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Cognitive profile in mild cognitive impairment with Lewy bodies

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ABSTRACT

Introduction: This study aimed to elucidate the cognitive profile of patients with mild cognitive impairment with Lewy bodies (MCI-LB) and to compare it to that of patients with mild cognitive impairment due to Alzheimer's disease (MCI-AD).

Methods: Subjects older than 60 years with probable MCI-LB (n = 60) or MCI-AD (n = 60) were recruited. All patients were tested with Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) to assess their global cognitive profile.

Results: The MCI-AD and MCI-LB patients did not differ in total MMSE and MoCA scores. However, some sub-items in MMSE and MoCA were shown to be screening markers for differentiating MCI-LB from MCI-AD. In the visuoconstructive test, the total score and *hands* subitem score in the clock-drawing test were significantly lower in MCI-LB than in MCI-AD. As for the executive function, the 'animal fluency test', 'repeat digits backward test' and 'take paper by your right hand' in MMSE all showed lower scores in MCI-LB compared with MCI-AD. As for memory, 'velvet' and 'church' in MoCA and 'ball' and 'national flag' in MMSE had lower scores in MCI-AD than in MCI-LB.

Conclusion: This study presents the cognitive profile of patients with MCI-LB. In line with the literature on Dementia with Lewy bodies, our results showed lower performance on tests for visuoconstructive and executive function, whereas memory remained relatively spared in the early period.

Keywords: clock-drawing test, Lewy bodies, mild cognitive impairment, mini-mental state examination, Montreal cognitive assessment

INTRODUCTION

Dementia with Lewy bodies (DLB) represents the second most common form of neurodegenerative dementia after Alzheimer's disease (AD). Its prevalence rate is up to 5% in the elderly population and 30% in the whole dementia population.[1,2] In community and secondary care, its prevalence is 4% and 7.7%, respectively, according to the 2005 revised International Consensus Criteria for DLB.[3] Mild cognitive impairment (MCI) is a crucial period when the disease is present but cognitive impairment is not severe enough to lead to functional deficits in activities of daily living. Similar to AD, DLB would also benefit from an early diagnosis and treatment.

There have been some achievements in the early detection of MCI. For example, some clinical symptoms could present very early, such as behavioural and psychiatric symptoms, constipation, hyposmia, rapid eye movement sleep behaviour disorder (RBD), etc.;[4-6] thinner grey matter in the insula in a neuroimaging study[7] or occipital hypometabolism by a functional imaging study[8] has been shown in prodromal DLB.

A cognitive profile is the main method of early detection of neurodegenerative disease. Much progress has been made in research on mild cognitive impairment due to Alzheimer's disease (MCI-AD), but mild cognitive impairment with Lewy bodies (MCI-LB) remains poorly characterised to date. The reasons may be the lower sensitivity and specificity of the DLB criteria. By contrast, MCI-AD and MCI-LB are similar in terms of cognitive impairment, rendering their differential diagnosis difficult. Although is not easy to investigate MCI-LB, some efforts in that direction have been made. Recently, research criteria for MCI-LB[9] were published, and mild cognitive impairment was one of the three main presentations. A few studies have examined cognitive profiles by screening or using a thorough neuropsychological test. For instance, in 2017, Kemp et al[10] conducted a comprehensive cognitive study of 37 patients and found that patients with prodromal DLB showed impaired visuoconstructive and

executive function, but their memory function was relatively spared. Another study on early DLB found similar results,[11-14] which were consistent with the cognitive impairment in DLB.[15-19] These studies provided good evidence of early cognitive impairment in DLB; however, many tests were employed in these studies, which made the studies time-consuming, and thorough neuropsychological tests were complex, which may not be suitable for an outpatient or community testing. Thus, it is necessary to find an effective screening method to detect MCI-LB.

The Mini-Mental State Examination (MMSE)[20] and Montreal Cognitive Assessment (MoCA)[21] questionnaires are validated and standardised tools that are widely used to evaluate global cognitive function in patients with dementia. Many studies have been performed focusing on global cognitive function in patients with DLB, AD and MCI-AD but seldom in those with MCI-LB. Therefore, it is necessary to investigate the characterisation of MMSE and MoCA in DLB. In 2013, Caffarra et al[22] established a method called the Qualitative Scoring Pentagon Test (QSPT) by dividing Pentagon Copying subtest in MMSE into five subitems: number of angles, distance between two pentagons/whether they intersect, closure/opening, rotation and closing-in, and they found that QSPT could be a sensitive measure of visuoconstructive abilities in patients with DLB. In 2014, Mitolo et al[23] found the QSPT to be a valid screening tool in an autopsy-confirmed DLB and AD study, and in 2015, Cagnin et al[24] found 91% specificity for the QSPT in the diagnosis of prodromal DLB. All the aforementioned studies found the score for the 'number of angles' subitem score lower in MCI-LB than MCI-AD, even if the total score did not differ between the MCI-LB and MCI-AD groups. However, in 2019, a study by Bertta et al[25] showed that DLB patients performed worse in the 'rotation' subitem in Pentagon Copying, but that there was no difference in the 'number of angles' item in Pentagon Copying between DLB and AD patients. The discrepancy in QSPT scores needs to be further examined.

Some findings[26,27] have been described previously in the Western population. The main aim of the present study was to determine the cognitive profile of MCI-LB patients using the MMSE and MoCA tests in the MCI period in the Chinese population and to explore whether some subitems of MMSE and MoCA could help differentiate MCI-AD and MCI-LB, besides the QSPT.

METHODS

We included 60 patients with MCI-LB and 60 with MCI-AD who were from dementia cohorts from a cognitive impairment speciality clinical service in Tianjin Huanhu Hospital, Beijing Tiantan Hospital and Tianjin First Central Hospital from June 2017 to July 2019. All patients were at least 60 years old.

Diagnosis was confirmed by a two-specialist panel (JY and SZH), and if an agreement on diagnosis could not be reached for a subject, the subject was excluded. Diagnosis followed the corresponding criteria: DLB based on 2017 criteria by McKeith et al;[28] AD and MCI-AD based on the National Institute of Aging and Alzheimer's Association criteria by McKhann[29] and Albert et al,[30] respectively, in 2011. No diagnostic criteria for MCI-LB had been established at the time of this study, probable MCI-LB was defined with a combination of MCI criteria by Petersen in 2011[31] and DLB criteria (two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers) were defined by McKeith et al in 2017.[28] All participants in MCI had an MMSE $\geq$ 20 and a Clinical Dementia Rating (CDR) score[32] of $\leq$ 0.5. Exclusive criteria included a major concurrent psychiatric illness or a history of other significant neurological illnesses such as stroke or alcohol/substance abuse. Patients who met both criteria of DLB and AD or MCI-LB and MCI-AD were excluded to reduce the mixed pathology effect. For example, if a patient was diagnosed as having probable MCI-LB at the same time as magnetic resonance (MR) imaging revealed severe hippocampal atrophy,

the patient was defined as having a mixed diagnosis and would be excluded from further analysis.

All participants provided written informed consent before enrolment. The study received ethical approval from the Tianjin Huanhu Hospital Ethics Committee (2011-1).

All patients underwent detailed physical and neurological examinations, including a complete medical history, laboratory tests, neuroimaging and neuropsychological evaluation. Neuropsychological tests were conducted by a doctor who was blinded to the diagnosis. The Clinical Dementia Rating (CDR) scale[32] was employed to determine the severity of dementia, Zhang Mingyuan's version of activity of daily living was used for functional status evaluation, Revised Unified Parkinson's Disease Rating Scale and Motor Sub-scale (UPDRS)[33] was used for parkinsonism profiles, and one-year rule between the onset of dementia and parkinsonism was applied. Cognitive fluctuations were estimated based on the subject's medical history. Autonomic dysfunction symptoms were investigated using a questionnaire and physical examinations. A total of four patients underwent the ^{123}I-2ß-Carbomethoxy-3ß-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane single photon emission computed tomography (^{123}I-FP-CIT SPECT).

The MMSE (Zhang Mingyuan's version) and MoCA (Beijing version) were employed to measure global cognition; there are 29 questions of six main subitems in MoCA and 32 questions in seven main subitems in MMSE.

Student's *t*-test for the independent sample was used for normal variables, and nonparametric tests (Mann-Whitney *U* test) were used for variables that were not normal distribution. Pearson's chi-square test was applied for categorical variables. The significance level was set at $p < 0.05$. Statistical analyses were performed with SPSS version 22.0 (IBM Corp, Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of the patients are summarised in Table I. The groups did not differ in age, gender, years of education, MMSE and MoCA. Subjects with MCI-LB showed a shorter duration of symptoms compared with the MCI-AD group. The mean age for MCI-LB was 70.25 ± 6.59 years and 55% of patients were male. The median year of duration of symptoms was shorter in the MCI-LB group than in the MCI-AD group (2 interquartile range [IQR] 1–2.75) vs. 3.25 [IQR 2–5], respectively, $p < 0.001$).

Table I. Demographic characteristics of MCI-LB and MCI-AD patients.

Characteristic	Median (IQR)		p-value
	MCI-LB (n = 60)	MCI-AD (n = 60)	
Male gender*	33 (55%)	31 (51.7%)	0.134
Age†	70.25 ± 6.59	68.68 ± 7.76	1.192
Years of education	12 (9–16)	12 (9–12)	0.360
Duration of symptoms	2 (1–2.75)	3.25 (2–5)	< 0.001‡
MMSE	24 (22–26.7)	23 (20–25)	0.056
MoCA	17.5 (15–21)	18 (17–20)	0.28

*Data presented as *no. (%) and †mean (standard deviation). ‡p < 0.05 is considered statistically significant. IQR: interquartile range; MCI-AD: mild cognitive impairment due to Alzheimer's disease; MCI-LB: mild cognitive impairment with Lewy bodies; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment*

The characteristics of the main subitems of MMSE and MoCA are summarised in Table II. No significant difference was found in most subitems except for the registration and recall subitems. Patients with MCI-LB differed from the MCI-AD group in registration and recall ($p = 0.026$ and $p = 0.002$, respectively), and the recall test showed a lower score in MCI-AD than MCI-LB.

Table II. Main subitem test scores of MMSE and MoCA in MCI-LB and MCI-AD patients.

Subitem	Median (IQR)		p-value
	MCI-LB (n = 60)	MCI-AD (n = 60)	
MMSE	24 (22–26.7)	23 (20–25)	0.056
Orientation	8 (7–10)	8 (6.25–8)	0.084
Registration	3 (3–3)	3 (3–3)	0.026*
Attention/calculations	4 (2.25–5)	5 (3–5)	0.9
Recall	1 (0–1)	0 (0–1)	0.002*
Language	7 (6–8)	7 (6–7)	0.38
Pentagon copying	1 (0–1)	1 (1–1)	0.107
MoCA	17.5 (15–21)	18 (17–20)	0.28
Visuospatial/executive	3 (2–4)	3 (2.25–4)	0.091
Animal naming	3 (2–3)	3 (2–3)	0.573
Attention	5 (4–6)	6 (5–6)	0.229
Language	1 (1–2)	1 (1–2)	0.9
Abstraction	1 (0–2)	1 (0–1.75)	0.681
Delayed recall	0 (0–2)	0 (0–1)	0.184
Orientation	5 (4–6)	5 (4–6)	0.799

**p < 0.05 is considered statistically significant. IQR: interquartile range; MCI-AD: mild cognitive impairment due to Alzheimer's disease; MCI-LB: mild cognitive impairment with Lewy bodies; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment*

All subitem test scores for MoCA in patients with MCI-LB and MCI-AD are shown in Table III. In the visuospatial/executive subitem the clock-drawing test (CDT) score was lower in MCI-LB than MCI-AD (p = 0.004), and in the CDT, the 'hands' score was significantly lower in MCI-LB than in MCI-AD (p = 0.003); in the Attention subitem 'repeat digits backward' differed between MCI-LB and MCI-AD (p = 0.017); in the Language subitem, the 'animal fluency test' showed a difference between MCI-LB and MCI-AD (p = 0.014). In Delayed Recall, the total scores did not show a difference between the two groups, but a significant difference was found in the 'velvet' and 'church' subitems.

Table III. All subitem test scores of MoCA in MCI-LB and MCI-AD patients.

Subitem	Median (IQR)		p-value
	MCI-LB (n = 60)	MCI-AD (n = 60)	
Visuospatial/executive			
Trail-making test	0 (0–0)	0 (0–0)	0.455
Cube-copying test	0 (0–1)	0 (0–1)	0.856
Clock-drawing test	2 (2–3)	3 (2–3)	0.004*

Contour	1 (1–1)	1 (1–1)	0.081
Numbers	1 (0–1)	1 (0.25–1)	0.420
Hands	0 (0–1)	1 (0–1)	0.003*
Animal naming			
Lion	1 (1–1)	1 (1–1)	0.466
Rhinoceros	1 (0–1)	1 (0.25–1)	0.835
Camel	1 (1–1)	1 (1–1)	0.311
Attention	3 (2–3)	3 (2–3)	0.108
Repeat digits forward	1 (1–1)	1 (1–1)	0.753
Repeat digits backward	1 (0–1)	1 (1–1)	0.017*
Tap at 1	1 (1–1)	1 (1–1)	0.285
Serial 7 subtraction starting at 100	5 (4–6)	6 (5–6)	0.460
93	1 (1–1)	1 (1–1)	0.081
86	1 (0.25–1)	1 (1–1)	0.832
79	1 (0–1)	1 (1–1)	0.533
72	1 (0–1)	1 (0–1)	0.844
65	1 (0–1)	1 (0–1)	0.703
Language			
Repeat1	0 (0–0.75)	0 (0–0)	0.667
Repeat2	0 (0–1)	0 (0–1)	0.094
Animal fluency test	1 (0–1)	1 (1–1)	0.014*
Abstraction			
Train-bicycle	0.5 (0–1)	1 (0–1)	0.466
Watch-ruler	0 (0–1)	0 (0–1)	0.848
Delayed recall			
Face	0 (0–0)	0 (0–0)	0.803
Velvet	0 (0–0)	0 (0–0)	0.041*
Church	0 (0–0)	0 (0–0)	0.019*
Daisy	0 (0–0)	0 (0–0)	1.000
Red	0 (0–1)	0 (0–1)	0.687
Orientation			
Date	1 (0–1)	1 (0–1)	0.583
Month	1 (1–1)	1 (1–1)	0.770
Year	1 (1–1)	1 (1–1)	0.659
Day	1 (0–1)	1 (1–1)	0.309
Place	1 (1–1)	1 (1–1)	0.081
City	1 (1–1)	1 (1–1)	1.000

**p < 0.05 is considered statistically significant. IQR: interquartile range; MCI-AD: mild cognitive impairment due to Alzheimer's disease; MCI-LB: mild cognitive impairment with Lewy bodies*

All subitem test scores of MMSE in MCI-LB and MCI-AD patients are shown in Table IV. The Orientation subitem score in 'which streets are we in?' differed between the two groups ($p = 0.002$) and the 'calculations' ($100 - 7 = 93$) subitem differed between the two groups ($p =$

0.043). In the Recall memory subitem, 'ball' and 'national flag' showed lower scores in MCI-AD than in MCI-LB (p = 0.045, p = 0.003, respectively) in the Language tests, and the score of the subitem 'take paper in your right hand' was different between the two groups (p = 0.014).

Table IV. All subitem test scores of MMSE in MCI-LB and MCI-AD patients.

Subitem	Median (IQR)		p-value
	MCI-LB (n = 60)	MCI-AD (n = 60)	
Orientation			
What is the year?	1 (0–1)	1 (1–1)	0.288
What is the season?	1 (1–1)	1 (1–1)	0.770
What is the month?	1 (1–1)	1 (1–1)	0.410
What is the day?	1 (0–1)	1 (0–1)	0.189
What is the date?	1 (0–1)	1 (0–1)	1.000
Which province or city are we in?	1 (1–1)	1 (1–1)	0.560
Which district are we in?	1 (1–1)	1 (0–1)	0.154
Which streets are we in?	1 (1–1)	1 (0–1)	0.002*
Which floor are we on?	1 (1–1)	1 (1–1)	0.823
What's this place? Or which hospital?	1 (1–1)	1 (1–1)	0.159
Registration			
Ball	1 (1–1)	1 (1–1)	0.300
National flag	1 (1–1)	1 (1–1)	0.095
Trees	1 (1–1)	1 (1–1)	0.156
Attention/calculations			
Calculations (93)	1 (1–1)	1 (1–1)	0.043*
Calculations (86)	1 (0.25–1)	1 (0.25–1)	1.000
Calculations (79)	1 (0–1)	1 (1–1)	0.309
Calculations (72)	1 (0–1)	1 (0–1)	0.846
Calculations (65)	1 (0–1)	1 (0–1)	0.715
Recall			
Recall (ball)	1 (0–1)	0 (0–1)	0.045*
Recall (National flag)	1 (0–1)	0 (0–1)	0.003*
Recall (trees)	0 (0–1)	0 (0–0)	0.051
Language tests			
Name wristwatch	1 (0)	1 (0)	1.000
Name pencil (mean + SD)	1 (0)	1 (0)	1.000
Repeat phrase	1 (0–1)	1 (0–1)	0.096
Read and obey (Close your eyes)	1 (1–1)	1 (1–1)	0.300
Take paper in your right hand	1 (1–1)	1 (0–1)	0.014*
Fold it in half	1 (1–1)	1 (1–1)	1.000
Put it on your left leg	1 (0–1)	1 (1–1)	0.067
Make up a sentence about anything (It must contain subject and predicate and make sense)	1 (1–1)	1 (1–1)	0.817
Copying			

Pentagon copying	1 (0–1)	1 (1–1)	0.107

**p < 0.05 is considered statistically significant. IQR: interquartile range; MCI-AD: mild cognitive impairment due to Alzheimer's disease; MCI-LB: mild cognitive impairment with Lewy bodies*

DISCUSSION

This study aimed to determine the global cognitive profile of patients with MCI-LB using MMSE and MoCA. The results revealed more visuoconstructive and executive deficits in MCI-LB and more memory registration and recall deficits in MCI-AD starting at a very early stage. There was no difference in total scores between the two groups, but some subitems in MMSE and MoCA were shown to be a screening marker for differentiating MCI-LB from MCI-AD. Similar to the visuoconstructive test, the total score and 'hands' subitem score in the CDT were significantly lower in MCI-LB than in MCI-AD. With regard to executive function, the 'animal fluency', 'repeat digits backward' and 'take paper in your right hand' tests in MMSE all showed lower scores in MCI-LB than in MCI-AD. With regard to memory, scores for 'velvet' and 'church' in MoCA and 'ball' and 'national flag' in MMSE were lower in MCI-AD than in MCI-LB.

Our results agree with previous findings that the total score in Pentagon copying was not significantly different in MCI-LB and MCI-AD,[24] but we did not score the Pentagon copying by QSPT, so we could not conclude on the subitem of pentagon copying. However, we had another finding that CDT score could be a marker for differentiating MCI-LB from MCI-AD, and the results agree with previous findings.[24] Moreover, when the CDT was divided into 'contour', 'numbers' and 'hands' subitems, we found more impairment in MCI-LB than MCI-AD when analysing performance of 'hand' in the CDT. CDT has been considered a test with its domain mainly in visuoconstructive function. Thus, visuoconstructive function impairment could be tested in the MCI stage by CDT, which is a widely used, validated, standardised tool. Also, the detection of visuoconstructive dysfunction in our study

agrees with the findings of Kemp et al[10] reported in 2017. The Rey-Osterrieth complex figure test has shown lower scores in prodromal DLB patients than in healthy control subjects. In 2019, Beretta et al[25] found two distinct pathological substrates with a deficit in the MMSE pentagon item in DLB and AD. They proposed that an altered visual-perceptual process was the reason for dysfunction in DLB with hypometabolism in the occipital cortex, whereas an altered visuospatial process was the reason for dysfunction in AD with hypometabolism in the parietal cortex, evidenced by ^{18}F-fluorodeoxy-glucose positron emission tomography (^{18}FDG-PET) by following the QSPT in DLB and AD. We did not perform FDG-PET for all patients; hence, the CDT total and 'hands' subitem score warrant further research.

Our results showed that executive function was also compromised in early DLB, as seen with the lower scores for 'animal fluency' and 'repeat digits backward' in MoCA and 'take paper in your right hand' in MMSE in MCI-LB than in MCI-AD. Our results partly agree with previous findings.[11-14] In the fluency study, letter fluency, semantic fluency and phonemic fluency were all used. Animal fluency in our study was related to executive function. The mechanisms underlying the verbal fluency deficits may be related to switching or clustering dysfunction. For instance, in Parkinson's disease research, switching difficulties are more common than clustering difficulties, thereby indicating an executive function disturbance. Notably, the scores for the 'repeat digits backward test' in MoCA and 'take paper in your right hand' were different in MCI-LB than in MCI-AD, but they cannot represent all executive functions because they are all too simple.

Our study found more severe memory impairment in MCI-AD than in MCI-LB by evaluating 'velvet' and 'church' in MoCA and 'ball' and 'national flag' in MMSE. The results agree with previous studies.[11-14] It should be noted that the results indicate that only rough memory dysfunction can be found using MMSE and MoCA; hence, a concise

neuropsychological assessment must be made to derive a definite conclusion, because the subtests in MMSE or MoCA are all too simple.

Our study has several strengths. First, to our knowledge, this was the first large-sample cohort study to evaluate the global recognition profiles of MCI-LB and MCI-AD. Second, we evaluated the global recognition profiles by MMSE and MoCA, which are widely used and standardised screening tests for determining global cognitive function in dementia patients. Some findings will facilitate the detection of MCI-LB, especially in a community or primary hospital. Third, subjects came from specialised clinics, and a precise diagnosis was made based on comprehensive tests and the latest criteria from McKeith et al.[28]

Even with these several strengths, the study also has some shortcomings. First, given that MMSE and MoCA cannot detect impairment thoroughly, some results should be viewed with caution. Second, the subjects came from specialised clinics, rendering it difficult to extend our findings to the general population.

In conclusion, this is the first study to show that there is some visuoconstructive and executive dysfunction, whereas memory remains relatively spared in the early period in MCI-LB according to MMSE and MoCA in the Chinese population. MMSE and MoCA were not able to detect cognitive impairment thoroughly, and MMSE is not an ideal instrument to elucidate the deficits most prominent in MCI-LB.[10,26] In our study, the MCI-AD and MCI-LB patients did not differ in total MMSE and MoCA scores as well. However, some subitems in MMSE and MoCA were shown to be significantly different between patients with MCI-LB and MCI-AD, such as the total score and 'hands' subitem score in the CDT and the 'animal fluency' test in MoCA; these subitems could provide good clues for clinicians to consider the possibility of prodromal DLB.

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