

The Evolution of Psychiatric Symptoms in Alzheimer's Disease: A Natural History Study

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OBJECTIVE: To characterize the natural history of Alzheimer's Disease (AD); in particular, to determine the prevalence and time of onset of psychiatric symptoms.

DESIGN: Retrospective medical records review.

SETTING: Regional brain bank operated by a university hospital.

PARTICIPANTS: One hundred randomly selected autopsy-confirmed AD patients.

MEASUREMENTS: The presence of psychiatric symptoms (e.g., anxiety, wandering, agitation) was documented, and the time of onset relative to diagnosis was measured.

RESULTS: Irritability, agitation, and aggression were documented in 81 patients (81%) an average of 10 months after diagnosis. A total of 72% of patients experienced depression, changes in mood, social withdrawal, and suicidal ideation more than 2 years before diagnosis (26.4 months). Hallucinations, paranoia, accusatory behavior, and delusions were documented around the time of diagnosis (0.1 months after diagnosis) in 45% of patients. Patients with early-onset disease, more years of formal education, and male gender experienced psychiatric symptoms later, relative to diagnosis, than their counterparts.

CONCLUSIONS: Psychiatric manifestations of depression may herald a diagnosis of AD, as such behaviors occurred more than 2 years before diagnosis, on average, in this cohort. Psychotic symptoms manifested around the time of diagnosis, perhaps even prompting diagnosis, whereas agitative symptoms occurred in the first year after diagnosis. The evolution of psychiatric symptoms in this cohort differed according to age at onset of disease, years of formal education, and gender. *J Am Geriatr Soc* 44:1078-1081, 1996.

The symptomatic progression of Alzheimer's disease (AD) is of interest to the clinician, researcher, social worker, health insurer, caregiver, and patient, to name only some of those affected by a clinical diagnosis of AD. Psychiatric symptoms are often the sequelae of cognitive decline in AD, affecting adversely the quality of life of AD patients and their caregivers. These symptoms are also known to play a role in the decision to seek institutionalization.¹ Little is known of the natural history of AD, in particular the time of onset relative to the time of diagnosis of various signs and symptoms, both behavioral (or psychiatric) and cognitive.

A chart review of 57 patients with a diagnosis of AD and Global Deterioration Scale (GDS) scores of 4 or greater was completed by Reisberg and colleagues in an effort to examine the incidence, nature, and treatment of behavioral symptoms in AD.² A GDS score of 4 or greater was used because patients scoring at or above this level tend to have negative outcomes; this score is, therefore, compatible with a diagnosis of early AD.³ A total of 58% of the observed patients displayed significant behavioral symptomatology. Women tended to exhibit more symptoms than men, though this observation was not statistically significant. A later study published by Reisberg and colleagues,⁴ using an extended cohort of 120 patients, further stratified behavioral symptoms by GDS score. The Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) instrument was used to assess 25 specific symptoms in seven symptomatic categories. Input to this instrument was obtained by interview of "knowledgeable intimates" and/or caregivers and direct observation. "People are stealing things" delusions and day-night disturbance were noted in approximately 25% of the sample. Visual and auditory hallucinations were recorded for 15% and 7%, respectively. Approximately 30% of patients in this study exhibited wandering, verbal outbursts, and anxiety "regarding upcoming events." Finally, tearfulness and agitation were displayed by 40% of patients in this sample.

The only study investigating the utility of symptom onset times in predicting disease progression was conducted by Mortimer and colleagues.⁵ Aggressive behavior and sleep disturbance during the first year of observation predicted faster cognitive progression (measured by MMSE scores). Paranoia and hallucinations in the first year were predictive of more rapid functional decline. Mayeux et al.⁶ completed a retrospective review of 138 patients meeting research criteria for dementia of the Alzheimer's type in an effort to characterize the influence of psychosis on the course of disease. Patients demonstrating psychosis (44%), defined as "persis-

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tent or recurrent thought disorder in the absence of altered consciousness," showed significantly greater impairment as well as a more rapid rate of deterioration than the other patients.

Although there have been numerous studies investigating the cognitive aspects of AD, few studies have focused on the evolution of psychiatric symptoms in AD. The aim of the present study is not to predict the rate of functional or psychiatric/behavioral or cognitive progression, but to assemble a template of onset times for psychiatric symptoms among AD patients in general and for specific patient/disease subgroups in particular.

METHODS

Data were obtained from a retrospective medical records review involving 100 randomly selected, autopsy-confirmed AD patients. Patients were enrolled in a regional brain bank. Registrants were identified through a university geropsychiatry clinic and by clinicians and caregivers in surrounding communities. A total of 16 psychiatric symptoms were surveyed. The symptom descriptors used reflect the terminology used in the clinicians' notes. Dates of onset for the psychiatric symptoms were abstracted directly from the medical records; when dates were unavailable, an entry was made to denote presence of the symptom. Chronological reference points known for each patient were date of birth, date of clinical diagnosis, date of institutionalization (if it occurred), and date of death. The methodology for data abstraction and data analysis has been described in a previous report.⁷

Three symptom groups were defined: (1) agitative symptoms, including irritability, agitation, and aggression; (2) depressive symptoms, including depression, mood change, social withdrawal, and suicidal ideation; and (3) psychotic symptoms, including hallucinations, paranoia, accusatory behavior, and delusions. Onset times for these symptom groups were calculated by first determining the earliest time of onset for any one of the component symptoms and then calculating the mean, standard deviation, and range for the set of patients exhibiting at least one of the component symptoms.

A time-density plot is a convenient method of demonstrating both the proportion of patients exhibiting a particular symptom (plotted on the y-axis) and the temporal relationships between symptoms (time is plotted on the x-axis). All time values in this natural history study have been converted to months before or after clinical diagnosis, which is designated as time zero in all plots. A negative time value denotes an event occurring before diagnosis, e.g., -14 means 14 months before diagnosis.

Subgroup analyses were conducted to determine the role, if any, of gender, years of education, age at disease onset, and family history on symptom onset. Gender was investigated because of the well known preponderance of females among patients with AD. The influence of education and occupation on the risk of developing AD has been researched, and this was the rationale for including education in the subgroup analysis. Similarly, the existence of a recognized subgroup of patients with early-onset familial AD prompted an analysis of the influence of age at onset and family history. All subgroup analyses were tested for statistical significance using the unpaired *t* test.

RESULTS

The most frequent behavior documented at any point in the medical records was agitation, noted in more than three-quarters (77%) of all patients studied. When agitative symptoms are considered in aggregate, i.e., given irritability defined as mild agitation and aggression defined as severe agitation, 81 patients (81%) displayed agitative symptomatology. Employing a similar grouping for depressive symptoms, i.e., broadening the definition of depression to include mood changes, social withdrawal, and suicidal ideation, 72 patients (72%) exhibited some form of depression. Disturbances in diurnal rhythm were noted in more than half (56%) of all patients. Psychotic symptoms such as hallucinations, paranoia, accusatory behavior, and delusions were documented in 45% of all patients. Wandering was documented in 43%. Less common, yet notable, were anxiety/phobias and socially unacceptable behavior. Sexually inappropriate behavior was present in this cohort, but was relatively uncommon, occurring in less than 5% of patients.

Social withdrawal was the earliest recognizable individual psychiatric symptom of AD, occurring an average of 33 months before diagnosis (see Figure 1). Other heralding symptoms were suicidal ideation, depression, paranoia, disturbances in diurnal rhythm, and anxiety/phobias. Agitation, hallucinations, and aggression were documented relatively late in the course of the disease, 1 to 2 years after diagnosis, on average. Depression and disturbances in diurnal rhythm were present at diagnosis in 11 and 10 patients, respectively. Hallucination was a presenting complaint in five patients. A total of four patients each exhibited paranoia, aggressive behavior, change in mood, and anxiety within 6 months of diagnosis.

Subgroup analyses for time of onset of psychiatric symptoms were conducted for early- (less than 65 years of age) versus late-onset disease, gender, presence or absence of family history of dementia, and education (less than 12 years vs 12 or more years of schooling). The greatest number of statistically significant differences was observed in the analysis of early- versus late-onset disease (see Figure 2). The onset times of three parameters were found to be significantly different: wandering (*P* = .004), aggression (*P* = .050), and

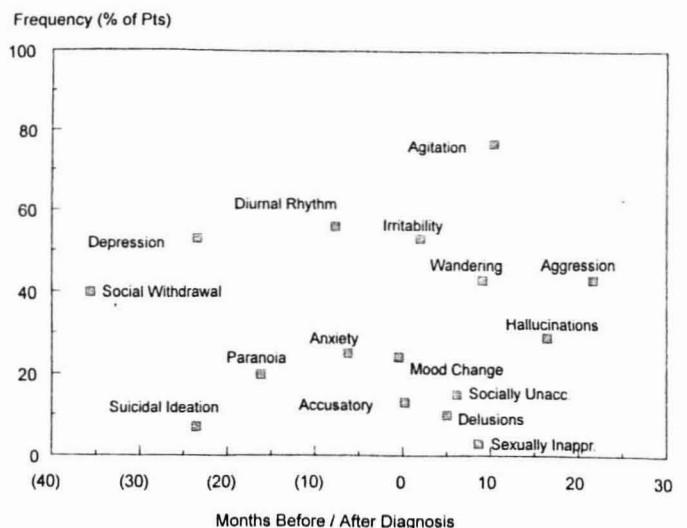


Figure 1. Time-density plot of psychiatric symptoms.

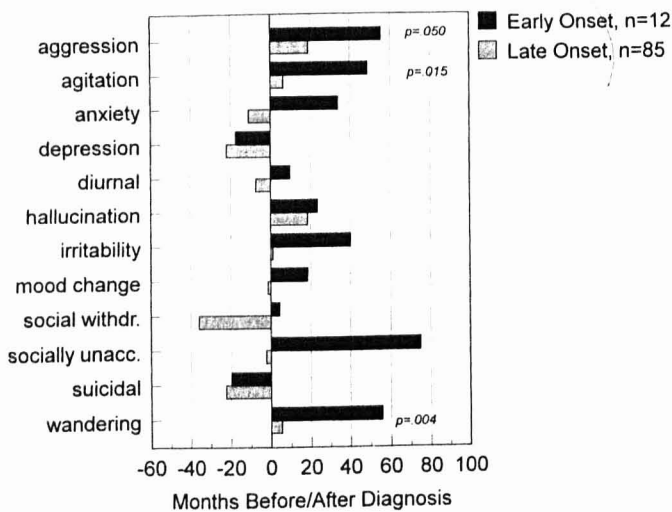


Figure 2. Onset of psychiatric symptoms: Early- versus late-onset disease.

agitation ($P = .015$). All symptoms manifested later in the course of the disease for patients with early-onset disease.

Only the time of onset of social withdrawal was significantly different for patients with more formal education compared with patients with less formal education. Patients with 12 or more years of education became withdrawn 30 months before diagnosis, on average, while patients with less than 12 months of education displayed this symptom nearly 10 months after diagnosis ($P = .055$). With the exception of changes in mood, paranoia (negligible difference), and social withdrawal, all other psychiatric symptoms manifested later in the course of the disease for persons with more years of formal education.

The time of onset of only one parameter, socially unacceptable behavior ($P = .026$), was significantly different between males and females (Figure 3). In general, males tended to display psychiatric symptoms later in the course of the disease than females.

Symptom onset times did not differ significantly for patients with a family history of dementia compared with patients with no such history. It is noteworthy, however, that

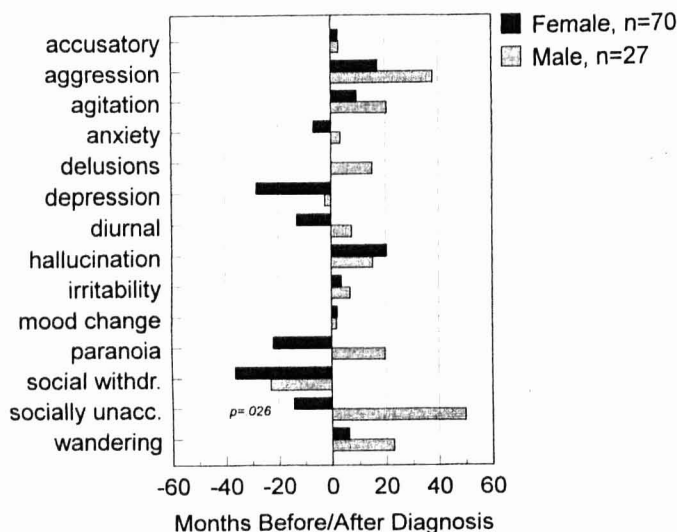


Figure 3. Onset of psychiatric symptoms: Gender.

patients with a family history tended to demonstrate accusatory behavior, anxiety, disturbances in diurnal rhythm, irritability, paranoia, and socially unacceptable behavior before diagnosis, whereas patients without a family history exhibited these symptoms after diagnosis. Overall, patients with a positive family history consistently experienced symptoms before their negative family history counterparts.

DISCUSSION

Agitative symptoms were the behaviors observed most commonly in this cohort of autopsy-confirmed patients and occurred in 81% of patients approximately 10 months after diagnosis. This rate is consistent with data from a study of 43 nursing home residents with dementia, in which 84% were found to have agitation and/or aggression problems.⁸ Irritability was noted in 23% of 44 patients with dementia of the Alzheimer's type in a study by Rubin and colleagues,⁹ a rate significantly lower than that noted in the present study (53% of patients exhibited irritability). Reisberg and colleagues reported agitation alone in only 42% of AD patients exhibiting behavioral symptomatology.⁴ Fairly close agreement was found between Reisberg's cohort and the present cohort in the prevalence of anxiety (28% vs 25%, respectively).

Reisberg et al. reported the presence of tearfulness in 37% of their study cohort. Similarly, the Predictors Study observed depression in 42% of patients studied.¹⁰ The prevalence of depression in demented patients is controversial, with estimates ranging from 0 to 50%.¹¹ The present finding that 53% of patients manifested depression is just beyond the range reported in the literature. Symptoms characteristic of depression (depressive symptoms) were documented an average of 26.4 months before diagnosis or approximately 6 months after symptom onset in this cohort, as reported in an earlier paper.⁶

The rate of psychotic symptoms exhibited by this cohort of patients, 45%, is in agreement with the prevalence of psychosis reported by Mayeux and colleagues, 44%.⁵ The findings in this study regarding psychosis are also similar to others in the literature when psychotic symptoms are considered individually. A total of 24% of patients exhibited delusions of any type, including 14% with delusions of the paranoid type, in the Predictors Study.⁹ If we interpret this to mean that 10% experienced delusions of the non-paranoid type, then this is in perfect accordance with the 10% prevalence of delusions demonstrated in this cohort. Morriss et al. have reported that 21% of nursing home patients with cognitive impairment experience delusions.¹² Berrios and Brook reported delusions in as many as 37% of 100 older demented patients referred to general practitioners for psychosocial incompetence.¹³ Only 8% of patients experienced hallucinations in the Predictors Study, compared with 29% in the present study, 28% in a study of patients with dementia of the Alzheimer's type by Merriam and colleagues,¹⁴ and 15% (visual hallucinations) in the study by Reisberg and colleagues.⁴ Psychotic symptoms manifested around the time of diagnosis (0.1 months after diagnosis, on average) in this autopsy-confirmed cohort. Such behaviors may have contributed to or substantiated the diagnosis in some cases.

Wandering behavior was observed in 43% of AD patients in the present study. Review of the literature on wandering is problematic because of inconsistencies in definition. It is known to occur at a significant rate, however. According to The National Center for Health Statistics, 11% of nursing

home residents wander¹⁵; moreover, it has been estimated that 20% of cognitively impaired nursing home residents wander.¹⁶ Reisberg and colleagues found that 29% of AD patients wandered in their chart review study.⁴ In the cohort discussed here, on average, wandering occurred relatively early in the course of the disease. The mean onset time was 11.6 months after diagnosis. In a study comparing patients with Alzheimer's disease and patients with vascular dementia, it was noted that patients with Alzheimer's dementia tended to begin wandering in the middle or late stage of disease.¹⁷

Depression and disturbances in diurnal rhythm were the most common presenting psychiatric symptoms in this cohort, present in 11% and 10%, respectively, of patients within 6 months of diagnosis. These complaints, or similar ones, were among the top six *primary* presenting complaints in the Predictors Study; disorientation was the primary complaint among 4% of patients studied, while depressed mood was the primary complaint among only 1.4% of patients.

The later onset of psychiatric symptoms, relative to diagnosis, that was observed among early-onset patients in this cohort may not be inconsistent with reports of a more rapid rate of decline in this subgroup.¹⁸⁻²⁰ These studies have typically measured rates of cognitive decline, not onset of symptoms or deficits. Persons with early-onset disease may be diagnosed earlier in the course of the disease than later-onset patients, thereby accounting for the apparent delay in symptom onset.

The statistically significant differences in time of onset for psychiatric symptoms between early- and late-onset patients may provide additional evidence that early-onset disease is a distinct subgroup within the AD population. The fact that these symptoms manifested later in the early-onset group may only reflect earlier diagnosis. Stratification by years of education also produced a statistically significant difference in symptom onset times. In general, patients with more years of formal education manifested symptoms later than those with less education. This finding is consistent with the hypothesis of Stern and his colleagues,²¹ namely, that increased educational attainment may impart a reserve allowing patients to cope longer before clinical expression. It is also plausible that an AD diagnosis may be more elusive in a patient with increased formal education, thereby resulting in a delay.

In summary, the temporal profile of psychiatric symptoms differs according to age at onset, level of formal education, and sex. Patients with early-onset disease, patients with more years of formal education, and male patients tend to manifest psychiatric changes later in the natural history of the disease, relative to diagnosis, than their counterparts.

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