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Patterns of neuropsychological impairment in Alzheimer's disease and mixed dementia

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ABSTRACT

Background: Mixed dementia (MD), i.e., the coexistence of Alzheimer's disease (AD) and cerebrovascular disease (CVD), is a common dementia subtype. Few studies have attempted to establish the cognitive profiles of mild–moderate MD and compare it to the profiles of AD using a comprehensive neuropsychological test battery. We aimed to establish the neuropsychological profile of mild–moderate MD in relation to mild–moderate AD.
Methods: Patients with consensus diagnoses of MD and AD of mild–moderate severity (Clinical Dementia Rating score of 1–2) were recruited from a memory clinic. Cognitive performance was measured by a formal neuropsychological battery covering domains of attention, language, verbal and visual memory, visuoconstruction, visuomotor speed and executive function. Cognitive domain scores are *z*-scores calculated using the mean and *SD*s of the AD group. ANCOVAs with age and education as covariates were employed to examine differences in mean score difference of cognitive domains and subtests between patients with MD and AD.
Results: 151 patients were recruited with the majority of AD ($n = 96$, 63.6%) and a minority of MD ($n = 55$, 36.4%). There were no significant differences in the demographic characteristics of patients with MD and AD. However, patients with MD were significantly more impaired than AD patients in global cognitive composite, attention and visuoconstruction (global cognitive composite: -0.32 ± 0.98 vs 0 ± 1, $p = 0.011$; attention: -0.32 ± 0.90 vs 0 ± 1, $p = 0.013$; visuoconstruction: -0.27 ± 0.99 vs 0 ± 1, $p = 0.024$, respectively).
Conclusion: The neuropsychological profile of patients with MD of mild–moderate severity is characterized by a poorer global performance, as well as attention and visuoconstruction than those with AD of mild–moderate severity.

1. Introduction

Mixed dementia (MD)—defined as the coexistence of Alzheimer's disease (AD) and cerebrovascular disease (CVD) [1]—has been identified as one of the most common subtypes of dementia by autopsy-based epidemiological studies [2,3]. However, MD has not been studied as extensively compared to other subtypes due to the lack of consensus on its diagnostic criteria and its heterogeneous neuropathological features [4,5]. Establishing the cognitive profile of MD relative to AD would be useful in elucidating the contribution of CVD to cognitive deficits in dementia, which in turn would facilitate optimization of clinical management and therapeutic strategies for individuals with MD [5], through the management of cerebrovascular risk factors.

There is strong evidence that the CVD exacerbates cognitive deficits associated with dementia. The Nun study reported that among participants with autopsy-defined AD, those with cerebral infarcts exhibited poorer abilities in memory, naming, verbal fluency and constructional praxis compared to their counterparts without infarcts [3]. Moreover, in a study conducted at a memory clinic, AD patients with silent cerebral infarction had poorer performance than those with AD in language and memory [6]. However, in another autopsy-based study, individuals with MD had slightly poorer but non-significant different performance in global cognitive composite scores and greater impairments in executive function than those with AD [7]. Furthermore, a clinical study which examined neuropsychological differences between patients with early AD and MD discovered their profiles to be closely similar except for poorer semantic fluency in the latter group [8].

These differences may be attributed to the following: 1) undifferentiated small vessel and large vessel etiology in patients with MD which is the key problem in previous studies [7,8]. Bowler and colleagues attributed this to the lack of a set of well-established diagnostic criteria

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for MD [8]; 2) different dementia severity, that is, patients in autopsy-based studies were more likely to have advanced stages of dementia [3,7] whereas patients with mild–moderate dementia severity were recruited in clinical studies [6,9]; and 3) different sample size in the previous studies [7,9], i.e., there was a smaller sample size in the group with mix pathology in the autopsy-based study (n = 9) [7] while the clinical study has a relatively larger sample size (n = 18) [9]. In addition, simple cognitive tests of no more than 3 domains [7] and no more than 5 subtests were used for the neuropsychological evaluation in the previous studies [9].

To date, no study has attempted to establish the cognitive profiles of MD and AD of mild–moderate dementia severity using a comprehensive neuropsychological test battery. Thus, we aimed to examine and compare the cognitive profiles of mild–moderate MD and AD by comparing their performance in global cognitive composite score, domain-specific scores and individual subtest scores. We hypothesized that patients with mild–moderate MD would have poorer performance in global cognitive composite scores. Consistent with previous study [6,7], we also hypothesized that patients with MD would have poorer performance in memory, visuomotor speed and visuospatial function than those with AD. Additionally, in keeping with a previous study [9], we hypothesized that patients with MD of mild–moderate dementia severity would have poorer performance than AD patients on subtests of semantic fluency. Furthermore, MD patients might be similar to patients with subcortical ischemic vascular dementia that their performance in memory, visuomotor speed and visuospatial function would be worse than those with AD [10].

2. Methods

2.1. Subjects

Consecutive patients attending the National University Health System Memory Clinic between February 2009 and mid-April 2011 were recruited. The study protocol was approved by the Domain-Specific Review Board (DSRB) of our institution, National Healthcare Group. Patients were excluded using the following criteria: 1) age ≤50; 2) had incomplete neuropsychological evaluation; 3) presented active psychiatric disease or were moderately to severely depressed (modified Geriatric Depression Scale score > 10) [11]; and 4) severe dementia defined by Clinical Dementia Rating (CDR) scale score = 3 [12].

2.2. Neuropsychological evaluation

All patients underwent formal neuropsychological evaluation administered by highly trained research psychologists in English, Chinese or Malay. The MMSE [13] and/or the Montreal Cognitive Assessment (MoCA) [14] were used as clinical measures of global cognition.

The formal neuropsychological battery adopted in this study has been locally validated on Singaporean elderly [15]. This battery covers the following domains: (1) attention (digit span test [16], visual span test [16], and auditory detection test [17]); (2) language (15-item modified Boston Naming Test (modified BNT) [18] and category fluency [19]); (3) visuoconstruction (visual reproduction subtest of the Weschler Memory Scale-Revised copy task [16], clock drawing [20] and the block design subtest of the Weschler Adult Intelligence Scale-Revised [21]); (4) visuomotor speed (digit cancellation [22], maze [23], and symbol digit modalities [24]); (5) verbal memory (word list recall [25] and story recall [16]); (6) visual memory (picture recall [16] and the visual reproduction subtest of the Weschler Memory Scale-Revised [16]); and (7) executive function (Frontal Assessment Battery [26]).

Education-adjusted cutoffs of 1.5 standard deviations (*SDs*) below the derived norms were used on individual tests. A domain was considered "impaired" in the event of failure in 50% or more of the tests within that domain.

2.3. Clinical diagnosis

All patients underwent uniform clinical assessment consisting of history taking, physical examination, laboratory tests, formal neuropsychological testing, and computed tomography (CT) and/or magnetic resonance imaging (MRI) scans of the brain. A diagnosis of dementia was made during a consensus meeting using DSM-IV criteria [27]. Mild and moderate dementia was defined by global CDR scores of 1 and 2. Differential diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association's (NINCDS–ADRDA) criteria [28] whereas that for mixed dementia was based on the same methodology adopted by McKhann and colleagues — etiologically mixed presentation was diagnosed if all the core clinical criteria for AD were fulfilled, together with evidence of (1) history of stroke related to onset or worsening of cognitive impairment, and (2) presence of multiple stroke and severe white matter changes (beginning confluence) [29]. Over half of the patients in this study had stroke (n = 80, 53.0%). Of these, the majority (n = 61, 76.3%) had lacunar infarcts, while a minority of patients had both lacunar and cortical infarcts (n = 10, 12.5%) or cortical infarcts alone (n = 9, 11.3%). As there were insufficient numbers of patients with large vessel strokes (n = 19), for analysis purposes, they were combined together with lacunar infarcts. In addition, White Matter Disease (WMD) was evaluated using the visual Age Related White Matter Changes Scale (ARWMC) which assessed WMD in the following areas: frontal, parietoccipital, temporal, infratentorial and basal ganglia. Severe WMD was defined on the presence of WMD in 2 or more regions [30]. Patients with MD and AD were matched for demographic characteristics, dementia severity, MMSE and MoCA scores.

2.4. Statistical analysis

Statistical analyses were performed with SPSS version 19.0. All individual test raw scores were transformed to standardized *z*-scores using the means and standard deviations (*SDs*) of the AD group. All *z*-scores were adapted so that greater value reflects better performance. The score for each domain was created case-wise by averaging the *z*-scores of the corresponding individual tests, and then standardized again using the composite mean and *SD* of the AD group. To obtain the global cognition domain *z*-score for each patient, the domain *z*-scores were averaged and then standardized using the composite mean and *SD* of the AD group. This procedure would assign the AD group a mean of 0 and *SD* of 1 for every domain, which would then show the relative performance of the MD group. These standardized *z*-scores also rendered performance metrics across domains comparable.

Between-group comparisons were conducted using *t*-tests for continuous variables, and Pearson's χ^2 tests for nominal variables. Analyses of covariance (ANCOVA), correcting for education and age, were conducted to test for significant differences in global cognitive impairment, domain-specific impairment, and individual test scores between the two groups.

3. Results

Of the patients who attended the Memory Clinic during this time period, 289 patients above 51 years of age were diagnosed with AD (n = 200) or MD (n = 89). Of the 116 patients with incomplete neuropsychological evaluation, 88 were due to severe cognitive impairment, 19 due to visual/hearing/physical impairment and 9 due to low level of motivation. There were 173 patients who completed the neuropsychological evaluation. Of these, we further excluded patients with severe dementia (CDR = 3, n = 18) and moderately depressed patients (score of ≥10 on the modified Geriatric Depression Scale, n = 4). Hence, the final sample consisted of 151 (96 AD, 55 MD) patients.

Patients with AD and MD had no significant differences in their demographic characteristics (age, education, sex, ethnicity), dementia