

Course and Determinants of Anosognosia in Alzheimer's Disease: A 12-Month Follow-up

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Abstract. Anosognosia in Alzheimer's disease (AD) has been associated with greater cognitive impairment and more behavioural and psychological symptoms of dementia (BPSD). This study examines the incidence, persistence, and remission rates of anosognosia over a 12-month period, as well as the related risk factors. This was an observational 12-month prospective study. The longitudinal sample comprised 177 patients with mild or moderate AD, and their respective caregivers. Anosognosia was assessed using the Anosognosia Questionnaire in Dementia, and we also evaluated cognitive status (Mini-Mental State Examination), functional disability (Disability Assessment in Dementia), and the presence of BPSD (Neuropsychiatric Inventory). Multinomial logistic regression was used to determine the variables associated with the incidence, persistence and remission of anosognosia. The prevalence of anosognosia was 39.5% (95% CI = 32.1–47.1) at baseline. At 12 months, incidence was 38.3% (95% CI = 28.6–48.0), persistence was 80.0% (95% CI = 69.9–90.1) and remission was 20.0% (95% CI = 9.9–30.1). The regression model identified lower age, more education, and the presence of delusions as variables associated with incidence, and more education, lower instrumental DAD score, and disinhibition as variables associated with persistence. No variables were associated with remission ($n = 14$). The presence of anosognosia in AD patients is high. Education and certain neuropsychiatric symptoms may explain a greater and earlier incidence of anosognosia. However, anosognosia also increases with greater cognitive impairment and disease severity.

Keywords: Alzheimer's disease, anosognosia, caregivers, epidemiological dementia study, incidence, insight, dementia, longitudinal studies, neuropsychiatric disorders

INTRODUCTION

The lack of insight regarding one's deficits is commonly referred to as anosognosia, which is defined as a disordered awareness of illness and of its severity and repercussions [1, 2]. Certain diseases are typically associated with the denial or minimization

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of the deficits associated with them. For example, denial of delusions is common among patients with schizophrenia who have mild cognitive impairment. A similar phenomenon may be observed in some neurological disorders. For instance, patients with hemiplegia following a stroke may deny their inability to move the contralateral extremity, while those with frontotemporal dementia often deny their cognitive impairment, executive dysfunction, and the need for help and supervision [3–6].

Anosognosia is also common in Alzheimer's disease (AD) and is directly linked to cognitive impairment; consequently, in the later stages of the disease it becomes indistinguishable from the consequences of impaired cognition [1, 7]. Anosognosic patients with AD also underestimate their limitations in activities of daily living (ADL), tend not to adopt compensatory strategies, describe themselves as they were before the disease onset, and are more likely to adopt dangerous behaviours [8–10]. In fact, anosognosia in AD is described as a lack of awareness of impairments in ADL or of neuropsychological deficits, and it has been associated with the presence of other behavioural and psychological symptoms of dementia (BPSD) such as apathy, disinhibition, agitation, irritability, or delusions [11, 12]. Various studies have also reported an inverse correlation between anosognosia and depression in dementia, although some authors have only found this relationship in cases of mild depression or dysthymia, while others describe a stronger association with the apathy component of depression [13, 14].

Although anosognosia is associated with cognitive impairment, it may also be present in the early stages of the disease (between 25.7% and 38.5% of patients with mild dementia present with anosognosia), where it has worse repercussions for both patients and caregivers [7, 15–17]. Currently, however, there is no biological marker or gold standard for detecting anosognosia, and several instruments have been developed [11, 18, 19]. Furthermore, in the context of AD, anosognosia has been defined in a variety of ways, not merely in relation to a lack of awareness of memory impairment but also of behavioural and functional deficits [18]. In AD, the reported prevalence of anosognosia ranges between 3.5% [19] and more than 50% of cases [20]. The heterogeneity in the severity of AD patients and the instrument used to assess anosognosia are two of the main factors contributing to this variability [1].

There are numerous issues still to be addressed by research on anosognosia, including the neuropatho-

logical pathways that underlie the phenomenon, the implications that amnesic syndrome has in implicit anosognosia, or the impact of executive dysfunction on the capacity for self-appraisal [21–23]. However, in all patients, whether they suffer from stroke, schizophrenia, or dementia, the consequences of anosognosia are similar, namely poor treatment adherence or denial of the need for treatment, and increased risk of dangerous behaviours. Importantly, anosognosia also impacts on quality of life and implies greater burden on caregivers [17, 19]. Furthermore, the tendency to underestimate symptoms or to ascribe them to mere aging often delays the request for a medical consultation or the provision of well-timed interventions [10].

In the context of research on anosognosia in AD, there are, to the best of our knowledge, no longitudinal studies that provide data regarding its incidence and course. Consequently, the aim of the present study was to identify the factors associated with the course of anosognosia over a 12-month period in patients with mild and mild-to-moderate AD.

METHODS

Design and study population

This 12-month prospective observational and analytic study included a convenience sample of outpatients seen at one of two memory clinics in Catalonia (Santa Caterina Hospital in Girona, or Bellvitge University Hospital in Barcelona). They were all diagnosed with AD according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria [24], scored between 10 and 28 on the Mini-Mental State Exam (MMSE) [25] and their severity was classified as mild or moderate severity according to the Global Deterioration Scale (GDS) [26]. The inclusion criteria included having a main caregiver, defined as the person who was continuously responsible for helping the patient with ADL. In order to exclude the presence of anosognosia due to other medical conditions, the following exclusion criteria were applied: psychosis, history of neurological disorder, vascular or traumatic events, and alcohol or substance dependency or abuse. Patients were also excluded if they had severe communication problems that prevented them from responding adequately to the assessment measures. The study was approved by the hospital's Clinical Research Ethics Committee.

Procedure

Neurologists from the memory clinics identified eligible patients according to the inclusion and exclusion criteria and then determined their cognitive function and GDS stage of dementia [26]. Of the total number of patients who met the inclusion criteria, only four families declined to participate. Recruitment took place between January and October 2011. The assessment protocol lasted 90 min and was administered by trained psychologists and neurologists, both at baseline and at 12 months. Prior to the initial assessment interview, the aims of the study were explained to patients and caregivers, and informed consent was obtained from all participants.

Instruments

Sociodemographic data (age, gender, education, marital status, and place of residence) for both patients and caregivers were collected by means of a standardized questionnaire. The other aspects assessed were as follows:

Anosognosia

This was assessed by the Anosognosia Questionnaire—Dementia (AQ-D), an instrument comprising 30 items, each with four possible response options (never, sometimes, often, always). The AQ-D has two forms, one for the patient and one for the caregiver. The total score is obtained by subtracting the scores on the patient's form from those on the caregiver's form, and ranges between 0 and 90. A discrepancy of more than 32 points (≥ 1 standard deviation) indicates the presence of anosognosia [27]. The AQ-D has high internal consistency (Cronbach's $\alpha = 0.91$) and good inter-examiner reliability (ICC = 0.90). Its factor structure comprises two factors, a cognitive-functional factor and a behavioural factor, which explain 38.9% of the total variance [12].

Cognitive function

Cognitive impairment was assessed with the MMSE. Scores on the MMSE range from 0 to 30, with a lower score indicating greater cognitive impairment [25].

Functional status

Specific functional disability was measured using the Disability Assessment in Dementia (DAD). This instrument is administered to caregivers and comprises 40 dichotomous (yes/no) questions that assess

the ability of the patient to execute 17 basic activities of daily living (BADL) and 23 instrumental activities of daily living (IADL) [28].

Behavioural and psychological symptoms of dementia

The Neuropsychiatric Inventory (NPI) is a validated method for assessing the presence of BPSD. It consists of 12 subscales that assess the frequency and severity of delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, night-time behavioural disturbances, and appetite and eating abnormalities. The score is the product of the frequency (range = 1–4) and the severity (range = 1–3) of symptoms, and the total score ranges from 0 to 144 points [29, 30].

Caregiver burden

Perceived burden was assessed using the Zarit Burden Interview (ZBI). This is a self-administered test that consists of 22 Likert-type items. Responses reflect the caregiver's perceptions and feelings, and the total score ranges from 22 to 110 points. Higher scores indicate greater perceived burden [31].

Severity of dementia

The severity of AD was measured by the GDS, which ranges from 1 (no cognitive decline) to 7 (severe cognitive decline). A GDS stage 4 corresponds to cases with mild dementia, GDS 5 and GDS 6 to cases with moderate dementia [26].

Statistical analysis

A descriptive analysis of the clinical and sociodemographic characteristics of the sample was carried out, using absolute and relative frequencies for qualitative variables and measures of central tendency and dispersion for quantitative variables. The prevalence of anosognosia was established using the relative frequency of each AQ-D group. Changes in anosognosia status groups were determined according to the presence/absence of anosognosia at baseline and at follow-up. Specifically, patients without anosognosia at baseline and presence at 12 months were considered incident cases, those with anosognosia at baseline but an AQ-D score below 32 at 12 months were considered a remission group, patients with anosognosia at both baseline and 12 months were considered persistent cases, and those without anosognosia throughout the study period were

classified as non-anosognosic patients. The incidence of anosognosia was established using the relative frequency of cases with incident anosognosia at 12-month follow-up. Persistence and remission of anosognosia were established using the AQ-D scores at baseline and at 12-month follow-up. Only cases with both baseline and 12-month follow-up data were considered in the analysis.

Clinical and sociodemographic differences in relation to the presence, incidence, persistence, or remission of anosognosia were analysed by means of parametric and non-parametric tests, in accordance with criteria of normality. When there was a significant difference between two measures, Cohen's (*d*) was calculated to determine the effect size.

A multinomial logistic regression model was then applied to identify the variables that could predict the incidence, persistence and remission of anosognosia after 12 months, using sociodemographic and clinical characteristics as covariables.

Results were expressed as absolute numbers, percentages, means, standard deviations, and 95% confidence intervals (CIs). The level of statistical significance was set at 0.05 to test hypotheses. All data processing and analysis was performed using SPSS v17.0 for Windows.

RESULTS

The baseline sample consisted of 243 patients, of whom 177 (72.8%) were re-assessed at 12 months. The reasons for drop-out were increased dementia severity or comorbidities (42.4%), caregiver-related problems (e.g., not present at patient's main residence, work commitments; 16.7%), death of patient (9.1%), and other causes (31.8%). The mean age at baseline of cases which completed the follow-up was 77.8 years (*SD* = 6.5); of these, 66.1% were women and 85.3% lived in their own home. At baseline, 62.7% of patients (*n* = 111) were diagnosed with mild dementia (GDS 4). Regarding caregivers, 46.9% were the spouse and 48.6% a son or daughter of the patient. The mean age of caregivers was 61.9 years (*SD* = 13.2), and the majority (67.2%) were women.

Anosognosia scores

The mean score on the AQ-D at baseline was 26.7 (*SD* = 18.3), rising to 32.4 (*SD* = 18.7) at 12 months ($\chi^2 = 19.6$; *df* = 1; *p* = 0.023). In terms of the severity of dementia, 27.0% of mild cases (GDS 4) presented anosognosia at baseline (95% CI 18.3–35.7), as com-

pared with 55.2% (95% CI 41.5–58.8) of patients with moderate dementia. Table 1 shows baseline clinical and sociodemographic characteristics of patients and caregivers according to the presence or absence of anosognosia.

There were differences between patients' and caregivers' AQ-D scores, and the change in these scores over time also differed. Specifically, while patient perceptions had not changed at 12 months (24.9 at baseline versus 25.5 at 12 months; *Z* = -0.649; *p* = 0.516), caregiver scores increased from 51.6 to 58.0 (*Z* = -6.5; *p* < 0.001).

Course of anosognosia over 12 months

The cumulative incidence rate at 12 months was 38.3% (95% CI = 28.6–48.0), the remission rate was 20.0% (95% CI = 9.9–30.1%) and the persistence rate over 12 months was 80.0% (95% CI = 69.9–90.1). The incidence among moderate and mild cases was 42.3% and 37.0%, respectively.

Differences in clinical measures were observed between baseline and the 12-month follow-up. The mean score on the MMSE fell by 1.6 points (*SD* = 3.6; *z* = -5.4; *p* < 0.001), while the mean DAD score was 3.4 points lower at 12 months (*SD* = 9.5; *z* = -6.0; *p* < 0.001). Although the overall score on the NPI did not change significantly during the follow-up period (*z* = 1.2; *p* = 0.208), a significant difference was observed on three of its subscales: delusions (*z* = -2.8; *p* = 0.006), apathy (*z* = -2.3; *p* = 0.017), and appetite and eating abnormalities (*z* = -3.4; *p* = 0.001). Table 2 shows the baseline characteristics of patients and caregivers according to the classification of cases at 12 months. In terms of sociodemographic characteristics, incident cases were significantly younger than patients with no anosognosia (Cohen's *d* = 0.48). Comparison of the clinical characteristics of the change in anosognosia status groups (i.e., incidence, persistence and remission) revealed no significant differences in their baseline MMSE score (Kruskal-Wallis = 1.8; *df* = 2; *p* = 0.402). However, a trend was observed across these three groups for functional disability (DAD) and the presence of BPSD (NPI), with greater functional deterioration being observed for activities of daily living, both BADL (Kruskal-Wallis = 18.8; *df* = 2; *p* < 0.001) and IADL (Kruskal-Wallis = 21.5; *df* = 2; *p* < 0.001). The comparative data recorded at baseline and at 12 month follow-up, stratified according to incidence, persistence and remission, are presented in Supplementary Table 1.

Table 1

Comparison of patient and caregiver clinical and sociodemographic characteristics according to the presence or absence of anosognosia at baseline

| | No Anosognosia n = 107 (60.5%) | Anosognosia n = 70 (39.5%) | p | d |
|-------------------------------------|-----------------------------------|-------------------------------|--------|------|
| Age of patient, mean (SD) | 76.8 (6.7) | 79.3 (6.0) | 0.016 | 0.39 |
| Gender of patient (female), n (%) | 76 (71.0) | 41 (58.6) | 0.087 | — |
| Education, n (%) | | | 0.858 | — |
| Low | 32 (29.9) | 22 (31.4) | | |
| Elementary | 65 (60.7) | 40 (57.1) | | |
| High | 10 (9.3) | 8 (11.4) | | |
| GDS, n (%) | | | <0.001 | 0.70 |
| 4 | 81 (73.0) | 30 (27.0) | | |
| 5-6 | 26 (39.4) | 40 (60.6) | | |
| MMSE, mean (SD) | 19.4 (4.3) | 18.4 (5.1) | 0.245 | — |
| NPI, n (%) | 13.1 (11.3) | 28.1 (20.4) | <0.001 | 0.91 |
| Delusions | 0.6 (2.2) | 1.1 (2.4) | 0.139 | — |
| Hallucinations | 0.2 (1.2) | 0.6 (2.0) | 0.056 | — |
| Agitation | 1.1 (2.6) | 2.4 (3.2) | 0.001 | 0.45 |
| Depression | 1.8 (2.5) | 2.4 (3.2) | 0.214 | — |
| Anxiety | 1.4 (2.4) | 1.8 (3.2) | 0.790 | — |
| Euphoria | 0.2 (0.9) | 0.8 (2.2) | <0.001 | 0.36 |
| Apathy | 3.0 (3.8) | 5.7 (4.1) | <0.001 | 0.68 |
| Disinhibition | 0.3 (0.9) | 1.8 (3.1) | <0.001 | 0.66 |
| Irritability | 2.0 (3.1) | 3.9 (3.8) | <0.001 | 0.55 |
| Aberrant motor disorders | 0.5 (1.7) | 2.9 (4.1) | <0.001 | 0.76 |
| Sleep disorders | 0.5 (1.7) | 1.3 (3.1) | 0.055 | — |
| Appetite/Eating | 1.3 (2.7) | 3.3 (3.9) | <0.001 | 0.60 |
| DAD, mean (SD) | 64.3 (9.4) | 57.0 (8.7) | <0.001 | 0.81 |
| Age of caregiver, mean (SD) | 60.3 (13.4) | 64.4 (12.7) | 0.054 | — |
| Gender of caregiver (female), n (%) | 66 (61.7) | 53 (75.7) | 0.052 | — |
| ZBI, n (%) | 34.0 (16.0%) | 47.7 (16.7%) | <0.001 | 0.83 |

GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment in Dementia; ZBI, Zarit Burden Interview.

Risk factors associated with the course of anosognosia

A binary multinomial logistic regression model was fitted in order to determine the variables associated with incidence, persistence, or remission of anosognosia after 12 months, using absence of anosognosia as the reference group. The results are shown in Table 3, and the model has high goodness-of-fit (Cox & Snell = 0.419; Nagelkerke = 0.524) and a good likelihood ratio ($\chi^2 = 119.2$; $df = 15$; $p < 0.001$). Age, education and delusions were found to be predictor variables for incident anosognosia, while education, DAD instrumental score, and disinhibition were associated with the persistence of anosognosia.

DISCUSSION

The main aims of this study were to determine cumulative incidence, persistence, and remission rates of anosognosia at 12 months, and to identify

variables that could predict the course of anosognosia at baseline.

Although a few studies offer longitudinal data on the course of anosognosia, their primary aim was not to study the epidemiology of anosognosia. The lack of a gold standard for defining and detecting anosognosia has led to several different instruments being developed to assess it [17, 32, 33], and this makes it difficult to compare our results with previous studies. Starkstein et al. also used the AQ-D in a longitudinal study and reported an accumulated incidence rate much lower than ours (21% versus 38%) [34]. Our higher incidence may be due to the fact that our sample contains more patients with moderate-severe and severe dementia, while the sample of Starkstein et al. included a higher proportion of patients with mild dementia, and even patients with mild cognitive impairment. Furthermore, in our study we analysed probable AD patients, whereas other studies included mixed dementia patients in the analysis and obtained certain differences in their results [35].

Incident cases were younger and had a higher education level than did those cases that remained

Table 2

Clinical and sociodemographic characteristics of patients and caregivers at baseline, stratified according to the classification of cases at 12 months

| | Baseline scores | | | |
|-------------------------------------|----------------------------------|-----------------------------|-------------------------------|----------------------------|
| | No anosognosia n = 66 (37.3%) | Incidence n = 41 (23.2%) | Persistence n = 56 (31.6%) | Remission n = 14 (7.9%) |
| Age of patient*, mean (SD) | 78.0 (5.9) ^a | 74.8 (7.4) ^d | 79.6 (6.0) | 78.1 (5.8) |
| Gender of patient (female), n (%) | 51 (77.3) | 25 (61.0) | 33 (58.9) | 8 (57.1) |
| Education, n (%) | | | | |
| Low | 25 (37.9) | 7 (17.1) | 16 (28.6) | 6 (42.9) |
| Elementary | 37 (56.1) | 28 (68.3) | 34 (60.7) | 6 (42.9) |
| High | 4 (6.1) | 6 (14.6) | 6 (10.7) | 2 (14.3) |
| GDS, n (%) | | | | |
| 4 | 51 (77.3) | 30 (73.2) | 22 (39.3) | 8 (57.1) |
| 5-6 | 15 (22.7) | 11 (26.8) | 34 (60.7) | 6 (42.9) |
| MMSE, mean (SD) | 19.5 (4.3) | 19.2 (4.4) | 18.6 (5.3) | 17.4 (4.1) |
| NPI*, mean (SD) | 12.9 (12.7) ^b | 13.3 (8.7) ^d | 30.4 (21.4) | 18.9 (12.4) ^f |
| Delusions* | 0.3 (1.5) ^b | 1.2 (2.9) | 1.4 (2.6) | 0.1 (0.3) |
| Hallucinations | 0.2 (1.1) ^b | 0.3 (1.3) | 0.8 (2.2) | 0.1 (0.3) |
| Agitation* | 1.0 (2.5) ^b | 1.4 (2.5) | 2.6 (3.5) | 1.5 (2.4) |
| Depression | 1.9 (2.5) | 1.5 (2.4) | 2.4 (3.2) | 2.4 (3.0) |
| Anxiety | 1.7 (2.7) | 1.0 (1.8) | 2.1 (3.5) | 0.8 (1.3) |
| Euphoria* | 0.1 (0.7) ^b | 0.2 (1.3) | 1.0 (2.4) | 0 (0.0) ^f |
| Apathy* | 3.0 (3.9) ^{b,c} | 3.1 (3.6) ^d | 5.7 (4.2) ^e | 5.4 (3.4) |
| Disinhibition* | 0.3 (1.0) ^b | 0.3 (0.9) ^d | 2.1 (3.0) | 0.9 (3.2) ^f |
| Irritability* | 2.0 (3.3) ^b | 2.1 (2.6) ^d | 4.2 (4.0) | 2.6 (2.7) |
| Aberrant motor disorders* | 0.5 (1.8) ^b | 0.6 (1.6) ^d | 3.1 (4.2) | 1.9 (3.3) |
| Sleep disorders | 0.8 (2.1) | 0.2 (0.7) ^d | 1.5 (3.2) | 0.8 (2.2) |
| Appetite/Eating* | 1.2 (2.5) ^b | 1.5 (2.8) ^d | 3.5 (4.1) ^e | 2.6 (3.3) |
| DAD*, mean (SD) | 65.1 (9.4) ^b | 63.0 (9.3) | 56.1 (8.6) | 60.5 (7.8) |
| Age of caregiver*, mean (SD) | 59.3 (13.4) ^c | 61.9 (13.2) | 63.4 (13.2) | 68.3 (10.4) |
| Gender of caregiver (female), n (%) | 39 (59.1) ^a | 27 (65.9) | 43 (76.8) | 10 (71.4) |
| ZBI, mean (SD) | 32.3 (17.0) ^b | 36.8 (14.1) ^d | 50.0 (16.5) | 38.8 (15.1) |

*Kruskal-Wallis test $p < 0.05$; ^aMann-Whitney U test (no anosognosia versus incidence) $p < 0.05$; ^bMann-Whitney U test (no anosognosia versus persistence) $p < 0.05$; ^cMann-Whitney U test (no anosognosia versus remission) $p < 0.05$; ^dMann-Whitney U test (incidence versus persistence) $p < 0.05$; ^eMann-Whitney U test (incidence versus remission) $p < 0.05$; ^fMann-Whitney U test (persistence versus remission) $p < 0.05$. GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment in Dementia; ZBI, Zarit Burden Interview.

without anosognosia at 12 months. In addition, incident cases presented not only a more pronounced decrease in both cognitive and functional performance than did the other cases, but also an increase in the frequency and severity of BPSD (mainly delusions). This rapid evolution is characteristic of patients with higher cognitive reserve [36]. Although cognitive reserve is usually related with less anosognosia [37, 38], our focus here was on the course of anosognosia, not simply its presence or absence at baseline. This means that cases with greater cognitive reserve did not present anosognosia at baseline, even though their pathophysiology could be representative of the persistent group. It should also be noted that incident cases may have an early alteration of the frontal lobe. A sharp decline in cognitive and functional performance has previously been described in patients with a high education level and increased cognitive reserve [39]. In addition, an increased fre-

quency and severity of delusions in young patients would fit with a frontal pattern, and neuroimaging studies have already associated anosognosia with a hypoperfusion of the orbitomedial prefrontal cortex [40–42], which occurs in cases with frontotemporal dementia (FTD) too. FTD is usually seen in younger patients, and anosognosia is one of the clinical criteria for diagnosis [40].

Severity of dementia is the main determinant of anosognosia [23], and it was also the factor that best discriminated between persistent and non-anosognosia cases in our study. Persistent cases, which accounted for 80% of cases with anosognosia at baseline, showed increased disability in IADL and more frequent and severe BPSD, notably disinhibition and apathy. Anosognosia and apathy have been reported by many studies to show a strong inter-relationship [12, 19, 34], and Starkstein et al. concluded that anosognosia is a significant predictor

Table 3
Forward multinomial logistic regression model for anosognosia status at 12 months

| Incidence | B | OR | <i>p</i> | 95% CI | |
|-------------------|--------|-------|----------------|--------|--------|
| Age of patient | -0.098 | 0.907 | 0.006 | 0.846 | 0.972 |
| Education | 1.184 | 3.267 | 0.003 | 1.508 | 7.076 |
| DAD-instrumental | -0.072 | 0.931 | 0.114 | 0.851 | 1.017 |
| BI | 0.024 | 1.024 | 0.130 | 0.993 | 1.055 |
| NPI disinhibition | -0.167 | 0.846 | 0.454 | 0.546 | 1.310 |
| NPI delusions | 0.361 | 1.435 | 0.015 | 1.071 | 1.923 |
| Persistence | | | | | |
| Age of patient | -0.17 | 0.983 | 0.669 | 0.909 | 1.063 |
| Education | 1.425 | 4.158 | 0.002 | 1.684 | 10.266 |
| DAD-instrumental | -0.290 | 0.749 | < 0.001 | 0.671 | 0.835 |
| BI | 0.084 | 1.084 | < 0.001 | 1.050 | 1.127 |
| NPI disinhibition | 0.344 | 1.410 | 0.015 | 1.070 | 1.859 |
| NPI delusions | 0.213 | 1.237 | 0.143 | 0.930 | 1.645 |
| Remission | | | | | |
| Age of patient | -0.018 | 0.983 | 0.733 | 0.888 | 1.087 |
| Education | 0.434 | 1.543 | 0.443 | 0.510 | 4.670 |
| DAD-instrumental | -0.163 | 0.850 | 0.011 | 0.750 | 0.963 |
| ZBI | 0.042 | 1.043 | 0.043 | 1.001 | 1.087 |
| NPI disinhibition | 0.199 | 1.220 | 0.244 | 0.873 | 1.704 |
| NPI delusions | -0.596 | 0.551 | 0.410 | 0.133 | 2.276 |

B, beta; OR, odds ratio; DAD, Disability Assessment in Dementia; NPI, Neuropsychiatric Inventory; ZBI, Zarit Burden Interview. Reference category, No anosognosia.

of apathy in AD [34]. Here, we observed an increased rating of apathy in both persistent and incident patients, a finding that is consistent with previous results [34]. Some studies have also demonstrated a common pathogenesis between anosognosia and apathy, linking the evolution of both [22, 23, 41, 42]. Likewise, several authors have described an inverse relationship between affective symptoms and anosognosia [13, 14, 19, 20, 43]. Assessing the presence of anosognosia could therefore help in differentiating symptoms of depression and apathy and in predicting apathetic symptoms and greater severity.

Remission of anosognosia was only observed in 14 of our patients. Obviously, this small sample offers low statistical power in terms of reliability, and incorrect baseline classification of these patients cannot be ruled out. It should also be taken into account that if anosognosia increases in line with impairment, the AQ-D may have a floor effect when it comes to detecting anosognosia in patients with moderate or moderate-to-severe dementia. These results are consistent with the hypothesis of the “petrified self” proposed by Mograbi and Morris, who attributed unawareness to the process of memory impairment [44]. In this regard, it should be noted that the mean AQ-D score of our patients remained stable (very low) over the 12-month period, whereas caregiver ratings were more negative at follow-up. A further point to consider is that AQ-D scores are based on

a patient-caregiver discrepancy, and therefore factors associated with caregiver perceptions should also be considered. Other authors have pointed out that instruments based on discrepancies between patients and caregivers may yield biased results, due to the effect of caregiver burden and emotional stress [45]. That said, in a previous study we found that caregiver burden had a minimal effect on the variability of the AQ-D [46].

Anosognosia is a complex problem that is influenced by factors ranging from the mere anatomical to the broader psychological and social spheres. Moreover, the results of the large population-based study conducted by Mograbi and Morris suggested that memory impairments or the resulting self-structure were unlikely to provide a full explanation for unawareness in AD. Consequently, the authors concluded that unawareness was associated with different aspects such as depression, dementia severity, education and socioeconomic level in different cultures [47]. Assessing the course of anosognosia might reveal this specificity across international regions, and thus unawareness should be seen not only as a common neurobiological feature of dementia, one that increases with severity of dementia, but also as a phenomenon influenced by social and cultural factors [48]. In this regard, it would be interesting to develop new instruments that could account for most of this variability.

The main limitations of the present study are those common to all research on anosognosia and relate to the intrinsic limitations of the instrument used to assess anosognosia and the lack of an operational definition of the phenomenon. As we noted earlier, anosognosia may be interpreted in various ways, as affecting cognitive, functional, and/or behavioural aspects of the patient, and this variation is likely to influence the results of its assessment [1, 18, 30]. Other specific limitations related to our study sample should also be taken into account when interpreting the results obtained. The sample comprised patients seen consecutively at our neurology department, whether for the purposes of diagnosis, symptom management, or a routine visit, and all those included were community dwellers. It is possible, therefore, that different results would have been obtained had we included patients living in residential care. It should also be noted that our sample includes moderate patients and eight moderate-to-severe cases, which increased the number of anosognosia patients across the study period. However, the degenerative process may make it impossible to distinguish anosognosia from cognitive impairment, and the AQ-D might not be specific enough with these kinds of patients. The education level of our sample was also low, which has an effect on cognitive reserve and may prevent some comparisons with other studies.

Finally, almost two of every five patients in our sample presented with anosognosia at baseline. Younger age, higher education level, and the presence of delusions were the main predictors for incident anosognosia, while higher education level, worse IADL, and disinhibition were associated with persistence. These data provide a platform for future research, since the presence of anosognosia is a factor to consider in new treatment studies using perceived quality of life and self-related pain as the dependent variable. The number of remitted cases in our study was small and prevents us from drawing firm conclusions, and this is another important issue that requires further research. The importance for clinicians of assessing anosognosia is that it could help to differentiate depressive and apathetic symptoms and to predict greater severity. For instance, anosognosia assessment could help to avoid not only a lack of treatment adherence but also risky behaviours related to driving or financial management [10]. These results are also relevant to the needs of caregivers of patients with AD, since anosognosia is known to be one of the key factors leading to greater burden.

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SUPPLEMENTARY MATERIAL

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