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Prevalence and comorbidity of neuropsychiatric symptoms in Alzheimer's disease

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Introduction. The objective of this study is to describe the frequency and severity of behavioral and psychological symptoms (BPS) in a group of 125 patients diagnosed of Alzheimer's disease (AD) (DSM-IV-TR and NINCDS-ADRDA criteria).

Methods. The evaluation of the BPS was carried out using the Neuropsychiatric Inventory (NPI; Cummings et al., 1994). The sociodemographic and personal background data of the patients were gathered and the dementia stage was established with the Global Deterioration Scale (GDS; Reisberg, 1982).

Results. A total of 122 patients (98%) presented BPS, with an average of five symptoms per patient. Frequency of presentation was the following: apathy (75%), irritability (66%), depression (60%), agitation (55%), anxiety (54%), aberrant motor activity (47%), delirium (38%), sleeping disorders (36%), disinhibition (29%), eating disorders (28%), hallucinations (20%) and euphoria (4%).

Conclusions. These results show the high incidence of BPS in AD patients and point to the necessity and importance of treating these disorders appropriately.

Key words:
Alzheimer's disease. Behavioral and psychological symptoms. Neuropsychiatric Inventory. Prevalence. Comorbidity.

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Prevalencia y comorbilidad de síntomas neuropsiquiátricos en la enfermedad de Alzheimer

Introducción. Se describe la frecuencia y gravedad de los síntomas conductuales y psicológicos (SCP) en un grupo de 125 pacientes diagnosticados con enfermedad de Alzheimer (EA) siguiendo criterios diagnósticos DSM-IV-TR y NINCDS-ADRDA.

Metodología. La evaluación de los SCP se realizó mediante el *Neuropsychiatric Inventory* (NPI; Cummings et al., 1994). Se recogieron los datos sociodemográficos y antecedentes personales de los pacientes y se estableció el estadio de la demencia mediante la *Global Deterioration Scale* (GDS; Reisberg, 1982).

Resultados. Un total de 122 pacientes (98%) presentaron SCP, con una media de cinco síntomas por paciente. La frecuencia de su presentación fue la siguiente: apatía (75%), irritabilidad (66%), depresión (60%), agitación (55%), ansiedad (54%), actividad motora aberrante (47%), delirios (38%), alteraciones del sueño (36%), desinhibición (29%), alteraciones del apetito (28%), alucinaciones (20%) y euforia (4%).

Conclusiones. Estos resultados demuestran la alta incidencia de los SCP en los pacientes con EA y muestran la necesidad e importancia de tratar adecuadamente estas alteraciones.

Palabras clave:
Enfermedad de Alzheimer. Síntomas conductuales y psicológicos. *Neuropsychiatric Inventory*. Prevalencia. Comorbilidad.

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INTRODUCTION

Alzheimer's disease (AD) is the most frequent cause of dementia in developed countries, accounting for 50% to 70% of all of them[1-3]. Its symptoms overlaps normal brain aging manifestations, follow a progressive course and present great heterogeneity that largely depends on the evolutive phase of the subject. The symptoms are manifested in three large settings: cognitive, behavioral and functional.

Although the cognitive and functional symptoms have been those characteristically identified in subjects with dementia, the behavioral and psychological symptoms (BPS) have been taking on increasing importance in recent years. It has been called by different names in the clinical practice in recent years (non-cognitive alterations, neuropsychiatric alterations, behavioral symptoms). However, based on the consensus obtained, the International Psychogeriatric Asso-

ciation recommended calling it Behavioral and Psychological Symptoms[4]. It is interesting to note that international classification systems of the dementia syndrome such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[5] and International Classification of Diseases (ICD-10)[6] still do not give the merited attention to non-cognitive symptoms. This occurs even though about 90% of patients with AD have psychiatric and behavioral complications such as depression, anxiety, hallucination, delusions, aggressivity, agitation, behavioral disinhibition, euphoria, apathy, irritability, aberrant motor alterations or sleep and eating disorders[7-9]. They may be predominant in some phases of the disease in the clinical picture or may even occur prior to the cognitive symptoms, although they generally occur simultaneously in both.

The presence of psychiatric and behavioral manifestations that accompany cognitive deterioration may have a great impact on the patient's quality of life, adding more deterioration to that already existing, in addition to increasing the emotional and behavioral burden of the patient's family members and caregivers. All of this contributes to greater demand by them for home help and, in many cases, precipitates admission of the patients to a geriatric center[10,11]. On the other hand, the importance of the BPS is increasing because most of them are susceptible to being treated effectively, mainly thanks to the use of drug measures and behavior modification techniques[12]. Thus, the description and analysis of psychiatric and behavioral symptoms that accompany AD are of interest.

We have studied the presence of BPS and its relationship with important aspects of AD, such as cognitive and functional status of the patient, severity and time of evolution of the dementia, sociodemographic variables and personal backgrounds of the patients and their relationship with the burden and presence of anxiety and depression in the caregiver in a large group of patients with AD and their principal caregivers. As far as we know, this is the most extensive study conducted in our country. In this article, we have focused our attention in the part of this extensive work that deals with the prevalence and comorbidity of BPS in AD making an analysis with the Neuropsychiatric Inventory (NPI)[13]. This has made it possible to evaluate the most frequent neuropsychiatric manifestations in dementias and also to determine their frequency and intensity.

MATERIAL AND METHODS

Subjects

The present work was conducted on a clinical sample made up of 125 patients diagnosed of AD, following the international diagnostic criteria of DSM-IV-TR5, NINCDS-ADRDA[14] and the recommendations of the Study Group of Neurology of Behavior and Dementias of the Spanish Society of Neurology[15]. These patients were seen in the Dementia Unit of the Instituto Andaluz de Neurociencia y Conducta (IANEC) in Malaga. Written informed consent was obtained from the patients. If they were incapacitated, this was obtained from a legal representative. The evaluation of the patients was conducted by a psychiatrist in every case.

Sociodemographic and clinical variables

The variables evaluated included: age, gender, civil status, years of schooling, personal psychiatric backgrounds, usage of psychodrugs, use of antidementia drugs, stage and time of evolution of the dementia from the initial diagnosis made by the specialist up to the time of evaluation. The presence of personal psychiatric backgrounds was evaluated based on the information provided by the patient or his/her relatives and by the review of the patient's clinical history. Special attention was given to the existence of a previous background of affective disorders, anxiety disorders or psychotic disorders that required psychiatric treatment and fulfilled international diagnostic criteria.

Evaluation instruments

The study of psychiatric and behavioral disorders was made using the NPI[13] in its validated version in Spanish[16]. The NPI consists of a structured interview based on the answers given by the principal caregiver of the patient. It is made up of 12 subscales that evaluate the most commonly occurring behavioral and psychological changes in patients with dementia: delusions, hallucinations, agitation/aggressivity, depression, anxiety, euphoria, apathy/indifference, disinhibition, irritability/emotional lability, aberrant motor activity, sleep disorders and eating disorders. If the disorder was present in each subscale, the caregiver scored it from 1 to 4 according to its frequency and from 1 to 3 in regards to its severity. A combined score for each subscale was obtained by multiplying frequency by severity, with a maximum of 12 points. Total NPI score can be obtained regarding frequency (maximum: 48 points), to the severity (maximum: 36 points) and to the combined one (maximum: 144 points). In addition, it contains a subscale (NPI-D) to measure the grade of suffering caused in the caregiver by each one of the symptoms that the patient in their care has. To do so, the amount of emotional malaise that said symptoms cause in him or her should be graded on a progressive scale of 5 points (maximum of 60 points).

The staging of the dementia was made with the Global Deterioration Scale (GDS)[17] that evaluates the intensity of the dementia over 7 levels that go from GDS 1 (absence of cognitive alteration) to GDS 7 (very severe cognitive defect). The present study only included patients included in GDS 4 stages (moderate cognitive defect), 5 (moderate-severe cognitive defect) and 6 (severe cognitive defect). Three

groups listed as mild dementia (GDS 4), moderate dementia (GDS 5) and severe dementia (GDS 6) were established.

Statistical analysis

For the comparison of means, the Student's *t* test was used in the case of variables with normal distribution and the Mann-Whitney test for those without normal distribution. Pearson's chi square test was used for comparison of proportions. The relationship between the different symptoms evaluated by the NPI was analyzed with Spearman's correlation coefficient. The relationship between evolution time of the dementia and the GDS stage was analyzed with Pearson's correlation coefficient. Significant level of $p<0.05$ was required.

RESULTS

Sociodemographic and clinical data

Table 1 shows the sociodemographic and clinical characteristics of the 125 patients. Mean age of the series was 76 years with a clear predominance of women (70%). Widows stand out among them with 45 cases (51.7%), while those married were more frequent in men with 29 cases (76.3%). According to study level of the patients, 49 (39.2%) had basic education (1-5 years; mean: 4.10 ± 1 years), 65 (52%) middle education (6-11 years; mean: 7.05 ± 1.25 years) and 11 (8.8%) higher education (12-18 years; mean: 12.45 ± 1.81 years).

Women had greater frequency of personal psychiatric background than men (30% versus 13%; $\chi^2 = 3.968$; $p < 0.05$). No significant differences were found between genders in regards to age, evolution time of the dementia, years of schooling, use of antidementia drugs and use of psychodrugs.

Staging of the dementia

The patients were grouped into the stages of the GDS scale 4 (33 patients, 26.4%), 5 (42 patients, 33.6%) and 6 (50 patients, 40%). A positive correlation was found between duration of the dementia and GDS stage ($r = 0.74$; $p < 0.01$). Thus, the series studied is representative of the AD severity spectrum.

Behavioral and psychological symptoms

A total of 122 patients (98%) had BPS. Each patient presented a mean of 5 symptoms (5.1 ± 1.87), with a range of 0-10 symptoms. Table 2 shows the distribution of the frequencies of the different symptoms evaluated by NPI. The most prevalent disorder was apathy, this being present in 74% of the cases. More than 50% of the patients presented irritability 866%), depression (60%), agitation (55%) and anxiety (54%). The least frequent disorders were euphoria (4%) and hallucinations (20%). Table 3 shows the mean combined scores of the sample in the NPI and table 4 shows the mean combined scores in the different subscales of the NPI. The mean score of the NPI-D was 14.28 ± 6.66 points.

Table 5 shows the correlations obtained among the different symptoms evaluated with the NPI. Due to the sample size and the elevated number of correlations obtained, only

Table 1 Sociodemographic and clinical characteristics of the 125 patients

Characteristics of the patients	Value
Age, mean ± SD (range)	76.4 ± 6.15 (57-95)
Women, n (%)	87 (69.6%)
Men, n (%)	38 (30.4%)
Civil status, n (%)	
Single	11 (8.8%)
Married	64 (51.2%)
Widow(ers)	50 (40%)
Months of evolution, mean ± SD (range)	62.21 ± 26.16 (18-120)
Years of schooling, mean ± SD (range)	6.34 ± 2.7 (1-13)
Psychiatric backgrounds, n (%)	31 (24.8%)
Use of psychodrugs, n (%)	48 (38.4%)
Use of anti-dementia drugs	88 (70.4)

SD: standard deviation.

Table 2 Number of patients who had BPD (n) and frequency of occurrence expressed in percentage (%)

	n	%*
Apathy	92	74
Irritability	82	66
Depression	75	60
Agitation	69	55
Anxiety	67	54
Aberrant motor activity	59	47
Delusions	47	38
Sleep disorders	45	36
Disinhibition	37	30
Appetite disorders	35	28
Hallucinations	25	20
Euphoria	5	4

*The sum of the percentages is greater than 100% since all the patients had several BPS.

Table 3 Mean total scores of the NPI

	Mean (SD) range
Frequency (0-48)	13.46 (6.05; 0-26)
Severity (0-36)	9.86 (4.56; 0-21)
Combined (0-144)	27.9 (16.22; 0-66)

NPI: Neuropsychiatric Inventory. SD: standard deviation.

those findings significant at the level of $p<0.01$ were considered to be of interest.

DISCUSSION

A total of 98% of the patients manifested some type of BPS. Only three patients (2%) with mild dementias did not present any BPS. Most of the works published in this regards[9,18-22] describe results that coincide with ours, with values between 90% and 100% of those affected. All of this confirms the high prevalence of the BPS in AD documented both in cross-sectional studies and in longitudinal ones[23-25].

In our study, the elevated number of BPS present in each patient, with a mean of five symptoms and a number between 0 and 10 different behaviors examined stands out. Other studies find values that are similar to ours, with a mean of 6 symptoms per patient and a number of 2 to 20 different alterations[21]; a mean of four symptoms per patient[18]. Another finds a range of 1 to 9 behaviors, in which 27.4% of the patients presented only one symptom, 26% had two symptoms and 15.1% had five or more symptoms[26], although these authors used the 10-item version of the NPI.

Table 4 Mean scores on the different subscales of NPI

	Frequency (mean ± SD)	Severity (mean ± SD)	Combined (mean ± SD)
Delusions	0.94 ± 1.33	0.66 ± 0.95	1.73 ± 2.97
Hallucinations	0.42 ± 0.93	0.30 ± 0.67	0.72 ± 1.95
Agitation	1.37 ± 1.32	1.13 ± 1.10	2.86 ± 3.21
Depression	1.80 ± 1.60	1.17 ± 1.07	3.84 ± 3.54
Anxiety	1.41 ± 1.43	1.00 ± 1.04	2.70 ± 3.23
Euphoria	0.08 ± 0.45	0.06 ± 0.32	0.14 ± 1.10
Apathy	2.25 ± 1.52	1.69 ± 1.12	5.30 ± 4.27
Disinhibition	0.55 ± 0.93	0.39 ± 0.68	0.78 ± 1.65
Irritability	1.66 ± 1.33	1.24 ± 1.03	3.18 ± 3.05
Aberrant motor activity	1.48 ± 1.72	1.13 ± 1.30	3.71 ± 4.87
Sleep disorders	0.94 ± 1.45	0.68 ± 0.99	1.78 ± 2.91
Appetite disorders	0.67 ± 1.15	0.51 ± 0.87	1.30 ± 2.39

NPI: Neuropsychiatric Inventory. SD: standard deviation.

Apathy (74%) was the most frequently found symptom, followed by irritability (66%), depression (60%), agitation (55%) and anxiety (54%), while euphoria (4%) and hallucinations (20%) were the least present. These data coincide with those provided by most of the works9,21,22, although some study found aberrant motor activity as the most frequent symptom[20]. However, in this case, the series was made up of patients with AD (53%) and another type of dementia and the predominance of aberrant motor activity was only manifested in the moderate and severe levels of deterioration. All the disorders were present during the different evolutive stages of dementia. Thus, although most of the symptoms (delusions, hallucinations, agitation, anxiety, apathy, irritability and aberrant motor activity) were more frequent and severe as the intensity of the dementia increased, all of which could be observed in its initial phases.

The mean total scores of NPI regarding frequency, severity and combined score and the mean combined scores corresponding to each one of the NPI subscales were superior to those obtained by Mega et al.[9] and similar to those of Binetti et al.[27]. One possible explanation would be found in the differences in the education level of the patients, since the sample of Mega et al.[9] is made up of individuals with twice the years of schooling than ours and that of Binetti et al.[27]. In this sense, some authors have stated the influence of the education level on the suffering of psychotic[28] and depressive symptoms[29], and in apathy, disinhibiton and aberrant motor behavior[26] in patients with dementia. Thus, a low education level could play a role in the increase of both the total scores of NPI and of some behaviors specifically. Therefore, for example, the patients in our study who had a low level of schooling had greater frequency of delusions and anxiety than those who had middle or higher schooling levels ($p<0.001$ and $p<0.05$, respectively).

Significant correlations were found between different BPS. The correlation between depression and anxiety and between delusions, agitation, anxiety, irritability and apathy stands out. The relationship between different BPS suggests the existence of symptoms groups in different clinical syndromes. Each one of these symptoms would make it possible to better describe the BPS and presumably would contribute to better knowledge of the pathophysiological mechanisms underlying these symptoms. Most of the studies done in this sense clearly describe three groups of symptoms[30-32] classified as: affective (depression and anxiety), psychotic (delusions and hallucinations) and lack of control (disinhibition, agitation, irritability, apathy and aberrant motor activity).

The mean score of the NPI-D was 14.28 ± 6.66 points, a value similar to that found by Craig et al.[22] and that corres-

Table 5 Correlations between mean combined scores of the 12 subscales of NPI

	Delusions	Hallucination	Agitation	Depression	Anxiety	Euphoria	Apathy	Disinhibition	Irritability	Motor	Sleep	Eating
Delusions		0,13	0,11	0,14	0,28*	−0,09	0,45**	0,05	0,06	0,11	−0,03	−0,12
Hallucinations			0,01	−0,11	0,11	0,10	0,02	0,15	0,03	−0,02	0,06	−0,18*
Agitation				0,09	0,14	−0,07	0,33**	−0,07	0,43**	0,22***	0,06	0,00
Depression					0,33**	−0,07	0,22***	−0,11	−0,08	−0,04	0,17	0,13
Anxiety						−0,08	0,30*	0,04	−0,04	−0,07	0,10	−0,13
Euphoria							−0,13	0,20***	−0,01	−0,02	−0,07	−0,03
Apathy								−0,12	0,25*	0,20***	0,12	0,03
Disinhibition									−0,01	0,09	0,23***	0,22*
Irritability										0,17	−0,06	0,07
Motor											0,28*	−0,01
Sleep												−0,11
Eating												

NPI: Neuropsychiatric Inventory. *p < 0.01. **p < 0.001. ***p < 0.05 (Spearman correlation coefficients).

ponds with the grade of moderate suffering according to the criteria presented by Chow et al.[33].

Although there are a large number of instruments to evaluate BPS in AD, in our study we have chosen the NPI for several reasons. In the first place, because the BPS evaluates a range of behaviors (some of which, such as apathy, are the most frequent in AD) that is more extensive than other tests (BEHAVE-Alzheimer's disease[34], Columbia University scale for the psychopathology in Alzheimer's disease[35], Hamilton Rating Scale for Depression[36]). In the second place, the NPI is superior to other instruments because it evaluates both the frequency and the severity of BPS, on the contrary to other tests that only evaluate frequency (The Revised Memory and Behavior Problems Checklist[37] or the CERAD Behavioral Rating Scale for Dementia[38]) or severity (Alzheimer's Disease Assessment Scale-Non Cognitive[39], BEHAVE-AD[34]). Finally, because NPI facilitates a rapid evaluation of the BPS, on the contrary to other tests that require greater application time (Neurobehavior Rating Scale)[40].

In conclusion, the systematic analysis of the AD is important since it generates malaise in the patient and caregivers[41] and, in general, precipitates admission in a geriatric center. Its early diagnosis makes it possible to establish an adequate treatment and prevent the appearance of the BPB[42].

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