Subtypes and predictors of mild cognitive impairment in patients with multiple system atrophy

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To the Editor: Multiple system atrophy (MSA) is a rare neurodegenerative disease with relentless progression and poor prognosis.[1] Cognitive impairment is an underrecognized field in MSA. Its profiles remain poorly characterized, and its predictors have not been clearly understood. Herein, we aim to characterize MSA-specific patterns of cognitive dysfunction, elucidate their subtypes and detailed characteristics, and ascertain sensitive neuropsychological tests. Furthermore, we assessed the potential utility of clinical assessments, brain volumes, and plasma markers in predicting the cognitive status of MSA. Our research is expected to provide a more accurate and comprehensive understanding of cognitive impairment in MSA.

This study included MSA patients with cognitively unimpaired (CU) or mild cognitive impairment (MCI) for analysis [Supplementary Figure 1, http://links.lww.com/CM9/C651]. Disease severity was assessed using the Unified Multiple System Atrophy Rating Scale (UMSARS)-II, Scale for the Assessment and Rating of Ataxia (SARA), and International Cooperative Ataxia Rating Scale (ICARS). Activities of daily living and autonomic function were rated by UMSARS-IV and Composite Autonomic Symptom Score (COMPASS) 31, respectively. Global cognition was evaluated with Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Auditory Verbal Learning Test (AVLT) and Rey-Osterreich Complex Figure (ROCF) tests were used to measure verbal memory and visuospatial function, respectively. Digit Span Tests (DST) and the Stroops Color Word Test (SCWT) were applied to evaluate attention function. For assessment of language function, Boston Naming Test (BNT) and Animal Fluency Test (AFT) were used. When evaluating executive function, Trails Making Test (TMT) was performed. This study was approved by the Ethical Standards Committee of Huashan Hospital, Fudan University (Nos. KY2020-116, KY2020-065) following the *Declaration of Helsinki*. Each participant or their legal guardians signed a written informed consent before participating in the study.

MSA patients were recruited from June 2019 to November 2021. Our study population involved 117 patients with MSA (80 probable MSA and 37 possible MSA; age 58.1 ± 7.7 years, 69 males [59.0%], disease duration 1.9 ± 1.0 years, and education 8.7 ± 4.2 years), of whom 81 (69.2%) and 36 (30.8%) were diagnosed with MSA-MCI and MSA-CU, respectively [Supplementary Figure 2A, http://links.lww.com/CM9/C651]. Sixty-eight (68/94, 72.3%) patients with MSA-cerebellar type (MSA-C) and 13 (13/23, 56.5%) patients with MSA-parkinsonian type (MSA-P) could be diagnosed as MSA-MCI. There was no significant difference in demographic data and scales related to symptom severity (including motor and non-motor symptoms) between patients with MSA-MCI and those with MSA-CU, while MSA-MCI patients performed

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worse in all neuropsychological tests except SCWT-time ($P = 0.07$) [Supplementary Table 1 and Supplementary Figure 3, http://links.lww.com/CM9/C651].

The majority of MCI patients were classified as amnestic multiple-domain (aMCI-md) (32/81, 39.5%), followed by nonamnestic single-domain (naMCI-sd) (17/81, 21.0%), amnestic single-domain (aMCI-sd) (16/81, 19.8%), and nonamnestic multiple-domain (16/81, naMCI-md) (19.8%) [Supplementary Figure 2B, http://links.lww.com/CM9/C651]. There was no significant difference in terms of age, sex, and disease duration among these subtypes, whereas the aMCI-md subtype had fewer education years than the aMCI-sd subtype. All MSA-MCI subtypes displayed similar performance on ICARS, UMSARS-II, UMSARS-IV, and COMPASS 31 tests, except that the aMCI-md group had lower SARA scores than the naMCI-md group. Regarding the neuropsychological tests [Supplementary Table 1 and Supplementary Figure 4, http://links.lww.com/CM9/C651], no differences were observed in DST results, whereas significant differences were found in the other tests. Specifically, patients with aMCI-md performed worse on both global cognitive tests (MMSE and MoCA) relative to those with aMCI-sd, and worse on MMSE than those with naMCI-sd. Patients with aMCI-sd and aMCI-md performed worse than those with naMCI-sd or naMCI-md in the three items of AVLT. When comparing the ROCF tests, patients with naMCI-md and aMCI-md had lower scores than those with aMCI-sd, and patients with aMCI-md also had lower scores than those with aMCI-sd in the ROCF-delay test. Regarding attention, the aMCI-md or naMCI-md group had poorer performance on both SCWT items relative to the naMCI-sd group, and naMCI-md patients performed worse than aMCI-sd patients on SCWT-number tests. Concerning the AFT, patients with aMCI-md and naMCI-sd performed worse than those in the aMCI-sd group. For the BNT, both aMCI-md and naMCI-md groups performed worse than the aMCI-sd group. Moreover, patients with aMCI-md and naMCI-md had lower scores than the other groups in terms of TMT tests.

Subtype distributions observed in MSA-MCI patients can also be noticed in the population with MSA-C, with a majority of patients (28 [28/68, 41.2%]) having aMCI-md, followed by 14 (14/68, 20.6%) naMCI-md patients and 13 (13/68, 19.1%) aMCI-sd or naMCI-sd patients. Among the MSA-P population, 4 (4/13, 30.8%) patients had aMCI-md or naMCI-sd, while 3 (3/13, 23.1%) patients had aMCI-sd and 2 (2/13, 15.4%) patients had naMCI-md [Supplementary Figure 2, http://links.lww.com/CM9/C651]. Imaging and plasma characteristics were shown in Supplementary Table 2, http://links.lww.com/CM9/C651.

In MSA-MCI populations, we found that the most commonly impaired cognitive domains were visuospatial (36/81, 44.4%) and memory functions (35/81, 43.2%), while attention (16/81, 19.8%), language (17/81, 21.0%), or executive (19/81, 23.5%) dysfunctions were less common [Supplementary Figure 5A, http://links.lww.com/CM9/C651]. The most frequently impaired neuropsychological tests included the ROCF (55/81, 67.9%), ROCF-delay (52/81, 64.2%), and TMT-A (49/81, 60.5%) tests. Conversely, the impaired frequencies in DST (17/81, 21.0%) and SCWT-correct number tests (14/81, 17.3%) were lower. In the identification of sensitive tests for assessing MSA-related cognitive dysfunction, we found that the AVLT recall and recognition tests were more sensitive in detecting memory deficits than the AVLT learning test. Both the ROCF and ROCF delayed tests performed well in identifying visuospatial dysfunctions, and the SCWT-time test was superior to DST or SCWT number test in detecting attentive deficits. The BNT was better than the AFT in detecting impairment of language function, while in terms of executive function, the TMT-A test performed better than the TMT-B.

We identified that UMSARS-IV ($\beta = 0.49$, $P = 0.04$) and education ($\beta = -0.10$, $P = 0.04$) could predict visuospatial and memory dysfunction, respectively [Supplementary Figure 5B–C, http://links.lww.com/CM9/C651]. UMSARS-II ($\beta = 0.09$, $P = 0.03$) was a predictor of attentive deficits [Supplementary Table 3, http://links.lww.com/CM9/C651]. However, no significant independent contributors were detected for language or executive dysfunction. Each single clinical, imaging, or plasma indicator performed poorly in predicting the cognitive status of MSA, with areas under the curve (AUCs) <0.75. Combining multiple cortical volumes yielded perfect accuracy (AUC = 1.00), superior to combining clinical features (AUC = 0.95), or subcortical volumes (AUC = 0.86). However, the combination of plasma markers failed to improve the accuracy (AUC = 0.64). Detailed information is shown in the Supplementary Material, http://links.lww.com/CM9/C651.

This study characterized the subtypes of MSA-MCI and comprehensively explored the relevant predictors. The main findings include: (1) cognitive impairment is evident in MSA, featuring predominantly amnestic multiple-domain deficits; (2) visuospatial or memory dysfunction was the most typical cognitive symptom, with UMSARS-IV and education being able to predict them, respectively; (3) commonly used cognitive tests vary greatly in their sensitivity to detect MSA-MCI, with ROCF and TMT-A being the most sensitive; (4) single clinical, imaging, or plasma measures performed poorly in predicting the cognitive status of MSA, whereas the combination of multiple brain volumes or clinical features enables an excellent prediction.

Both our research and previous research suggested that cognitive impairment might be an underrecognized area of MSA.[2–6] We reported a lower prevalence of MCI in MSA than in a previous, smaller study of 35 cases after excluding patients with dementia, with 82.9% of patients exhibiting cognitive impairment in at least one domain.[7] This frequency was, however, far higher than that reported in pathological autopsies, where cognitive impairment occurred in 22–37% of neuropathologically proven MSA cases.[2–4] Considering differences in population characteristics, ethnicity, assessment methods (e.g., different neuropsychological tests were used), and definition of cognitive impairment (e.g., whether 1, 1.5, or 2 standard deviations [SDs] below the normative mean were applied as a cutoff for impairment), it is acceptable

that the frequency of MSA-MCI reported in different studies varies widely. From another perspective, although the clinical diagnoses of all patients with MSA included in our study were validated by at least one follow-up visit and updated criteria, there is an urgent need for pathological diagnostic confirmation studies to illuminate the cognitive patterns and MCI subtype classifications of MSA. This is a direction for future research.

Of all the MSA-MCI subtypes, the aMCI-md subtype performed worst in various screening tests. This was in agreement with the findings of the PD-MCI study and indicated that the aMCI-md subtype might be "closest" to developing dementia.[8] The lowest MMSE and MoCA scores in the aMCI-md subtype also supported this. Other observations, such as the lower Scale for SARA scores in the aMCI-md group compared with the naMCI-md group, need to be further confirmed by future studies. As expected, no significant differences in domains other than memory were observed between aMCI-sd and naMCI-sd subtypes.

A notable strength of our study is that our participants received comprehensive clinical and neuropsychological evaluations, plasma testing, and imaging scans, whereas many previous studies have been hampered by assessing only a limited number of items. Another advantage lies in the large sample size of patients with MSA whose clinical diagnosis has been repeatedly verified. However, some caveats need to be mentioned. First, a fuller understanding of cognitive patterns in MSA requires large-scale studies with pathological confirmation of the diagnosis, where possible. Second, although the total sample was large enough, the sample size for each MSA-MCI subtype was relatively small. Future studies with larger samples are needed to validate our findings. Third, obtaining data of patients with MSA from large external cohorts with full clinical, imaging, and plasma indexes is currently unavailable. Verification of our findings in future independent large-sample studies is warranted.

The cognitive deficits observed in patients with MSA were evident, featuring predominantly amnestic deficits and multiple-domain phenotypes. Of the domains, visuospatial functions and memory abilities were primarily affected. The combination of multiple brain volumes or clinical assessments enables an excellent prediction of MSA-MCI. Our study is important for better recognizing and characterizing cognitively impaired patients with MSA, which is a prerequisite for further research and intervention trials.

Conflicts of interest

None.

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