PREVALENCE AND CORRELATES OF ANXIETY IN ALZHEIMER'S DISEASE

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We assessed a consecutive series of 398 patients with probable Alzheimer's disease (AD) for the presence of Generalized Anxiety Disorder (GAD) using a standardized neuropsychiatric evaluation. Five percent of patients showed GAD during the 4 weeks preceding the psychiatric evaluation. AD patients with GAD showed significantly higher scores of depression, irritability, overt aggression, mania, and pathological crying than AD patients without GAD. The most severe symptoms of anxiety were those of tension, fears, insomnia, and physical complaints. Depression and Anxiety 7:166–170, 1998. *© 1998 Wiley-Liss, Inc.*

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INTRODUCTION

Mood disorders are frequent findings in patients with Alzheimer's disease (AD). In a recent study that included a consecutive series of 103 patients with AD who were assessed with a structured psychiatric interview we found that 51% were depressed (28% had dysthymia and 23% had major depression) (Migliorelli et al., 1994). Whereas both depression groups had significantly higher Hamilton Anxiety Scale scores as compared to nondepressed AD patients, the presence of anxiety disorders in the absence of depression has not been, up to our knowledge, empirically examined.

In recent studies, we also examined the prevalence and clinical correlates of apathy, irritability, and emotional lability in AD. We found that 46% of a consecutive series of AD patients had apathy, which was significantly associated with more severe impairments in activities of daily living, more severe extrapyramidal signs, and a significantly higher frequency of both major depression and dysthymia. Irritability was found in 13% of the patients, and was significantly associated with higher depression and anosognosia scores. In a separate study, we found pathological affect in 41% of the patients (22% showed pathological crying, 13% showed pathological laughing, and 6% showed both laughing and crying episodes).

Anxiety symptoms in AD may be construed as either a psychological response to the progressive cognitive decline, or as nonspecific symptoms of the illness, such as difficulties with concentration, agitation, or paranoid thinking. Alternatively, anxiety in AD may be due to the stress of cognitive decline in vulnerable individuals with premorbid risk factors, such as personal or familial psychiatric disorders. The aim of the present study was to examine the prevalence and correlates of generalized anxiety disorder (GAD) in AD. We assessed a large consecutive series of AD patients using a structured psychiatric interview and scales that measured the presence of cognitive impairments, social functioning, deficits in activities of daily living, and behavioral and mood disorders.

PATIENTS AND METHODS

PATIENTS

We examined a consecutive series of 398 patients who attended the neurology clinic of our Institute due to progressive cognitive decline. The inclusion criteria were the following: 1) NINCDS-ADRDA criteria (Mc Khann et al., 1984) for probable AD, 2) normal laboratory test results, 3) no history of closed head injuries with loss of consciousness, strokes, or other neurologic disorders with central nervous system involvement, 4) no focal lesions on the CT or MRI

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scan, and 5) a Hachinski Ischemic score 4 (Hachinski et al., 1975).

PSYCHIATRIC EXAMINATION

After informed consent, patients were assessed by a psychiatrist with the following instruments.

Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1992). The SCID is a semi-structured diagnostic interview for making the major Axis I DSM-III-R (American Psychiatric Association, 1987) diagnoses, and was carried out with the patient and at least one first-degree relative. Based on the SCID responses, DSM-III-R Axis I diagnoses were made.

Structured Clinical Interview for DSM-III-R-Personality Disorders (SCID-II) (Spitzer et al., 1992). The SCID-II is a 100-item questionnaire designed to evaluate DSM-III-R personality disorders. It was filled out by the patient with the help of at least one first-degree relative. They were asked to answer the questions on the basis of the patient's behavior before the onset of the cognitive impairment. Several days later the patient and the relative were interviewed a second time and were questioned about those answers rated positive. On the basis of these answers, a diagnosis of personality disorder was made by using DSM-III-R criteria.

Hamilton Depression Scale (HAM-D) (Hamilton, 1960). The HAM-D is a 17-item interviewer-rated scale that measures psychological and autonomic symptoms of depression.

Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959). The HAM-A is an 11-item interviewer-rated scale that measures the severity of generalized or persistent anxiety.

Bech Mania Scale (Bech et al., 1986). This scale assesses the severity of manic symptoms, such as euphoria, hyperactivity, flight of ideas, hypersexuality, decreased need of sleep, etc.

Pathological Laughing and Crying Scale (PLACS) (Starkstein et al., 1995a). This instrument is an interviewer-rated scale that quantifies aspects of pathological affect, including the duration of the episodes, their relation to external events, degree of voluntary control, inappropriateness in relation to emotions, and degree of resultant distress. The scale is administered to the patient and at least one first-degree relative or caretaker in close contact with the patient. The scale consists of 16 items (eight assessing pathological laughter [PLACS-L] and eight assessing pathological crying [PLACS-C]) which are scored from 0 to 3 points. Both the reliability and validity of this scale in AD have been previously demonstrated (Starkstein et al., 1995a).

Apathy Scale (Starkstein et al., 1995b). This scale includes 14 items which are scored by the patient's relative or caretaker. Each question has four possible answers, which are scored from 0 to 3. Thus, the Apathy Scale scores range from 0 to 42 points, and higher scores indicate more severe apathy. We have demonstrated the reliability and validity of the Apathy Scale in AD (Starkstein et al., 1995).

Irritability Scale (Starkstein et al., 1995b). This is a 14-item scale which is rated by the patient's relative or caretaker. Scores range from 0 to 42, and higher scores indicate more severe irritability. We have demonstrated the validity and reliability of this scale in AD.

Dementia Psychosis Scale (DPS) (Migliorelli et al., 1995). This is an 18-item scale which quantifies the severity and types of delusions in demented patients at the time of the psychiatric evaluation. This scale was rated by a psychiatrist with the patient and at least one close relative or caretaker. We have demonstrated the validity and reliability of this scale in AD.

Functional Independence Measure (FIM) (Granger et al., 1986). This instrument assesses self-care, sphincter control, mobility, locomotion, communication, and social cognition on a low level scale. Higher scores indicate less impairments in activities of daily living (ADLs).

Overt Aggression Scale (OAS) (Yudofsky et al., 1995). The OAS measures specific aspects of aggressive behavior based on observable criteria. Aggressive behaviors are divided into four categories: verbal aggression, and physical aggression against objects, against self, and against others. Within each category, descriptive statements and numerical scores are provided to define and rate four levels of severity.

Social Ties Checklist (Starr et al., 1983). This is a 10-item scale which assesses the quantity and quality of social supports. Scores range from 0 to 10, and higher scores indicate better social supports.

Clinical Dementia Rating (CDR) (Hughes et al., 1982). The CDR is a global rating device which was found to distinguish unambiguously among older subjects with a wide range of cognitive functions, from healthy to severely impaired. Based on CDR findings, patients were classified into groups with mild, moderate, or severe dementia.

STATISTICAL ANALYSIS

Statistical analysis was carried out using means and SDs, unpaired *t*-tests, analysis of co-variance (ANCOVA) and post-hoc planned comparisons, and Mann-Whitney U tests. Frequency distributions were compared using chi-square tests with a Yates' correction for cell sizes <5. Regression analyses were calculated with forward stepwise regressions. All *P* values are two-tailed.

RESULTS

Eighteen of the 398 AD patients (5%) met DSM-III-R criteria for GAD (excluding the general medical condition); eight patients met criteria for Panic Disorder, and one patient met criteria for a Simple Phobia. To examine demographic and clinical correlates of anxiety in AD we compared the 18 AD patients with GAD with a consecutive series of 36 AD patients without affective or anxiety disorders.

DEMOGRAPHIC AND CLINICAL FINDINGS

No significant between-group differences were found in age, gender, and duration of illness (Table 1). Most AD patients with GAD had mild or moderate dementia.

PSYCHIATRIC FINDINGS

AD patients with GAD showed a significantly higher frequency of personal history of psychiatric disorders (mostly depression) as compared to AD patients without GAD ($\chi^2 = 8.70$, df = 1, $P < .01$), but no significant between-group differences were found in family history of psychiatric disorders (Table 2). Patients with GAD showed significantly higher Hamilton anxiety ($t = 10.2$, $P < .0001$) and Hamilton depression ($t = 2.96$, $P < .01$) scores as compared to the control group. After we excluded from the HAM-D those items that overlapped with the DSM-III-R clinical criteria for GAD, between group-differences still remained significant (AD-GAD [mean ± SD] = 4.1 ± 3.7, AD control = 1.5 ± 1.9, $t = 3.2$, $P < .01$). Patients with GAD also showed higher scores of irritability ($t = 2.73$, $P < .01$), overt aggression (six patients had no OAS scores) ($t = 2.72$, $P < .01$), pathologic crying ($t = 3.01$, $P < .01$), mania ($t = 2.70$, $P < .01$), and delusions ($t = 4.74$, $P < .0001$). After using an ANCOVA (with MMSE scores as the covariate), all the significant differences remained unchanged (delusions F[1,45] = 25.4, $P < .0001$; depression F[1,45] = 7.5, $P < .01$; anxiety F[1,45] = 97.4, $P < .0001$; mania F[1,45] = 7.04, $P < .01$; pathological crying F[1,45] = 9.27, $P < .01$; and overt aggression F[1,39] = 7.59, $P < .01$). After using a nonparametric test (Mann-Whitney U test) two variables lost statistical significance (mania $P = .30$, and overt aggression $P = .06$) which may be due to the skewed distribution of their respective scores.

To examine the profile of anxiety symptoms in AD, we compared scores on each item of the HAM-A between the AD-GAD and the AD control group (Table 3). The AD-GAD group had significantly higher scores for the following HAM-A items: anxious mood (F[1,52] = 25.9, $P < .0001$), tension (F[1,52] = 27.6, $P < .0001$), fears (F[1,52] = 22.6, $P < .0001$), insomnia (F[1,52] = 25.4, $P < .0001$), muscular symptoms (F[1,52] = 29.9, $P < .0001$), somatic symptoms (F[1,52] = 24.0, $P < .0001$), cardiovascular symptoms (F[1,52] = 23.1, $P < .0001$), respiratory symptoms (F[1,52] = 17.4, $P < .001$), gastrointestinal symptoms (F[1,52] = 17.4, $P < .001$), and autonomic symptoms (F[1,52] = 14.5, $P < .001$). No significant between-group differences were found for the following items: concentration and memory, depressed mood, genito-urinary symptoms, and behavior at interview.

We calculated a stepwise regression analysis, using HAM-A scores as the dependent variable and demographic data and psychiatric scales scores as independent variables. The overall regression was significant ($R^2 = .63$, F[9,44] = 7.22, $P < .0001$), and the variables that accounted for a significant part of the variance were the Psychosis Dementia Scale ($R^2 = 0.40$, F = 30.8, $P < .0001$); PLACS-crying ($R^2 = 0.15$, F = 0.15, $P < .001$), and the Overt Aggression Scale ($R^2 = .04$, F = 3.88, $P < .05$).

Since 36% of the AD patients without GAD were on psychoactive drugs (which could potentially mask the presence of anxiety symptoms), we carried out further statistical comparisons between the AD-GAD group and the AD group without GAD not on psychoactive treatment. All psychiatric differences still remained significant (HAM-D $t = 4.74$, $P < .0001$; Mania Scale $t = 2.17$, $P < .05$; Irritability Scale $t = 2.71$, $P < .01$; PLACS-crying $t = 3.60$, $P < .001$; Overt Aggression Scale $t = 2.26$, $P < .05$; and Dementia Psychosis Scale $t = 4.31$, $P < .0001$).

TABLE 1. Demographic findings*

	AD GAD	AD control
Number of patients	18	36
Age (mean years)	74.3 (7.0)	73.5 (6.3)
Education (mean years)	10.7 (6.7)	13.5 (6.8)
Gender (% female)	55	55
Duration of illness (mean years)	3.7 (2.1)	2.6 (2.2)
Medical illness (%) (axis III DMS-III-R)	38	33
CDR-stage		
Mild (%)	39	72
Moderate (%)	44	22
Severe (%)	17	6

**SDs are in parentheses.*

TABLE 2. Psychiatric findings[a]

	AD GAD	AD control
Mini-Mental State Exam	20.7 (5.8)	20.8 (5.6)
Overt Aggression Scale*	1.5 (2.5)	0.2 (0.6)
Hamilton Depression Scale*	8.5 (4.9)	4.2 (5.0)
Hamilton Anxiety Scale**	14.1 (4.6)	3.6 (2.7)
Bech Mania Scale*	4.6 (8.7)	0.6 (1.1)
Pathological Laughing Scale	0.7 (2.6)	0.5 (0.6)
Pathological Crying Scale*	5.2 (6.0)	1.3 (3.5)
Apathy Scale	14.6 (10.4)	14.8 (10.7)
Irritability Scale*	17.9 (12.0)	10.2 (8.3)
Psychosis Dementia Scale*	3.7 (3.3)	0.7 (1.4)
Social Ties Checklist	3.3 (1.4)	3.3 (1.9)
Functional Independence Measure	62.1 (11.7)	65.5 (5.5)
Personality disorders (%)	22	13
Personal history of psychiatric disorders (%)*	55	16
Family history of psychiatric disorders (%)	27	16
Psychoactive drugs		
Anxiolythics (%)	17	30
Antidepressants (%)	17	8
Neuroleptics (%)	5	5

[a]*SDs are in parentheses.*
*P < *.05*; **P < *.0001.*

TABLE 3. Hamilton Anxiety Scale—individual items[a]

	AD GAD	AD control
Anxious mood*	1.8 (0.8)	0.7 (0.7)
Tension*	1.6 (0.8)	0.4 (0.6)
Fears*	1.1 (0.9)	0.1 (0.5)
Insomnia*	1.3 (1.0)	0.2 (0.5)
Concentration and memory	2.1 (1.0)	1.3 (1.2)
Depressed mood	0.7 (0.9)	0.3 (0.5)
Muscular symptoms*	1.0 (0.9)	0.08 (0.2)
Somatic symptoms*	0.5 (0.6)	0 (0)
Cardiovascular symptoms*	0.6 (0.8)	0 (0)
Respiratory symptoms*	0.5 (0.9)	0.05 (0.2)
Gastrointenstinal symptoms*	0.7 (1.0)	0.02 (0.1)
Genito-urinary symptoms	0.2 (0.5)	0.05 (0.3)
Autonomic symptoms*	0.4 (0.7)	0 (0)
Behavior at interview	0.8 (0.9)	0.2 (0.5)

[a] *SDs are in parentheses.*
*$P < 0.5$.

DISCUSSION

This study examined the prevalence and correlates of GAD in AD, and there were several important findings. First, the overall prevalence of anxiety disorders in a large series of consecutive patients attending a dementia clinic was 7%, with 5% showing GAD, 2% with a Panic Disorder, and only one patient with a Simple Phobia. Second, patients with GAD showed significantly higher scores of depression, irritability, overt aggression, mania, and pathological crying than AD patients without GAD but with similar age and severity of cognitive deficits (as measured with the MMSE). On the other hand, neither social functioning nor more severe deficits in activities of daily living were associated with more severe GAD. Third, the most prominent symptoms of anxiety in AD were those of tension, fears, insomnia, and physical complaints.

Before further comments, some limitations of our study should be pointed out. First, this is a cross-sectional study, and whether there is a different prevalence of GAD in early vs. late stages of AD should be determined in longitudinal studies. Second, about one-third of non-GAD AD patients were on psychoactive drugs, which may potentially mask the presence of anxiety symptoms. However, even after excluding these patients, between-group differences remained significant. Finally, we excluded from our study patients with GAD and concomitant depression, and the clinical implications of this important association should be examined in future studies.

In this study we found in a nonselected sample of AD patients a prevalence of anxiety disorders of 7%. The Epidemiology Catchment Area study (Myers et al., 1984) reported in the elderly population a rate of anxiety of 2% (although 50–75% of these cases also had concomitant depression). The Duke Community Sample study (Blazer et al., 1991) reported among individuals >65 years of age a 6-month prevalence of GAD of 1.9%. Thus our present findings demonstrate that the prevalence of GAD in AD is about two to four times greater than in an age-comparable normal community sample.

One of the most important findings of this study was that AD patients meeting DSM-III-R criteria for GAD (excluding the organicity criterion) had a significantly higher severity of additional behavioral problems as compared to AD patients without GAD. AD patients with GAD showed significantly higher scores of depression (even after excluding the anxiety-related items), significantly more frequent episodes of pathological crying, and a higher frequency of personal history of depression as compared to AD patients without GAD, suggesting that GAD in AD may indicate a subsyndromal depressive state. Future studies should examine the prevalence and clinical correlates of anxiety and concomitant depression in AD.

Other frequent behavioral findings in AD are delusions (Migliorelli et al., 1995), irritability (Starkstein et al., 1995b), disinhibition (Migliorelli et al., 1995), and aggressive outbursts (Patel and Hope, 1993). The present study showed that AD patients with GAD had significantly higher scores of delusions, aggression, mania, and irritability than AD patients with no GAD but similar MMSE scores. Moreover, a regression analysis demonstrated that severity of delusions, pathological crying, and aggressive behavior accounted for most of the variance with anxiety scores. These findings suggest that rather than being part of an affective disorder, symptoms of anxiety may be part of a more complex disinhibition syndrome. Alternatively, both mechanisms could be valid, and whereas a subgroup of AD patients may show GAD as part of a subsyndromal depressive disorder, other AD patients may show GAD as part of a more widespread disinhibition syndrome. Future studies using comprehensive neuropsychological batteries should examine whether different cognitive profiles characterize AD patients with depression or a disinhibition syndrome.

In conclusion, we found a low prevalence of GAD in AD. AD patients with GAD showed higher scores of depression and other behavioral disorders as compared to AD patients without GAD. Whether GAD characterizes a subtype of depression or is part of a disinhibition syndrome should be examined in future studies.

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