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Comparison of neuropsychological profiles in patients with Alzheimer's disease and mixed dementia

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ABSTRACT

Objects: We designed this study to extensively compare the neuropsychological profiles of Alzheimer's disease (AD) and mixed dementia (MD) in a large multicenter cohort of patients. Specifically, we performed subgroup analyses to examine group differences associated with dementia severity.
Methods: A total of 1021 AD patients and 577 MD patients were included from the Clinical Research Center for Dementia of South Korea (CREDOS) Study. All patients underwent comprehensive neuropsychological and functional ratings, as well as complete physical and neurological examinations. To avoid floor confounds, only patients with Clinical Dementia Rating (CDR) scores of 0.5–2.0 were included.
Results: Overall, MD patients showed worse performance in frontal/executive function than those with AD. Stratification by dementia severity revealed a significant difference in global cognitive function scores between AD and MD patients only in the low severity groups (CDR 0.5). Also, MD patients showed worse performance in frontal/executive function domains in the CDR 0.5 groups whereas they had better performance in the memory domain in the CDR 1 groups than did AD patients. Additionally, AD patients showed better performance than MD patients with respect to activities of daily living at CDR levels 0.5 and 1. All differences had disappeared at the CDR 2 level of global dementia severity.
Conclusion: This study suggests that there are significant differences in neuropsychological profiles between AD and MD patients, with the pattern of this difference varying distinctively according to dementia severity.

1. Introduction

Alzheimer's disease (AD) and vascular pathology are the two most common causes of dementia [1,2]. AD is a progressive and degenerative disease of the brain, which causes impairment in multiple cognitive areas, and results in a decline of functional abilities and behavioral changes. Vascular dementia (VaD) is the second most common form of dementia after AD, and comprises a group of syndromes relating to a variety of vascular pathologies [3,4].

Recent reviews reported that ischemic lesions influence the clinical expression of AD [5]. Snowdon et al. [6] identified that 47% of their demented patients had both AD and brain infarcts, and that the patients with brain infarcts showed poorer cognitive function than did those without infarcts. These findings provide evidence that AD and vascular pathology interact in important ways and that many dementia patients have comorbid pathological processes of AD and VaD. This co-occurrence of AD and VaD is often termed mixed dementia (MD) [1,2]. Specifically, MD is defined as cognitive decline sufficient to impair independent functioning in activities of daily living resulting from the combination of AD and vascular pathology [2].

In community-based autopsy studies, MD is one of the most common subtypes of dementia [7,8]. Identifying the clinical and

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neuropsychological features of MD is important for ensuring that clinicians appropriately recognize and manage the vascular risk factors.

MD has not been studied extensively. Schmidtke et al. [9] reported that neuropsychological profiles of AD and MD patients were very similar, except for a lower word fluency score in MD. In another study, Reed et al. [10] suggested that most cases of AD had Low Memory while only 10% of cases showed Low Executive profile, whereas MD cases had Low Executive profile more commonly than in AD. Study results regarding cognitive profiles were not consistent.

More recently, Dong and colleagues [11] proposed that these inconsistencies could be attributed to different vascular etiologies in the MD group, different dementia severity, and inadequate sample sizes. Thus, researchers compared the cognitive profiles of mild-moderate MD and AD and reported that MD patients were more impaired than AD patients in global cognitive composite function, attention, and visual construction tasks. However, Dong et al. could not consider issues regarding dementia severity and different etiologies because of the acknowledged relatively small sample size [11]. Moreover, studies related to the neuropsychological characteristics of MD have been limited, with few studies having examined activities of daily living and neuropsychiatric symptoms, as well as neuropsychological battery profiles.

We designed this study to extensively compare the neuropsychological profiles of AD and MD in a large multicenter cohort of patients. Specifically, we performed subgroup analysis to examine the differences according to dementia severity. This stratification is important because the pathologies of AD and MD patients increasingly overlap as the dementia progresses [12]. We hypothesized that patients with MD would show greater impairment of function in frontal executive domains than patients with AD, and that AD and MD patients would present similar deficits in global cognitive function. Additionally, we expected that the magnitude of difference in neuropsychological profiles between AD and MD patients would decrease as the dementia severity increased.

2. Methods

2.1. Subjects

Patient data were collected from the Clinical Research Center for Dementia of South Korea (CREDOS), a prospective, multi-center, hospital-based cohort study ongoing since 2005. This study was performed as part of the CREDOS study. More description about CREDOS has been detailed elsewhere [13]. This study included the cohort from 2005 to 2010. Only patients diagnosed with AD and MD as per the inclusion criteria were selected for the present study. Patients diagnosed with neurological and psychiatric illnesses such as schizophrenia, mental retardation, or epilepsy were excluded. Patients with significant physical illnesses such as hearing or visual impairment, and severe cardiac or respiratory disorders were also ruled out. We also excluded severely demented patients defined by a Clinical Dementia Rating (CDR) of 3 in order to remove the floor effect. Additionally, patients with CDR Sum-of-Boxes (CDR-SOB) scores < 2.0 were excluded in an effort to avoid confound of Mild Cognitive Impairment [14]. Patients with AD and MD were matched for age, gender, and dementia severity. This study was approved by the Institutional Review Board of the participating centers and signed informed consent was obtained from both caregivers and patients.

2.2. Clinical and cognitive assessments

All patients underwent a comprehensive diagnostic work-up, which included medical histories, physical and neurological examination, neuropsychological testing, routine laboratory tests, and brain magnetic resonance imaging (MRI) under a uniform protocol. Specifically trained psychiatrists and neuropsychologists administered the tests.

The Korean version of the Mini-Mental State Examination (K-MMSE) was used to assess global cognitive impairment [15,16], and the CDR scale was used to assess global dementia severity.

Activities of daily living were evaluated using the Barthel Index for Daily Living Activities (Barthel-ADL) and the Seoul-Instrumental Activities of Daily Living (S-IADL) [17,18]. The Barthel-ADL was used to evaluate basic ADLs and scores can range from 0 to 20 with higher scores indicating better functioning. The S-IADL is composed of 15 items to assess patients' instrumental and social activities of daily living with a possible range from 0 to 45, with lower scores indicating better functioning.

The Korean-Neuropsychiatric Inventory (K-NPI) was used to assess behavioral and psychological symptoms [19,20]. It comprises 12 common neuropsychiatric symptoms in dementia. For scoring, the frequency (a scale of 1 to 4) and the severity (a scale of 1 to 3) ratings are multiplied to give overall domain scores (total score of 0 to 144 with higher scores indicating more impaired functioning).

We obtained extensive neuropsychological assessments with the Dementia version of the Seoul Neuropsychological Screening Battery (SNSB-D) [21]. The SNSB has been one of the most widely used instruments for assessing cognitive functioning in patients with stroke, head trauma, Parkinson's disease, and dementia in Korea [22]. The SNSB-D was used for this study and it differs from the original SNSB in providing global cognitive function (GCF) score that represented a sum of the five cognitive domains. These were: (1) attention (digit span forward, digit span backward); (2) language and related function (short form of Korean-Boston Naming Test (K-BNT), calculation); (3) visuospatial function (Rey-Complex figure test (RCFT) copy); (4) memory (orientation, Seoul verbal learning test (SVLT) free/delayed recalls, SVLT recognition, RCFT immediate/delayed recalls, RCFT recognition); and (5) frontal/executive function (motor impersistence, contrasting program, go-no-go test, fist-edge-palm, category word fluency, phonemic word fluency, Stroop test-color reading). Completion of the SNSB-D generally required 40–50 min, with a higher score indicating better functioning.

2.3. Clinical diagnosis

A diagnosis of dementia was made in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria [23]. AD or probable AD was diagnosed using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA) [24]. Inclusion criteria for MD were as follows: (1) patients who met the above AD criteria and (2) who displayed moderate severity of white matter hyperintensities (WMH) as rated by the CREDOS protocol. In the CREDOS protocol, we evaluated the severity of WMH according to the modified Fazekas ischemia criteria [25] using the T2 axial or fluid attenuated inversion recovery (FLAIR) images. WMH were assessed separately as periventricular white matter hyperintensities (PWMH) and deep white matter hyperintensities (DWMH). DWMH were rated as D1 (<10 mm), D2 (≥10 mm, <25 mm), or D3 (≥25 mm) based on the longest diameter of lesions. PWMH were divided into P1 (cap and band <5 mm), P2 (≥5 mm, <10 mm), or *P*3 (cap or band ≥ 10 mm) based on the maximum length, which were perpendicular and horizontal to the ventricle, respectively. These two ratings were combined to provide a representative rating as minimal (D1P1, D1P2), moderate (D1P3, D2P1, D2P2, D2P3, D3P1, D3P2), or severe (D3P3). We excluded the patients with severe ischemia (D3P3) not to include pure vascular dementia. The inter-rater reliability for the PMWH and DWMH in the CREDOS study was preciously found to be good (Cohen κ, 0.73–0.91) [26].

2.4. Statistical analyses

All statistical analyses were carried out using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined at the 0.05 level. Prior to analysis, the Kolmogorov-Smirnov test was conducted