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Prevalence of neuropsychiatric syndromes in Alzheimer's disease (AD)

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ABSTRACT

This study aimed to estimate the prevalence and explore the multidimensional complexity of the neuropsychiatric syndromes of AD. Neuropsychiatric symptoms and syndromes of 216 subjects with probable and possible AD diagnosed by NINCDS-ADRDA criteria were evaluated by the Korean version of behavior rating scale for dementia (BRSD-K). The prevalence rate of six neuropsychiatric syndromes (depressive symptoms, inertia, vegetative symptoms, irritability/aggression, behavioral dysregulation, psychotic symptoms) and comorbid neuropsychiatric syndromes were calculated according to the Clinical Dementia Rating scale. To investigate the relationship among neuropsychiatric syndromes, logistic regression analyses were performed. About 95% of patients with AD had one or more neuropsychiatric symptoms and syndromes during the past month. Among the neuropsychiatric syndromes, irritability/aggression (76.2%) was the most frequent, followed by apathy (72.3%) and depressive symptoms (68.0%). About 90% of the subjects had one or more comorbid neuropsychiatric syndromes. The mean numbers of comorbid neuropsychiatric syndromes were significantly varied according to the severity of disease ($p < 0.05$). Depressive symptoms were significantly associated with vegetative symptoms and irritability/aggression ($p < 0.05$). Inertia and psychotic symptoms were significantly associated with vegetative symptoms and behavioral dysregulation, respectively ($p < 0.05$). This study demonstrated that neuropsychiatric syndromes of AD were highly prevalent and involved complex relationships among them.

1. Introduction

Neuropsychiatric symptoms should be regarded as one of the central symptoms of AD. They have been associated with a greater degree of cognitive impairment (Jeste et al., 1992; Perez-Madrinan et al., 2004), rapid disease progression (Mortimer et al., 1992; Stern et al., 1997), caregiver burden (Rabins et al., 1982; Dunkin and Anderson-Hanley, 1998) and early institutionalization (Steele et al., 1990; O'Donnell et al., 1992).

Neuropsychiatric symptoms of AD are not a unitary concept (Robert et al., 2005). They include a very wide range of individual symptoms. The prevalence estimates of these varied, from 60% to 90%, mainly as a result of differences in the evaluation method and clinical characteristics of the study sample (Mack et al., 1999; Lyketsos et al., 2002; McKeith and Cummings, 2005). Because neuropsychiatric symptoms of AD were closely linked with one or more other symptoms, a syndromatic approach which conceptualized the neuropsychiatric symptoms of AD as constellations of several syndromes like depression, psychosis and agitation (Harwood et al., 1998; Mack et al., 1999; Aalten et al., 2007) has an advantage in identifying the biological correlates and estimating the treatment response (Robert et al., 2005; Aalten et al., 2007). Based on the results of studies using this approach, several others proposed a classification system of neuropsychiatric symptoms of AD (Lyketsos et al., 2001a,b; Robert et al., 2005). However, several issues regarding neuropsychiatric syndromes of AD should be further investigated. For example, the prevalence of neuropsychiatric syndromes of AD has been rarely investigated (Aalten et al., 2007). In spite of the evidence that neuropsychiatric syndromes of AD are not likely to appear alone and most likely to occur with other syndromes (Dechamps et al., 2008), interrelationships among the neuropsychiatric syndromes of AD have rarely been examined. Thus, this study aimed to estimate the prevalence and explore the multidimensional complexity of the neuropsychiatric syndromes of AD.

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2. Subjects and methods

2.1. Subjects

Two hundred sixteen subjects with probable and possible AD, according to the NINCDS-ADRDA criteria (McKhann et al., 1984), were enrolled from two special dementia clinics: the Seoul National University Hospital and Kyunggi Provincial Hospital for the Elderly. Most subjects were community dwellers at the time of behavioral evaluation. On entry into the study, informed consent was obtained from patients or their family caregivers according to the guidelines issued by the institutional review boards of the hospitals involved.

All participants were evaluated in accordance with the clinical assessment protocol of the Korean version of CERAD (CERAD-K) (Lee et al., 2002). Severity of dementia was evaluated using the clinical dementia rating (CDR) scale (Hughes et al., 1982). Final diagnosis and severity were assigned by a consensus panel comprised of at least four geriatric psychiatrists with expertise in dementia research after reviewing the available neuropsychological test results and neuroimaging data. Although medications were not controlled during this study, most of the subjects were evaluated before taking any medication to reduce BPSD. Subjects without a reliable informant were excluded from the study.

2.2. Behavioral assessment

Neuropsychiatric symptoms and syndromes were evaluated by the Korean version of the behavior rating scale for dementia (BRSD-K) which consists of 46 questions related to the neuropsychiatric symptoms of AD (Tariot et al., 1995; Youn et al., 2008). Thirty-eight items of the 46 items were scaled by frequency with possible ratings as follows: 0 = not occurred since illness began; 1 = present 1–2 days in the past month; 2 = present 3–8 days in the past month; 3 = present 9–15 days in the past month; 4 = present 16 days or more in the past month; 8 = occurred since illness began but not in during the past month; 9 = unable to rate. To calculate the prevalence of clinically relevant neuropsychiatric symptoms, a symptom was recorded as present if symptoms were present at least 3 days within the past month. The remaining eight items (items 9, 10, 12, 14, 5, 17, 26, 32) were framed relative to "before dementia began" and were rated as present or absent. The presence of six neuropsychiatric syndromes (depressive symptoms, inertia, vegetative symptoms, irritability/aggression, behavioral dysregulation, psychotic symptoms), which were included as subscales in BRSD-K, were rated as being present when any items in the subscales were rated as present in the previous month. The BRSD-K was administered within 3 months of a CERAD evaluation for each subject.

2.3. Statistical analysis

Frequencies of neuropsychiatric symptoms and syndromes of AD, according to the severity of disease, were calculated. Frequencies of comorbid neuropsychiatric symptoms and syndromes were also calculated. To evaluate the likelihood that subjects exhibiting one neuropsychiatric syndrome would also exhibit another neuropsychiatric syndrome, forward logistic regression analyses using age, sex, education, APOE genotype and CDR score as independent variable were performed. All statistical analyses were performed by SPSS 11.0.

3. Results

3.1. Demographic and clinical characteristics of the subjects

The age of the subjects ranged from 48 to 98 years, with a mean age of 72.9 ± 9.9 years. About 70% of the subjects were female. While mean education years was relatively low (6.3 ± 5.7), there was a broad range in years of school completed (0–20). Diagnosis of probable AD was 66.7%. More than half of subjects had dementia below the mild level of severity. Thirty subjects had CDR 0.5; 90 subjects, CDR 1; 61 subjects, CDR 2; 35 subjects, CDR 3. A total 172 subjects completed the MMSE and the mean score was 14.4 ± 2.5. Most of the informants lived with the study subjects (81%) and were the spouse (37.5%) or children (33.8%) of the subjects (Table 1).

Table 1
Demographic and clinical characteristics of study subjects.

	Number	Mean ± S.D.	*n* (%)
Age (years)	216	72.9 ± 9.9	
Female	216		150 (69.4)
Education (years)	216	6.3 ± 5.7	
Diagnosis	216		
Probable AD			144 (66.7)
Possible AD			72 (33.3)
CDR	216		
0.5			30 (13.9)
1			90 (41.7)
2			61 (28.2)
3			35 (16.2)
Duration of illness (years)	205	4.1 ± 2.5	
MMSE	172	14.4 ± 6.0	
Blessed ADL	216	6.0 ± 3.9	

3.2. Prevalence of neuropsychiatric symptoms and syndrome

Nearly all (96.3%) of the subjects had one or more neuropsychiatric symptom during the past month. The frequencies of neuropsychiatric symptoms ranged from 1.9% (item 35, misidentification of objects; item 39, belief that the caregiver is an imposter) to 70.4% (item 30, verbal repetitiveness) (Table 2). Neuropsychiatric symptoms of AD with the highest frequencies were, in decreasing order, verbal repetitiveness (70.4%), loss of enjoyment (51.9%), irritability (44.9%), loss of initiative (41.2%) and tiredness (36.1%). In line with neuropsychiatric symptoms, 94.4% subjects had one or more neuropsychiatric syndromes. Inertia (70.4%) was the most frequent, followed by irritability/aggression (67.3%), depressive symptoms (54.2%), behavioral dysregulations (51.4%) and psychotic symptoms (25.0%) (Table 3).

Frequencies of neuropsychiatric symptoms and syndromes were varied according to the severity of disease. Among 45 items, frequencies of 20 neuropsychiatric symptoms were significantly different with respect to the severity of AD ($p < 0.05$). Frequencies of most neuropsychiatric symptoms peaked in moderate to severe stages of AD other than two symptoms (item 9, loss of enjoyment; item 31, social withdrawal) both of which had their highest frequencies in mild level of disease severity. Frequencies of all neuropsychiatric syndromes except vegetative symptom were significantly different in relation to the severity of disease ($p < 0.05$) and the highest was observed in moderate to severe stages. Inertia showed the highest frequency in mild stages.

3.3. Comorbid neuropsychiatric symptoms and syndromes

Most of the study subjects (92.1%) had two or more neuropsychiatric symptoms and the mean number of neuropsychiatric symptoms per individual was 9.0 ± 6.6. A large percentage of the subjects (85.5%) also had one or more comorbid neuropsychiatric syndrome with a mean number of comorbid syndrome per individual of 3.1 ± 1.7. The mean number of comorbid neuropsychiatric symptoms and syndromes also varied significantly according to the severity of disease ($F = 6.72$, df = 3, $p = 0.001$ for neuropsychiatric symptom; $F = 8.64$, df = 3, $p = 0.001$ for neuropsychiatric syndrome).