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RESEARCH ARTICLE

Cognition in multiple system atrophy: a single-center cohort study

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Abstract

Objective: Cognitive impairment in multiple system atrophy (MSA) is common, but remain poorly characterized. We evaluated cognitive and behavioral features in MSA patients and assessed between-group differences for MSA subtypes and the effect of orthostatic hypotension (OH) on cognition. **Methods**: This retrospective study included 54 patients with clinical diagnosis of possible and probable MSA referred to the Department of Neurology at Medical University of Innsbruck between 2000 and 2018. Neurological work-up included comprehensive neuropsychological testing including Consortium to Establish a Registry for Alzheimer's Disease (CERAD-plus) test battery, Frontal Assessment Battery (FAB), digit span test (DST), clock drawing task (CLOX1), and Hospital Anxiety and Depression Scale (HADS-D). **Results**: The mean MMSE score was 27.6 points. Overall, slight to moderate cognitive impairment was noted in up to 40% of patients, with predominant impairment of executive function and verbal memory. Patients with the cerebellar variant performed significantly worse than patients with the parkinsonian type ($P < 0.05$) in a screening of executive functions (FAB) and in phonemic verbal fluency. Depression and anxiety scores were elevated in 28% and 22% of MSA patients, respectively. Cognitive profile, depression, and anxiety levels were comparable between patients with and without OH. **Interpretation**: Cognitive deficits are relatively frequent in MSA and primarily affect executive functions and verbal memory. Future comparative studies including Parkinson dementia, Lewy body disease, and MSA cases with and without OH are required to elucidate disease-specific cognitive profiles in these synucleinopathies and to examine the influence of cardiovascular autonomic dysfunction on cognitive function in MSA.

Introduction

Multiple system atrophy (MSA) is a rare neurodegenerative disorder clinically defined by severe autonomic failure, parkinsonism, and/or cerebellar ataxia.[1,2] Neuropathologically, glial cytoplasmic inclusions (GCIs) are found particularly in the striatonigral and olivopontocerebellar systems of MSA brains.[3] According to the predominant motor phenotype, MSA can be subclassified into a parkinsonian (MSA-P) and a cerebellar variant (MSA-C).[4] In recent years, nonmotor and nonautonomic symptoms have been increasingly recognized in MSA.[5,6] The degree of cognitive impairment in MSA patients ranges from normal to moderate decline and affects memory, executive, attentional, and visuospatial functions.[7–9] Accordingly, cognitive impairment has been reported in up to 37 % of neuropathologically proven MSA cases.[9–11] In contrast, severe cognitive decline that significantly disrupts daily living is uncommon in MSA; hence, dementia has been regarded as a nonsupporting feature in the current diagnostic criteria.[4] Comparative studies on cognitive impairment in both motor subtypes

have been conducted but reported heterogeneous results.[8,12–17] Kawai and colleagues observed a multidomain cognitive decline in MSA-P but not in MSA-C.[12] Another study reported a more pronounced executive and verbal memory dysfunction in MSA-C,[14] and a third found comparable cognitive profiles in both variants.[8] Cognitive deficits in MSA may be explained by underlying degeneration of basal ganglia and to secondarily disrupted striato-pallido-thalamocortical circuits.[7,18] In patients with cerebellar disorders, deficits in executive, memory, visuospatial, and language domains have been shown, thus indicating that the cerebellum plays an important role in higher order functions,[19] and further support the concept of "subcortical dementia." Beyond that, it is also suggested that with disease progression a primary cortical involvement becomes apparent.[9,20,21]

It is well established that anxiety and depression are both frequently found in MSA patients[22–25] and possibly influence cognitive function. Additionally, orthostatic hypotension (OH) may also be associated with cognitive impairment in MSA, although the underlying mechanisms have not been established yet.[26,27]

A recent study identified Dementia with Lewy bodies (DLB) as the most common misdiagnosis of MSA during life,[9] highlighting the need for better characterization of MSA-specific patterns of cognitive dysfunction. Previous reports on cognitive and behavioral features in MSA patients have produced inconsistent results, in part due to different definitions of cognitive impairment, nonstandardized assessment methods or lack of standardized norms. Therefore, the objective of this study was the evaluation of cognitive and behavioral features in patients with MSA by the use of a standardized and validated neuropsychological test battery with age- and education-specific norms. Moreover, we aimed to assess group differences between MSA subtypes as well as between patients with and without OH.

Materials and Methods

Subjects

We retrospectively reviewed the medical records of 54 MSA patients referred to the movement disorder unit at the Department of Neurology, Medical University of Innsbruck, between January 2000 and May 2018. Patients were clinically diagnosed by movement disorder specialists with possible or probable MSA-P or MSA-C according to revised Gilman criteria.[4] At time of neuropsychological examination, 18.5% of patients fulfilled the diagnostic criteria of possible MSA. However, all these patients fulfilled the criteria for probable MSA 24 months later at last available follow-up and therefore were included in the final analysis. The following demographic and clinical information were abstracted from medical records: gender, education level, age at symptom onset and neuropsychological examination, subjective response to levodopa, disease duration, global disability (Unified Multiple System Atrophy Rating Scale UMSARS part IV,[28] Hoehn and Yahr (H&Y) stage[29]), and medication. Median disease duration was selected to define a cut-off value for comparison of the cognitive profile of early versus late disease course. Additionally, results from head-up-tilt or, if not available, from standing test, were abstracted to analyze the effect of orthostatic hypotension and supine hypertension on cognition. Age of symptom onset was defined as occurrence of either motor symptoms (parkinsonism and/or cerebellar symptoms) or autonomic dysfunction (symptoms of OH and/or urogenital features). OH was defined as a systolic blood pressure (BP) drop of at least 20 mmHg and/or a reduction in diastolic blood pressure of at least 10 mmHg within 3 min of standing or head-up tilt.[30,31] Neurogenic supine hypertension (SH) was defined as systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg in supine position.[32] Moreover, mean standing BP after 3 min of head-up tilt or standing test, mean BP change after 3 min of head-up tilt or standing test, and mean supine BP were calculated. Given the retrospective nature of the following study, the quality of medical records was inconsistent. Therefore, inadequate documentation was considered as exclusion criteria. Patients not able to read and write as well as severe psychiatric comorbidity were also excluded.

This study was approved by the Institutional Review Board of Medical University of Innsbruck and conducted in accordance with the Declaration of Helsinki.

Neuropsychological and behavioral assessment

The following standardized and validated neuropsychological test battery was applied by neuropsychologists. Test scores were obtained from medical records.

CERAD-plus battery

All participants performed the CERAD-plus battery[33,34] assessing global cognition, object naming, verbal memory (learning, recall, and recognition), constructive abilities (copying geometrical shapes), figural memory (reproduction of geometrical shapes), semantic (animals/minute) and phonological (s-words/minute) word fluency, psychomotor speed (TMT-A), and cognitive flexibility (Trail Making B/Trail Making A). TMT (B/A) ratio was calculated to diminish the influence of motor impairment on

part B providing a purer measure of executive function.[35] When patients could not finish TMT-B, a maximum score of 400 sec was assumed and entered in the database. The CERAD-plus battery provides norms adjusted for age, education, and gender, allowing the transformation of the single scales' raw scores into *z*-scores based on a large and representative standardization sample. In this study, cognitive impairment was defined as a *z*-score below −1.28, collapsing slight to severe deficits, which has the best discriminative power.[36]

DST

All subjects performed the digit span test[37] to evaluate attention span (digit span forward, DSF) and working memory (digit span backward, DSB). Performance was evaluated according to age-scaled norms.

CLOX1

The clock drawing task[38] was performed in 52 patients and was used to evaluate executive functions. The cut-off was set at ≤10.

FAB

The Frontal Assessment Battery[39] is a screening test to evaluate frontal-executive and behavioral functions composed of six subtests and a maximum possible score of 18. An age and education-specific cut-off was used (<5th percentile) to define patients that performed in the impaired range[40]. It has to be noted that data were available for 43 patients.

HADS

The Hospital Anxiety and Depression Scale was applied in 50 patients to evaluate anxiety and depression.[41] Cut-off scores for detection of anxiety or depression measured by The Hospital Anxiety and Depression Scale (HADS) were ≥11/21.[42]

Statistics

All statistical analyses were performed using SPSS (IBM SPSS Statistics, Chicago, IL, USA, Version 24). A chi-square or Fisher's exact test was used to calculate differences in categorical data as appropriate. For analyses of continuous variables and demographic data, Mann–Whitney *U* test or *t*-test was conducted according to the distribution of data. The significance level was set at $P < 0.05$. Pearson' s correlation test was used to evaluate the relationship between raw scores of the CERAD-plus battery, DST, FAB, CLOX1, and clinical variables, including disease duration, age of onset, UMSARS part IV, Hoehn and Yahr, orthostatic hypotension, supine hypertension, mean standing BP, mean supine BP, mean BP change, anticholinergics, depression, and anxiety. Due to multiple testing, *P* values were corrected by the Bonferroni method.

Results

Demographic and clinical data

In this study we enrolled 54 patients of which 55.6% ($n = 30$) were men. Thirty-nine (72.2%) patients predominantly had parkinsonian symptoms (MSA-P), and 15 (27.8%) mainly cerebellar features (MSA-C). Average age of disease onset was 60 years without any significant difference between MSA-P and MSA-C patients ($P = 0.827$). 81.5% ($n = 44$) fulfilled diagnostic criteria for probable MSA. The mean disease duration between disease onset and neuropsychological assessment was 4 years (±2.9). Patients were educated on average for 10 years, which was comparable between MSA-P and MSA-C ($P = 0.161$). In 57.4% of individuals, cardiovascular autonomic failure was confirmed by tilt table testing or standing test. A high proportion of MSA-P patients (76.9%) received levodopa therapy, in contrast to a minority of 13.3% in the MSA-C group ($P < 0.001$). No patient had a persistent subjective response to levodopa. Additionally, subjects were treated with antidepressants (53.7%), anticholinergics (20.4%), and hypnotic agents (22.2%). Demographic and clinical features are summarized in Table 1.

Neurocognitive assessment

Comparison of raw scores

Raw scores are summarized in detail in Table 2. MSA-C patients performed significantly worse compared to MSA-P in the FAB score ($P = 0.036$) and in phonemic verbal fluency ($P = 0.024$).

Classification according to age-, gender-, and education adjusted z-scores

Following age-, gender-, and education adjusted z-scores (CERAD-plus), global cognition (MMSE) was impaired in 35.2% ($n = 19$) of MSA cases with a substantial cognitive decline in four patients (7.4%). Deficits in verbal memory (learning, recall, and recognition) were noted in up to 37.7% ($n = 20$) as demonstrated by word list learning. 23.1% ($n = 12$) of patients showed deficits in reproduction of geometrical shapes, evaluating figural memory. Attention span and working memory were widely maintained and reduced in only 11.1% ($n = 6$) and 14.8%

Table 1. Demographic and clinical characteristics of patients with multiple system atrophy.

	Overall	MSA-P	MSA-C	*P*
n (%)	54 (100)	39 (72.2)	15 (27.8)	
Gender				
Male, *n* (%)	30 (55.6)	20 (51.3)	10 (66.7)	NS
Diagnostic certainty				
Possible, *n* (%)	10 (18.5)	6 (15.4)	4 (26.7)	NS
Probable, *n* (%)	44 (81.5)	33 (84.6)	11 (73.3)	NS
Clinical features				
Education in years, mean (SD)	10.2 (2.8)	9.9 (2.6)	11.0 (3.0)	NS
Age symptom onset, mean (SD)	59.8 (7.5)	59.7 (7.6)	60.1 (7.6)	NS
Age at neuropsychological assessment, mean (SD)	63.9 (6.5)	64.2 (6.2)	63.3 (7.5)	NS
UMSARS part IV, mean (SD)	3.2 (1.0)	3.3 (1.0)	3.1 (1.0)	NS
H&Y, mean (SD)	3.3 (1.0)	3.3 (1.0)	3.4 (1.0)	NS
Orthostatic hypotension, *n* (%)	31 (57.4)	25 (64.1)	6 (40.0)	NS
Supine hypertension, *n* (%)	23 (42.6)	18 (46.2)	5 (33.3)	NS
Medication				
Levodopa, *n* (%)	32 (59.3)	30 (76.9)	2 (13.3)	<0.001
Anticholinergics, *n* (%)	11 (20.4)	10 (25.6)	1 (6.7)	NS
Antidepressants, *n* (%)	29 (53.7)	21 (53.8)	8 (53.3)	NS
Hypnotic agents, *n* (%)	12 (22.2)	8 (20.5)	4 (26.7)	NS

MSA-C, multiple system atrophy cerebellar subtype; MSA-P, multiple system atrophy Parkinsonism subtype; UMSARS, Unified Multiple System Atrophy Rating Scale part IV; H&Y, Hoehn and Yahr; SD, standard deviation.
P-values are shown in domains with significant group differences (ns not significant).

($n = 8$), respectively. Results of the FAB indicated executive dysfunction in 41.9% ($n = 18/43$). Semantic (animals/minute) and phonological (s-words/minute) verbal fluency exhibited a decrease in 24.1% ($n = 13$) and 21.3% ($n = 10$), respectively. Psychomotor speed was impaired in 32.7% ($n = 16$) and cognitive flexibility in 21.3% ($n = 10$). Difficulties in the clock drawing test was noted in 23.1% ($n = 12$) and in object naming in 20.4% ($n = 11$) of patients. Constructional praxis was preserved in most cases (impaired in 13.2%; $n = 7$).

Comparison MSA-C and MSA-P subtype

Interestingly, MSA-C patients showed impairment in the FAB battery more frequently than MSA-P (80% vs. 30%, $P = 0.003$). Figure 1 shows the proportion of MSA-C and MSA-P patients scoring in the impaired range. Comparison of raw scores yielded also a significant difference in phonemic word fluency, which, however, was not found in age-scaled norms. In addition, to compare the cognitive profile of early versus late disease course a cut-off value of 3 years has been selected. Adjusted for age, gender, and education a significant difference was only present for global cognition (defined as MMSE), which was impaired in 21% of patients with short disease duration compared to 50% of patients with disease duration over three years ($P = 0.045$). Therefore, with exception of global cognition status, deficits were already present in early stage of disease and no significant difference has been found between MSA-P and MSA-C.

Comparison OH+ and OH−

The neuropsychological profile (raw scores and z scores) of patients with preserved blood pressure regulation (without orthostatic hypotension and supine hypertension (OH−/SH−) was similar to patients with orthostatic hypotension and with/without supine hypertension (OH+/SH−, OH+/SH+) (Table 2 and Fig. 2).

Assessment of anxiety and depression

Average score of HADS-D was 7.6 (±4.2) for anxiety and 7.4 (±4.0) for depression. Assessment of anxiety and depression showed an increase in 30% of patients (HADS-D anxiety 22% $n = 11$, HADS-D depression 28% $n = 14$). No differences were observed between MSA-P and MSA-C or OH + and OH−.

Cognitive impairment and clinical variables

Correlation analyses indicated that UMSARS part IV and H&Y were inversely correlated with the following neuropsychological subtests: MMSE ($r = -0.429$, $P = 0.001$; $r = -0.409$, $P = 0.002$) and semantic verbal fluency ($r = -0.493$, $P = 0.001$, $r = -0.508$, $P = 0.001$). Age of onset correlated positively with Trail making test A ($r = 0.475$, $P = 0.001$). We found no significant association between cognitive deficits and depression, anxiety, anticholinergics, mean standing BP, mean BP change, mean supine BP, the presence of OH (see Table 2) or SH.

Discussion

In the last decade, awareness of cognitive dysfunction and neuropsychiatric features as non-motor features in MSA has increased. Several studies found a broad spectrum of deficits in cognition and behavior in MSA.[7] However,

Table 2. Neuropsychological test battery (raw scores) and between-group differences for MSA-P vs. MSA-C and OH + vs. OH−.

	Overall	MSA-P	MSA-C	*P*	OH+	OH−	*P*
Global cognitive status, mean (SD)							
MMSE	27.6 (2.4)	27.6 (2.6)	27.7 (1.9)	NS	27.4 (2.8)	28.0 (1.8)	NS
Memory function, mean (SD)							
CERAD word list							
Wordlist learning sum	17.9 (3.9)	17.6 (3.8)	18.7 (3.9)	NS	17.6 (3.9)	18.3 (3.7)	NS
Wordlist delayed recall	5.8 (2.0)	5.7 (1.8)	6.1 (2.5)	NS	5.7 (2.0)	6.0 (2.0)	NS
Wordlist savings (%)	78.3 (22.0)	77.6 (23.2)	80.4 (19.2)	NS	76.1 (24.7)	81.4 (17.8)	NS
Wordlist recognition	9.1 (1.1)	9.1 (1.2)	9.0 (1.1)	NS	9.1 (1.2)	9.1 (1.1)	NS
False positive	0.3 (0.7)	0.3 (0.6)	0.3 (0.8)	NS	0.4 (0.8)	0.2 (0.5)	NS
CERAD constructional praxis recall							
Constructional praxis recall	8.4 (2.3)	8.5 (2.2)	8.0 (2.4)	NS	8.1 (1.9)	8.8 (2.7)	NS
Constructional praxis savings (%)	80.2 (22.5)	82.2 (20.0)	75.1 (28.2)	NS	77.6 (19.1)	83.7 (26.3)	NS
Executive function, mean (SD)							
CERAD verbal fluency							
Animal naming	18.0 (6.1)	18.6 (6.6)	16.3) (4.4)	NS	17.7 (6.6)	18.4 (5.5)	NS
S-words	10.4 (4.4)	11.3 (4.5)	8.2 (3.4)	0.024	10.8 (4.6)	9.9 (4.2)	NS
Trail Making A	58.3 (23.1)	54.7 (21.7)	66.3 (24.8)	NS	57.2 (23.6)	59.5 (23.0)	NS
Trail Making B/A	3.6 (4.1)	3.9 (4.8)	2.8 (1.1)	NS	4.3 (5.2)	2.6 (0.6)	NS
CLOX 1	11.4 (1.9)	11.5 (1.9)	11.1 (2.0)	NS	11.4 (1.8)	11.4 (2.0)	NS
FAB	14.7 (2.7)	15.2 (2.7)	13.3 (2.6)	0.036	14.8 (2.9)	14.5 (2.4)	NS
Attention span, mean (SD)							
Digit span forwards	6.5 (1.8)	6.7 (1.8)	6.1 (1.5)	NS	6.8 (2.0)	6.2 (1.4)	NS
Working memory, mean (SD)							
Digit span backwards	5.1 (1.3)	5.3 (1.2)	4.6 (1.3)	NS	5.1 (1.3)	5.0 (1.2)	NS
Language functions, mean (SD)							
Boston Naming Test	13.8 (1.3)	13.7 (1.4)	14.1 (1.2)	NS	13.8 (1.2)	13.8 (1.5)	NS
Visuospatial functions, mean (SD)							
Constructional praxis copy	10.3 (0.9)	10.3 (1.0)	10.3 (0.8)	NS	10.3 (1.1)	10.3 (0.8)	NS
Mood and behavior, mean (SD)							
HADS-D anxiety	7.6 (4.2)	7.8 (4.3)	7.1 (3.9)	NS	8.0 (4.5)	7.0 (3.7)	NS
HADS-D depression	7.4 (4.0)	7.7 (3.8)	6.8 (4.5)	NS	8.2 (4.2)	6.2 (3.6)	NS

MMSE, The Mini-Mental State Examination; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease; CLOX, The clock drawing task; FAB, The Frontal Assessment Battery; HADS-D, The Hospital Anxiety and Depression Scale; MSA-C, multiple system atrophy cerebellar subtype; MSA-P, multiple system atrophy parkinsonism subtype; OH+, with orthostatic hypotension; OH−, without orthostatic hypotension; SD, standard deviation.

cognitive patterns in MSA remain poorly characterized, as differences in definitions, methods, and study designs have led to inconsistent results.[7]

The present cohort showed a relatively good performance of general cognitive ability (as indicated by MMSE) that was only mildly to moderately impaired in 35% of patients. These findings are supported by previous studies that have shown mild cognitive deficits in MSA patients.[43–47] In accordance with data from postmortem studies,[48–51] a more pronounced cognitive impairment, with MMSE ≤24 points, was present in 7.4% of cases, indicating dementia in a small group of patients. Nonetheless, it has to be mentioned that the sensitivity of MMSE to detect executive dysfunction and language deficits remains controversial.[52] Therefore, in this study a comprehensive neuropsychological test battery including the CERAD-plus test battery,[53] the digit span test,[37] the Frontal Assessment Battery,[54] the clock drawing task,[38] and the Hospital Anxiety and Depression Scale[42] were used. Our study shows that approximately 40% of patients had a documented slight to moderate cognitive impairment in at least one domain, wherein executive functions were most often affected in line with previous findings.[8,46,54–56] In detail, executive dysfunction in MSA comprised deficits in semantic and phonemic verbal fluency[12,56–58] as well as processing speed, cognitive flexibility, and working memory,[14,16,45] being impaired in up to 42% in this cohort. Whereas verbal memory was affected in a similar percentage, which is in agreement with previous reports,[8,43,56] figural memory and attention span were

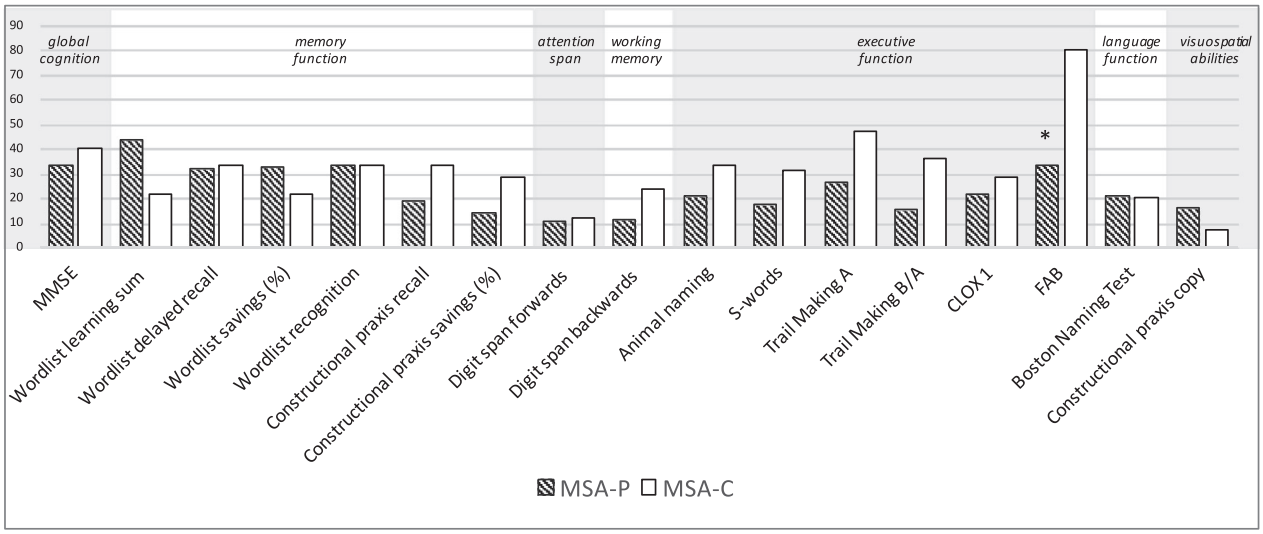

Figure 1. Percentage of multiple system atrophy (MSA) patients with cognitive impairment for MSA subtypes (MSA-C vs. MSA-P). The proportion of patients scoring in the impaired range in the FAB battery was significant higher in patients with MSA-C compared to MSA-P (80% vs. 30%, $P = 0.003$). No significant difference was found in the other subtests. For definition of cut-off score see method section. MSA-C, multiple system atrophy cerebellar subtype; MSA-P, multiple system atrophy parkinsonism subtype; MMSE, The Mini-Mental State Examination; CLOX, The clock drawing task; FAB, The Frontal Assessment Battery; $*P < 0.05$.

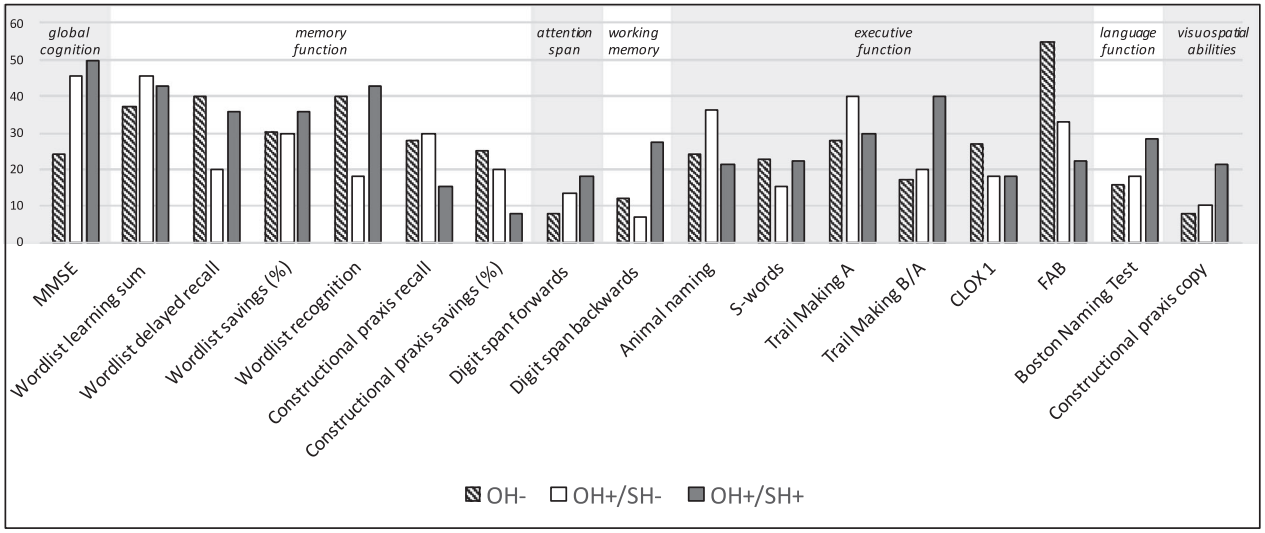

Figure 2. Percentage of multiple system atrophy (MSA) patients with cognitive impairment for patients with and without preserved blood pressure regulation (OH− vs. OH+/SH− vs. OH+/SH+). The cognitive profile was comparable in patients with and without cardiovascular autonomic failure. For definition of cut-off score see method section. MSA-C, multiple system atrophy cerebellar subtype; MSA-P, multiple system atrophy parkinsonism subtype; OH, orthostatic hypotension; MMSE, The Mini-Mental State Examination; CLOX, The clock drawing task; FAB, The Frontal Assessment Battery; SH, supine hypertension.

widely preserved. With regards to visuospatial functions, previous studies reported conflicting results, with some suggesting preserved function[43,59] and others reporting difficulties in this domain.[12,45,56] In this study, only a small proportion of MSA patients showed impaired visuospatial function. Confirming previous reports, 20% of MSA patients showed deficits in object naming.[45,55,60] The following results emphasize that patients with MSA and DLB show a similar pattern of neurocognitive deficits, which still remains a diagnostic dilemma. A comparison of cognitive profile in patients with synucleinopathies has been performed, which has shown that executive functions, memory, and visuospatial functions were impaired in both groups.[45] Nonetheless, the

level of cognitive impairment was severe in patients with DLB and intermediate in patients with MSA,[45] which was also confirmed in the following study. Nonetheless, the cardinal characteristics of the natural history of disease in patients with DLB remain fluctuations in cognition and the presence of visual hallucinations.[7] Although this was beyond the scope of the following study and therefore has not been assessed, these major distinctive features are usually not present in patients with MSA.[7]

So far, few studies have addressed the possible differences between patients with predominant cerebellar or parkinsonian presentation,[12–17] and the focus has been mainly on MSA-P patients. In this study, a comparison of raw scores revealed lower performance of MSA-C patients than MSA-P patients in a screening of executive functions and in phonological verbal fluency. After adjustment for age, education, and gender, a greater proportion of patients with MSA-C compared to MSA-P patients were impaired on the FAB. In concordance with these results, cognitive deficits in executive function tests[8,14,15,55] including verbal fluency[14,43] and TMT -B[14] have been reported in MSA-C. Nonetheless, there are conflicting results and heterogeneous data have been published regarding the differences between MSA-C and MSA-P. Previous studies suggested a comparable performance,[8,17,45] a more prominent decline of executive function and verbal memory in MSA-C[14,15,26,55] or a more pronounced cognitive dysfunction in MSA-P.[12,13]

Although the neuropathological underpinnings of cognitive deficits in MSA remain incompletely understood, it is assumed that due to degeneration of subcortical structures, circuits from the frontal cortex to basal ganglia and thalamus are disrupted,[7] leading to cognitive deficits.[61] While deafferentation of subcortical structures impact the cognitive decline to a large extent, there is increasing evidence that with disease progression intrinsic cortical pathology becomes more apparent.[7] Recently, neuropathological studies reported an association of neuronal cytoplasmatic inclusions in neocortex or limbic regions and cognitive impairment in MSA.[9,20,21] Additionally, imaging data also suggest that beside atrophy of subcortical regions, thinning of neocortices may contribute to cognitive impairment.[61–63] In this study, MSA-C patients showed to be more frequently impaired in a screening of executive function, possibly resulting from disruption of cerebrocerebellar circuits. This phenomenon has also been observed in other cerebellar disorders, as the cerebellum functionally modulates higher cognition. Typical symptoms encompass deficits in executive function, language, spatial cognition, affect regulation and they are subsumed under the term "cerebellar cognitive affective syndrome."[19]

Furthermore, it has to be noted that cognition performance may be related to a number of factors such as mood disturbances[26] or blood pressure fluctuations.[27] In this cohort, symptoms of depression and anxiety were present in 28% and 22% of MSA patients, respectively. These results are consistent with previous findings reporting a prevalence for depression ranging from 20 to 80%,[8,9,17,22,44,45] and for anxiety up to 40%.[24,45] As reported previously,[8,12] we did not find any difference in depression and anxiety between the two MSA variants and no significant correlations were observed between cognitive impairment and mood. Thus, cognitive impairments observed in this study cannot be attributed to depressive or anxiety disorders.

This study also evaluated the impact of OH on cognition. Studies in PD suggested that OH is associated with cognitive impairment[64–67] and may underlie a posture-mediated exacerbation.[68,69] To our knowledge, only few studies have addressed this issue in MSA with controversial findings.[16,46,51,70] In this study, we could not identify any difference in cognition in MSA patients with and without OH, and we did not find any correlation between cognitive impairment and cardiovascular dysfunction. Hence, it may be speculated that the influence of cardiovascular autonomic failure on cognition is rather acute and reversible. Nonetheless, due to the retrospective design and incomplete information on duration of orthostatic symptoms in each patient, we could not investigate eventual time-dependent cumulative effects to this end.

One of the main strengths of this study represents the large sample size of MSA patients that has been recruited from one single center. Moreover, the neuropsychological assessment performed in this study included the CERAD-plus battery, which allows a standardized assessment of various cognitive functions, an evaluation according to age-, gender-, and education-matched norms and which may be easily used for comparison purposes in other study cohorts. Moreover, to our knowledge, only CERAD subtests have occasionally been applied in previous studies in MSA so far. Nonetheless, some methodological issues, which may have an influence on our conclusions, have to be acknowledged and merit discussion. First, the risk of a selection bias limits this study since, following second consensus criteria, patients with severe cognitive deficits may have been excluded. Moreover, patients were clinically diagnosed and neuropathological diagnosis is not available, possibly leading to a misclassification of a subgroup of patients. Second, given the retrospective nature of the study, no standardized study protocol was available and therefore, a reporting bias cannot be excluded. Third, neuropsychological tests were performed in the sitting position, where patients usually do not experience OH symptoms. Thus, posture-mediated changes were not assessed.

Conclusion

Despite these inevitable shortcomings, this study reaffirms previous findings of a wide spectrum of cognitive and behavioral impairments in MSA. Slight to moderate deficits frequently involve executive functions and verbal memory, whereas global cognitive ability (as indicated by the MMSE screening) remains intact in the majority of cases. Further comparative studies including PDD (Parkinson dementia), LBD (lewy body disease) and MSA cases and a standardized neuropsychological test battery are required to improve diagnosis in clinical practice.

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Conflict of Interest

Sabine Eschlböck: nothing to declare. Margarete Delazer: nothing to declare. Florian Krismer: Research Grant MSA coalition. Thomas Bodner: nothing to declare. Alessandra Fanciulli: nothing to declare. Beatrice Heim: nothing to declare. Antonio Heras Garvin: nothing to declare. Christine Kaindlstorfer: nothing to declare. Elfriede Karner: nothing to declare. Katherina Mair: nothing to declare. Christoph Rabensteiner: nothing to declare. Cecilia Raccagni: Travel Grant MSA coalition. Klaus Seppi: Klaus Seppi reports personal fees from Teva, UCB, Lundbeck, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal and Abbvie, honoraria from the International Parkinson and Movement Disorders Society, research grants from FWF Austrian Science Fund, Michael J. Fox Foundation, and International Parkinson and Movement Disorder Society, outside the submitted work. Werner Poewe: Werner Poewe has received consultancy and lecture fees in relation to clinical drug programs for PD from AbbVie, AstraZeneca, BIAL, Biogen, Biohaven, Britannia, Grünenthal, Intec, Ipsen, Lundbeck, Novartis, Neuroderm, Orion Pharma, Oxford Biomedica, Prexton, Regenera, Roche, Sunovion, Sun Pharma, Takeda, Teva, UCB and Zambon. Royalties: Thieme, Wiley Blackwell, Oxford University Press and Cambridge University Press. Gregor K. Wenning: Gregor Wenning has received consultancy and lecture fees in relation to clinical drug programs for MSA from AbbVie, AstraZeneca, Biogen, Lundbeck, Novartis, Takeda, UCB and Zambon.

Author Contributions

Sabine Eschlböck: Execution of the project, statistical analysis and interpretation of data, writing of the first manuscript. Margarete Delazer: Execution of neuropsychological test battery, execution of the project, statistical analysis and interpretation of data, critical revision of the manuscript. Florian Krismer: Statistical analysis and interpretation of data, critical revision of the manuscript, contribution of patients. Thomas Bodner: Execution of neuropsychological test battery, critical revision of the manuscript. Alessandra Fanciulli: Interpretation of data, critical revision of the manuscript, contribution of patients. Beatrice Heim, Antonio Heras Garvin, Katherina Mair: Conception of the study, Critical revision of the manuscript. Elfriede Karner: Execution of neuropsychological test battery, critical revision of the manuscript. Christoph Rabensteiner: Execution of the project, critical revision of the manuscript. Cecilia Raccagni: Critical revision of the manuscript, contribution of patients. Klaus Seppi, Christine Kaindlstorfer, Werner Poewe: Conception of the study, Critical revision of the manuscript, contribution of patients. Gregor K. Wenning: Conception and organization of the project, statistical analysis and interpretation of data, critical revision of the manuscript.

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