Anosognosia Is a Significant Predictor of Apathy in Alzheimer's Disease

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Anosognosia and apathy are among the most common behavioral and psychological disorders of Alzheimer's disease and are significantly associated in cross-sectional studies. The aim for this study was to carry out for the first time a longitudinal assessment of this association with the aim of clarifying the predictive role between anosognosia and apathy in Alzheimer's disease. A consecutive series of 213 patients with probable Alzheimer's disease were assessed for the presence of apathy and anosognosia using a specific neuropsychiatry assessment. One hundred fifty four of the patients (72%) had a follow-up assessment between 1 and 4 years after the baseline evaluation. Patients with anosognosia at baseline had a significant increase in apathy scores during follow-up relative to patients without anosognosia at both assessments. Conversely, patients with or without apathy had an increase of similar magnitude in anosognosia scores. In conclusion, anosognosia is a significant predictor of apathy in Alzheimer's disease. This may be related to a specific pattern of progression of neuropathology and/or to poor adjustment of Alzheimer's disease patients with poor insight into their functional deficits.

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Anosognosia, or loss of insight into one's cognitive and functional problems, is one of the most common neuropsychiatric problems among patients with Alzheimer's disease. Using clinically validated diagnostic criteria, we have recently reported that about 30% of patients with mild dementia have anosognosia.[1] Apathy is among the most common behavioral changes in Alzheimer's disease.[2] The frequency of apathy in Alzheimer's disease has been reported to range between 19% and 76%, and this discrepancy may be mainly related to different diagnostic methods and the inclusion of patients with different severities of dementia.[3]

Cross-sectional studies reported a significant association between anosognosia and apathy,[4] but to our knowledge, whether anosognosia may predict apathy or vice versa has never been examined. Furthermore, longitudinal studies of apathy and anosognosia in Alzheimer's disease are few.[5,6] In recent longitudinal studies we found that apathy in Alzheimer's disease is a

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significant predictor of depression, faster functional and cognitive decline, and more severe parkinsonism.[5,7]

The present study is, to our knowledge, the first to examine the longitudinal association between anosognosia and apathy in Alzheimer's disease. We expected both anosognosia and apathy to increase in parallel with increasing cognitive decline, which may be related to progression of pathology in brain regions common to apathy and anosognosia. Alternatively, we expected anosognosia to predict apathy based on the hypothesis that patients with anosognosia may have more limitations in adapting to their functional deficits due to their poor insight and more severe disinhibition and irritability.[4,8]

METHODS

Participants

The Alzheimer's disease group included a consecutive series of 354 outpatients attending the Dementia Clinic at a tertiary neurology center in Buenos Aires, Argentina, between January 1996 and October 2001 for evaluation and treatment of progressive cognitive decline (more information on this sample was reported elsewhere).[5,7] The main aim of the original study was to examine the longitudinal progression of apathy in Alzheimer's disease, and assessments of anosognosia were started after the study was commenced. Therefore, 213 of the 354 patients were assessed with scales of anosognosia, and this is the sample included for our present study.

All patients met the following inclusion criteria: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease[9]; no history of closed head injuries with loss of consciousness, strokes, or other neurological disorder with CNS involvement; normal results on laboratory tests (to rule out other causes of dementia); no focal lesions on MRI scan; and a Hachinski Ischemic Scale score less than 4.[10] The institutional human subjects committee approved the study.

Psychiatric Examination After written informed consent was obtained from patients and their respective caregivers, a psychiatrist blind to the neurological findings assessed patients with the following instruments.

The Structured Clinical Interview for DSM-IV (SCID)[11] is a semistructured diagnostic interview for making the major axis I DSM-IV diagnoses. Based on the SCID responses, the DSM-IV axis I diagnosis of major depressive episode and the DSM-IV research diagnosis of minor depression were made.[12]

The Mini-Mental State Exam (MMSE)[13] is an 11-item examination found to be valid and reliable in assessing a limited range of cognitive functions in a global way.

The Apathy Scale[14] includes 14 items which are scored by the patient's relative or caregiver. We have demonstrated the reliability and validity of the Apathy Scale in Alzheimer's disease.[14] Diagnoses of apathy were generated based on caregivers' ratings on the Apathy Scale using the procedure and the diagnostic criteria for apathy previously validated.[15]

The Anosognosia Questionnaire for Dementia (AQ-D)[4] is a 30-item questionnaire divided into two sections. The first section assesses performance of basic and instrumental activities of daily living, whereas the second section examines changes in mood and behavior. There are two forms for this questionnaire: Form A is answered by the patient alone and Form B is answered by a next of kin or caregiver. Forms A and B are rated blind to each other, and the final score is obtained by subtracting the scores on Form B from those on Form A. Thus, positive scores indicated that the caregiver rated the patient as more impaired than the patient's own self-evaluation. Patients were interviewed first. Simultaneously, caregivers, who were blind to the results of these interviews, rated the AQ-D. Finally, the psychiatrist administered the SCID to each patient, with both the patient and the caregiver present. We demonstrated the reliability and validity of the above instruments in Alzheimer's disease.[4,8,14,16,17] Diagnoses of anosognosia were generated based on AQ-D discrepancy scores using the procedure validated in a recent publication.[1]

The Hamilton Depression Rating Scale (HAM-D) is a 17-item interviewer-rated scale that measures psychological and autonomic symptoms of depression.[18]

Follow-Up Examination A follow-up evaluation was carried out on 154 of the 213 patients (72%) between 1 and 4 years after the initial evaluation using the same instruments assessed at baseline. Lack of follow-up was due to death during the follow-up period (n=12, 6%), severe dementia that precluded assessment (n=27, 13%), relocation to another city or inability to be traced (n=9, 4%), or refusal to sit for another evaluation

(n=11, 5%). There were no significant demographic or clinical differences between patients in the follow-up group and those not in the follow-up group on the following factors: age (mean years=71.7 [SD=7.1] compared with mean years=69.6 [SD=7.6], respectively; t=1.87, df=211, p=0.06); education (mean years=12.9 [SD=7.9] compared with mean years=13.0 [SD=6.0], respectively; t=0.14, df=211, p=0.88); and duration of illness (mean years=4.45 [SD=12.3] compared with mean years=6.58 [SD=19.0], respectively; t=0.89, df=211, p=0.37).

Statistical Analysis

Statistical analysis was carried out using means and standard deviations, one-way and repeated measures analysis of variance (ANOVA) and covariance (ANCOVA) followed by Tukey's Honestly Significant Difference. Frequency distributions were calculated using chi-square and Fisher's exact tests. All p values are two-tailed, and the alpha value was set at 0.05.

RESULTS

Frequencies of Anosognosia and Apathy

Fifty-five patients (36%) had no anosognosia at baseline or follow-up, 32 patients (21%) with no anosognosia at baseline developed anosognosia during the follow-up period, 17 patients (11%) with anosognosia at baseline had no anosognosia at follow-up, and 50 patients (32%) had anosognosia at both baseline and follow-up.

Seventy-nine patients (51%) had no apathy at baseline and follow-up, 28 patients (18%) with no apathy at baseline developed apathy during the follow-up period, six patients (4%) with apathy at baseline had no apathy at follow-up, and 41 patients (27%) had apathy at both baseline and follow-up.

Anosognosia as a Predictor of Apathy

This analysis included patients with (n=29) or without (n=48) anosognosia at baseline and follow-up, and no apathy at baseline (i.e., patients with apathy at baseline were excluded from the comparison). There were no significant between-group differences on age, education, gender, duration of illness, and follow-up interval between patients with no anosognosia at baseline and follow-up and patients with anosognosia at both time points (Table 1). Patients with anosognosia had the expected higher scores on the AQ-D compared with patients without anosognosia (t=11.0, df=75, p<0.0001), as well as lower MMSE scores (t=2.60, df=75, p<0.05) and higher Apathy Scale scores (t=2.57, df=75, p<0.05) (Table 1).

A two-way ANCOVA was calculated with presence of anosognosia as the grouping variable, Apathy Scale scores as the repeated measure, and baseline MMSE as the covariate. There was a significant group effect (F=19.1, df=1, 74, p<0.0001): patients with anosogno-

TABLE 1. Demographic and Clinical Findings for Alzheimer's Disease Patients With or Without Anosognosia at Baseline and Follow-Up

	No Anosognosia (n=48)		Anosognosia (n=29)	
Item	**n**	**%**	**n**	**%**
Female	29	60	19	66
Antidepressants	4	8	1	3
Anxiolytics	7	15	3	10
Cholinesterase inhibitors	4	8	2	7
Major depression	6	13	6	21
Minor depression	12	25	5	17
No depression	30	62	18	62
	Mean	**SD**	**Mean**	**SD**
Age (years)	71.5	7.6	71.4	5.8
Education (years)	13.4	6.1	13.2	6.5
Mini-Mental State Exam score	23.7	4.1	20.9	5.5
Hamilton Rating Scale for Depression score	7.5	5.5	9.5	5.5
Interval (baseline to follow-up, months)	17.2	7.3	19.7	9.3
Apathy Scale score (baseline)	11.3	6.5	15.6	7.9
Apathy Scale score (follow-up)	13.8	6.9	24.0	8.3
Anosognosia score (baseline)	1.8	8.9	28.6	12.2
Anosognosia score (follow-up)	1.6	9.4	34.0	15.6

Patients with apathy at baseline were excluded from comparison.

sia had significantly higher Apathy Scale scores than patients without anosognosia. The time effect was significant ($F=36.2$, $df=1, 75$, $p<0.0001$): there was an increase on apathy scores over time. Finally, there was a significant group × time interaction ($F=10.6$, $df=1, 75$, $p=0.001$): patients with anosognosia showed a significantly higher increase on Apathy Scale scores over time than patients without anosognosia (Table 1). When HAM-D scores were entered as an additional covariate, the group × time interaction remained statistically significant ($F=6.52$, $df=1, 75$, $p=0.01$).

Apathy as a Predictor of Anosognosia

This analysis included patients with (n=16) or without (n=59) apathy at baseline and follow-up, and no anosognosia at baseline. There were no significant between-group differences on age, education, gender, duration of illness, MMSE scores, AQ-D scores at baseline and follow-up, or interval between patients with no apathy at baseline and follow-up or apathy at both time points (Table 2). Patients with apathy at baseline had the expected higher scores on the Apathy Scale relative to patients without apathy ($t=8.52$, $df=73$, $p<0.0001$) (Table 2). While there was no significant group × time interaction for apathy scores ($F=2.37$, $df=1, 72$, $p=0.12$), lack of significance may be related to a ceiling effect for apathy scores for the apathy group.

A two-way ANCOVA was calculated with presence of apathy as the grouping variable, AQ-D scores as the repeated measure, and baseline MMSE scores as the covariate. There was no significant group effect ($F=3.36$, $df=1, 72$, $p=0.070$): patients with or without apathy had overall similar AQ-D scores. The time effect was significant ($F=15.5$, $df=1, 73$, $p=0.0001$): there was an increase on AQ-D scores over time. Finally, there was no significant group × time interaction ($F=2.78$, $df=1, 73$, $p=0.10$): patients with or without apathy showed a similar increase on AQ-D scores over time (Table 2).

DISCUSSION

To our knowledge, this is the first study to examine the association between apathy and anosognosia among patients with Alzheimer's disease in the context of a longitudinal study. The main finding was that anosognosia at baseline was a significant predictor of more severe apathy at follow-up. Additional relevant findings were that the severity of both anosognosia and apathy significantly increased over time, suggesting that these phenomena are robust psychological and behavioral constructs in Alzheimer's disease, and that remission is rare.

Before further comments, several limitations of our study should be pointed out. First, 24% of our baseline sample did not have a follow-up. However, there were no significant differences between patients with or without a follow-up on the main demographic variables. Second, the follow-up assessment ranged from 1

TABLE 2. Demographic and Clinical Findings for Alzheimer's Disease Patients With or Without Apathy at Baseline and Follow-Up

	No Apathy (n=59)		Apathy (n=16)	
Item	**n**	**%**	**n**	**%**
Female	39	66	11	69
Antidepressants	5	8	2	12
Anxiolytics	10	17	0	
Cholinesterase inhibitors	5	8	2	12
Major depression	9	15	3	19
Minor depression	13	22	7	43
No depression	37	63	6	38
	Mean	**SD**	**Mean**	**SD**
Age (years)	71.1	7.2	73.0	7.7
Education (years)	13.1	6.2	11.6	5.9
Mini-Mental State Exam score	22.8	4.8	20.5	5.6
Hamilton Rating Scale for Depression score	7.3	5.4	9.0	4.6
Interval (baseline to follow-up, months)	18.3	8.5	16.5	4.7
Apathy Scale score (baseline)	12.4	6.4	26.9	3.8
Apathy Scale score (follow-up)	13.7	5.8	26.7	5.9
Anosognosia score (baseline)	1.5	9.9	3.5	13.8
Anosognosia score (follow-up)	7.1	13.4	17.3	21.6

Patients with anosognosia at baseline were excluded from comparison.

to 4 years after baseline, but there were no between-group differences on the mean duration of follow-up. Third, a small group of patients (11% of the sample) had anosognosia at baseline but no anosognosia at follow-up, and this interesting phenomenon of improved awareness in dementia will require further studies in larger samples. This finding could be related to patients being repeatedly confronted with their functional limitations in the context of preserved self-knowledge learning abilities. Finally, an important question is whether patients with anosognosia throughout follow-up had more severe apathy at follow-up than patients who developed anosognosia during the follow-up. We only had eight patients who developed anosognosia during the follow-up period and had no apathy at baseline, and future studies with larger samples should examine this interesting issue.

Anosognosia is a clinically relevant phenomenon in Alzheimer's disease. In a recent study, we found that anosognosia is already present in about one-third of patients with mild dementia and is associated with memory and language deficits.[1] Apathy is among the most frequent relevant behavioral changes in Alzheimer's disease, and we have recently demonstrated that it predicts more severe depression, a faster cognitive and functional decline, and more severe parkinsonism.[5,7]

Cross-sectional studies reported a significant association between anosognosia and apathy in Alzheimer's disease.[14] Our present study examined the direction of this association, and the main finding was that patients with anosognosia had a significantly greater increment on apathy scores over time relative to patients without anosognosia. The question now arises as to the mechanism of this association. One possibility is that patients with depression may have an increased rating for developing apathy, but we demonstrated recently that depression at baseline does not predict apathy at follow-up.[5]

Anosognosia and apathy are both related to frontal lobe dysfunction. Recent studies showed a significant association between apathy in Alzheimer's disease and metabolic and pathological changes in specific regions of the frontal lobes. We found a significant association between apathy and the volume of frontal white matter hyperintensities in Alzheimer's disease patients assessed with MRI volumetry.[19] Marshall et al.[20] found that apathy scores (as measured with the Neuropsychiatric Inventory) were significantly correlated with neurofibrillary tangle counts in the anterior cingulate. Using structural MRI, the same group reported a significant positive correlation between apathy severity and gray matter atrophy in the bilateral anterior cingulate and the left medial frontal cortex.[21] Using fluorodeoxyglucose positron emission tomography (FDG-PET), Marshall et al.[22] reported that Alzheimer's disease patients with apathy had significantly more severe hypometabolism in the bilateral anterior cingulate region than subjects without apathy. Finally, an MRI volumetric study[23] confirmed the association between apathy and more severe bilateral gray matter atrophy in the anterior cingulate, orbitofrontal cortex, and frontal dorsolateral cortex. The involvement of the anterior cingulate in most of the above studies is of interest, since this structure has been consistently related to the initiation of motivated goal-orientated behaviors.[24]

Similarly, anosognosia in Alzheimer's disease has also been related to frontal lobe dysfunction. In an early study using single photon emission CT that included 12 Alzheimer's disease patients with anosognosia and 12 patients without anosognosia matched for age, duration of illness, and cognitive impairment, we found that patients with anosognosia had significant perfusion deficits in the right frontal lobe relative to the comparison group.[25] More recent FDG-PET studies showed significant correlations between increased anosognosia scores and lower metabolism in bilateral dorsolateral frontal temporo-parietal, left inferior frontal, and orbitofrontal regions.[26]

To summarize, there is strong evidence that both anosognosia and apathy are related to dysfunction in specific frontal regions. The present finding that anosognosia predicts more severe apathy suggests an asynchrony in frontal lobe involvement in Alzheimer's disease: whereas anosognosia may arise as an early response to frontal lobe damage, apathy may develop with further frontal involvement.

An alternative explanation for the present findings is that patients with anosognosia may have a poorer adaptation response to their functional limitations than patients without anosognosia. More specifically, when Alzheimer's disease patients with good awareness are faced with severe limitations performing some of their usual interests and chores due to the increasing cognitive impairment, they may look for and engage in activities that are compatible with their current functional capacities. On the other hand, patients with anosognosia may fail to search for alter-

native activities due to their inability to recognize their increasing functional limitations. Patients with anosognosia may become frustrated (which may account for the increased irritability often reported in this group[27]) and may eventually lose motivation for most activities.

In conclusion, our study demonstrated that both anosognosia and apathy in Alzheimer's disease increased significantly in severity after a mean period of 18 months. We also demonstrated that anosognosia is a significant predictor of apathy in Alzheimer's disease. Future studies should examine whether this clinically relevant association is related to regional variances in the progression of Alzheimer's disease neuropathology and/or to behavioral changes and adjustment difficulties produced by loss of awareness.

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