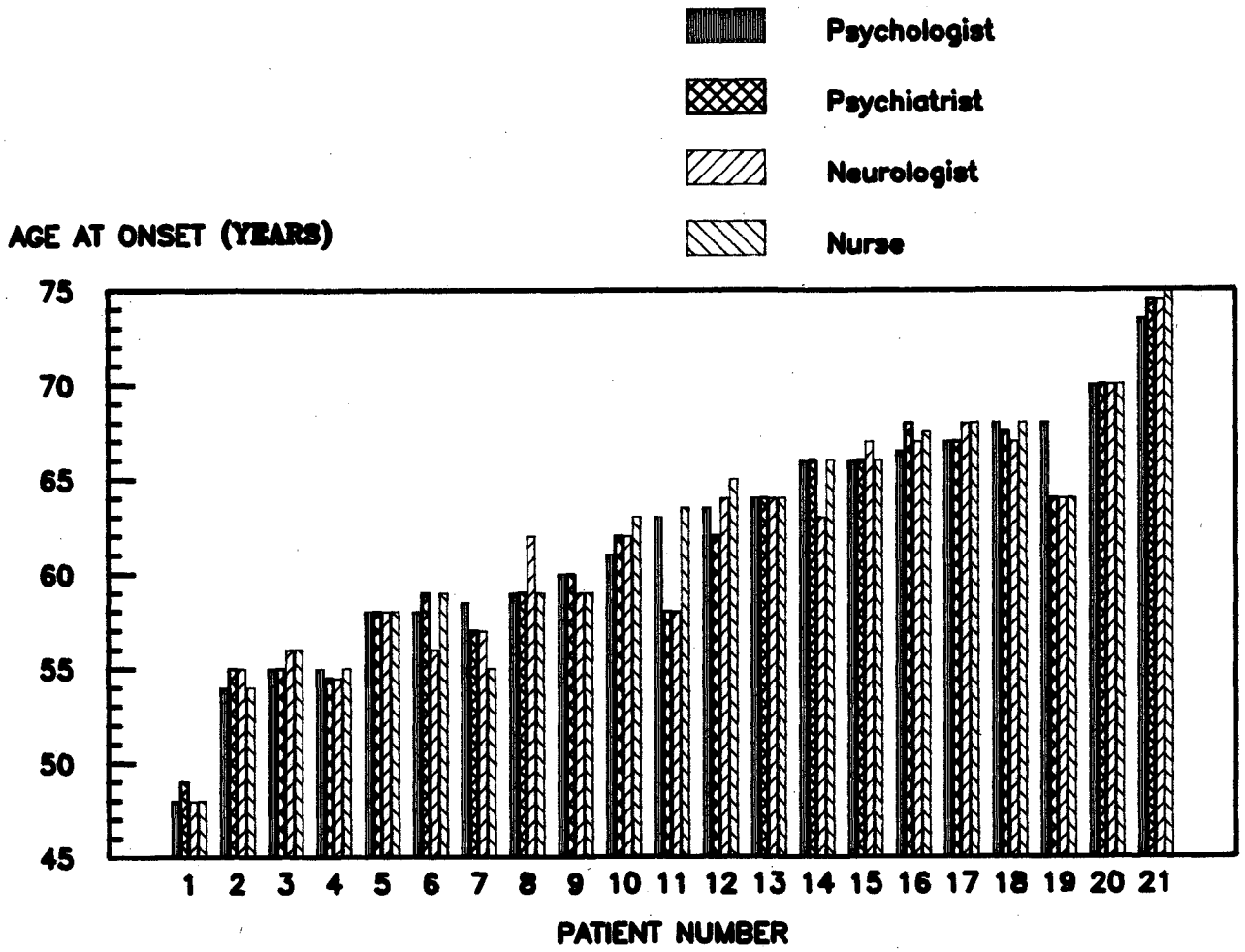

FIGURE 1
Age at onset—determinations of four clinicians.

a mean of 66.43 ± 5.99. The distribution of age at onset and age at shift for our sample was not bimodal but instead approached a normal distribution. Age at onset correlated highly with age at shift ($r = 0.95$, $P < 0.0001$), suggesting that these patients experienced similar rates of decline since the reported onset of illness. Age at shift and age at onset did not correlate with several other variables, including rate of decline, duration of illness, years of education, and severity of illness.

Although histories were obtained from the same informants, there was variability in age at onset, as determined by the different health care professionals (Figure 1). There was total agreement for only 3 of the 21 patients. For one patient, the range for age at onset was 5.5 years. When we looked at response patterns for individual health care professionals, the average differences from the mean age at onset were as follows: nurse, +0.30 years; neurologist, −0.25 years; psychiatrist, −0.16 years; and psychologist, +0.25 years. Despite this variability, when we ranked the ages at onset for each rater and calculated the Kendall coefficient of concordance, agreement was statistically significant ($W = 0.96$, $\chi^2 = 76.8$, $df = 20$, $P < 0.005$).

To determine the degree of agreement for age at shift, we counted the number of total agreements for diagnosing probable AD after the initial visit (ie, all three clinicians agreed) for the 17 patients who received two or more follow-up examinations; data for the 4 patients who received only one follow-up examination each were excluded from this calculation. Under these circumstances, the probability for total agreement by chance is 0.11, whereas the calculated t value is 0.87 ($\chi^2 = 96.39$, $df = 1$, $P < 0.0001$).

Discussion

Although agreement among clinicians was statistically significant, we found variability in determination of age at onset, even when histories were obtained from the same informants. Response patterns differed among the various professionals, with the physician interviewers (geriatric psychiatrist and neurologist) identifying earlier ages at onset than the nonphysician interviewers (psychologist and nurse). Educational and prior professional experience, as well as other factors, such as personal experience, interview style, and countertransference, may have influenced these determinations. Despite this variability in assessments, there was statistically a high level of concordance, which may reflect, in part, the relatively wide range of age at onset (48 to 75 years of age) in this sample population. When more narrow age ranges are studied, the level of concordance will be lower. The use of standardized interview schedules in dementia research could eliminate some of this variability, though such widely used instruments as the Diagnostic Interview Schedule or the Standard Clinical Interview for *DSM-III* have not yet been fully developed for adequate assessment of cognitive disorders.[11] Even if standardized questions are used, other sources of variability remain. These include how well the informant knows the patient, the distortion introduced by emotionally laden memories of past events, and variability of the informant's recall over time.

Even though informants may agree on age at onset, their reports may be inaccurate. Considering that patients early in the course of AD tend to deny symptoms, critical points in clinical characterization may be unobserved in these early stages. In a study of 16 patients with probable AD, Watson and colleagues[12] found rough validity to relatives' recall of dementia symptoms and their progression over time. They compared relatives' ratings of function at initial and follow-up evaluations with retrospective estimates of the extent of change over the same time period, and found that informants tended to report slightly less change than what had actually taken place. Other investigators[13] found a tendency for relatives to underreport symptoms of prior psychopathology.

Our data demonstrate the reliability of using age at shift as a clinical descriptor of AD in prospective longitudinal studies, although there was diasgreement on some of our cases. The NIH Consensus Criteria specify the kinds of information (eg, clinical history, laboratory test results) necessary to diagnose probable AD, but operational procedures for obtaining such information are not provided, which may explain some discrepancies. Moreover, the Consensus Criteria suggest standardized rating scales, but do not provide cutoff points for these scales. We recommend further delineation of and operational definitions for existing diagnostic criteria to help minimize disagreement.

In our study, age at onset correlated highly with age at shift, suggesting that the rate of deterioration for patients was similar regardless of age. The small sample size may explain the lack of correlation between age at onset or age at shift with other variables. Whether age at shift has greater precision than age at onset in determining subtypes of AD is a question awaiting further study using larger samples. The problems of basing the determining factor on retrospective reports from relatives are eliminated by using age at shift. Some of the controversy regarding subtyping AD may thus be resolved.

The accepted convention for subdividing AD has been to identify two groups, early-onset and late-onset. Most investigators use a cutoff age of 65 years, some use the age of 60 years, adding further confusion when attempts are made to compare results of studies using different criteria.[14] Given the small sample size and uniformity in rate of decline for this sample, it would be premature to assign such a cutoff age to separate "early-shift" from "late-shift" patients. Moreover, the distributions in age at onset and age at shift in our sample were not bimodal. These distributions suggest that using correlational statistics rather than group comparisons may be a more valid way of studying variables, given our current level of knowledge.

Bondareff and colleagues[15] reported on the usefulness of age at death in differentiating two subtypes of AD. Though age at death is determined with certainty, its use in clinical studies is limited for obvious reasons. The need for a clinical descriptor that falls between the onset of the illness and the demise of the patient is clearly called for in AD research. Age at shift from questionable to probable AD, according to the NIH Consensus Criteria, offers a logical reference point for such a descriptor. Because clinicians use standardized criteria to determine age at shift, it is less dependent than age at onset on potential inaccuracies introduced by informants' reports. Although its use is limited to longitudinal clinical studies, it may assist in refining the characterization and subtyping of patients with Alzheimer's disease.

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