Cognitive and Sleep Features of Multiple System Atrophy: Review and Prospective Study

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Key Words

Cognitive neurology · Dementia · Neuropsychology · Parkinsonism · Sleep disorders

Abstract

Background: The profile and degree of cognitive impairment in Multiple System Atrophy (MSA) and the impact of sleep disorders, REM sleep behavior disorder (RBD) in particular, in parkinsonism-related cognitive deficits are currently being debated. **Summary:** We reviewed the cognitive, affective and sleep findings in MSA and also carried out a longitudinal investigation of 10 MSA patients. At the first evaluation, 3 patients showed isolated cognitive deficits. After a mean of 16 months, these patients remained unchanged, while 1 patient worsened from a normal condition. No significant differences emerged when the cognitive, affective and video-polysomnographic findings of MSA-P and MSA-C were compared. Depression was present in half of the patients, although it did not influence their cognitive performance. Comparisons between the first and second evaluation data showed significant worsening in visual attention and in ADL/IADL and UMSARS. **Key Messages:** Isolated cognitive deficits are evidenced in a minority of MSA patients

with the absence of a clear-cut diagnosis of dementia in the early stages of the disease. Attention and executive functions are often impaired. This study with a short follow-up period showed that RBD, although present in almost all patients affected by MSA, does not appear a clear early marker of cognitive impairment. Future longer-term studies with a larger patient sample are thus encouraged.

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Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset, progressive neurodegenerative disease characterized clinically by parkinsonism, cerebellar ataxia, autonomic failure, and corticospinal signs with poor or no response to levodopa, and pathologically by cell loss, gliosis, and glial cytoplasmic inclusions in several neural cell systems (striatonigral, olivopontocerebellar, autonomic) [1].

The analysis of cognitive functions in MSA has gained interest and the related profile and degree of cognitive impairment along the course of the disease is yet a subject of debate. The presence of dementia, particularly at onset,

is a not supporting feature to the diagnosis of MSA. We reviewed literature about this topic and matched it with sleep disorders data in MSA. In fact, sleep disorders, and REM sleep behavior disorder (RBD) in particular, have often been involved in parkinsonism-related cognitive deficits [3–5]. We also investigated longitudinally cognitive functions and sleep characteristics in a group of probable MSA patients.

Review on Cognitive Impairment in MSA

Cognitive Deficits

MSA patients display a milder degree of cognitive impairment with respect to corticobasal degeneration, progressive supranuclear palsy (PSP) and Lewy body dementia (LBD). With respect to PD without dementia, not definite differences seem to emerge [6–15].

Heterogeneous cognitive dysfunctions in MSA have been reported by many authors [6–8, 14–33]. The executive functions are described as the most frequent impaired abilities but other cognitive domains that can be involved are memory, visuospatial, and constructional functions. Brown et al. [7] in a large cohort of MSA patients found that approximately two-thirds of subjects showed no significant cognitive impairment. In a single cognitive domain, impairment was found in 28.6%, while in two or more domains, it was present in 13.5% and global cognitive impairment was observed in 11–32% of patients. Cognitive impairment was predicted by factors like greater motor disability, educated for less than 10 years, male gender, and the presence of cardiovascular dysautonomia. It is however noteworthy that in the cognitive impaired group, the diagnosis was further pathologically confirmed in 64.4% of cases, while a final diagnosis of PSP, LBD or amyotrophic lateral sclerosis was ascertained in the remaining cases; in the unimpaired group, the diagnosis of MSA was confirmed in 94.6% of cases.

Dementia was recently reported by some authors [16, 17, 22, 23, 34, 35]. Wenning et al. [34] in a retrospective, pathologically confirmed case study, showed that dementia was detected in 15.7% of a sample of 38 MSA cases and in none of them dementia onset was reported within the first 5 years. In another study [35], 14% of a sample of 83 pathologically confirmed cases were identified as demented. Finally, in a recent cross-sectional multicenter study, Siri et al. [17] did not find general cognitive decline in the first 5.7 years of the disease but a selective impairment in executive functions.

Evolution of Cognitive Deficits

Soliveri et al. [6] investigated a group of 14 patients affected by striatonigral degeneration-type of MSA (SND), according to Quinn's criteria [36]. At the first evaluation, the MSA patients showed a significant deficit in a test of verbal fluency when compared with a group of PD patients. After a mean of 21 months follow-up, patients did significantly worse on a visual search test. No patients were clearly demented at either evaluation. Lyoo et al. [25], analyzing the progression of MSA by PET and neuropsychological examination in MSA patients with different disease duration, found that patients with a shorter disease duration showed executive and verbal memory dysfunctions, while patients with longer disease duration had multiple-domain cognitive impairment, including visuospatial deficits.

Difference of Cognitive Deficits between MSA-P and -C

Kawai et al. [24] compared 21 MSA-P with 14 MSA-C patients. In respect to controls, the MSA-P patients showed involvement of visuospatial and constructional function, verbal fluency, and executive functions, while the MSA-C patients were impaired only in visuospatial and constructional functions with a milder degree of involvement compared with MSA-P patients. These data suggest a more severe and widespread impairment in MSA-P patients, despite similar disease duration. Other studies [8, 9, 15] obtained heterogeneous and even conflicting data. Bak et al. [9], in fact, did not find visuospatial impairment in a group of MSA-P patients of long disease duration and evidence of other cognitive domains impairment. These data are consistent with those of Robbins et al. [15] on a group of MSA-P patients and with those of Bürk et al. [26] on an MSA-C sample. On the contrary, Kao et al. [8] confirmed the presence of visuospatial deficits in an MSA group of patients. Siri et al. [17] did not find significant cognitive differences between the two subtypes of MSA.

Neuropsychiatric Symptoms

Kao et al. [8] described depression in 50% of patients of a group of MSA subjects, anxiety in 33.3% and disinhibition in 10%. Schrag et al. [20] confirmed these data, while Kawai et al. [24] and Brown et al. [7] found a smaller prevalence of depression (about 21–22%) and Chang et al. [23] confirmed a significant presence of anxiety in a group of MSA-C patients. Balas et al. [19] also made the analysis of the impact of mood, anxiety and depression, on cognitive functions of an MSA group of subjects com-

pared with the controls and PD patients. The MSA-P and PD patients had significant greater state anxiety, trait anxiety, and depression than did controls, and the MSA-C patients had significant increased state anxiety compared to controls. These authors conclude that anxiety and depression are related to cognitive decline. Recently, Siri et al. [17] found that depression was more frequent in MSA group than in PD and it correlated with motor symptoms, but it did not show a significant influence on cognitive performances in all groups.

Pathogenetic Mechanisms of Cognitive Deficits

Kawai et al. [24] found that the severity of cognitive impairment in MSA-P patients correlated with a hypoperfusion in the dorsolateral prefrontal cortex. Frontal cortical atrophy has been detected bilaterally in MSA-C by means of a voxel-base morphometry study together with bilateral cerebellum gray matter reduction [23]. Lyoo et al. [25] found that hypometabolism started from the frontal and cerebellar regions, sparing the basal ganglia in the less-than-one-year disease-duration group, while patients with longer duration showed hypometabolism in more widespread cerebral cortical areas involving the frontal, temporal, parietal and cingulate cortices. The hypometabolism is supposed to be caused by the diffusion of glial cytoplasmic inclusions than by cortical loss, especially in the first phases of the disease. A progressive alteration of the afferent cortical inputs is also supposed to arise from the subcortical nuclei (e.g., locus coeruleus and substantia nigra), thus linking the subcortical and cortical structures.

The effect of orthostatic hypotension on cognitive function in MSA is still controversial [16, 21, 37–39]. Also, the correlation between MMSE, Frontal Assessment Battery and the values for oxygen saturation, apnea index, and apnea-hypopnea index during sleep has not been found [21].

Review on Sleep Disturbances in MSA

Sleep-Related Complaints

A clinical questionnaire-based study by Ghorayeb et al. [40] showed that 70% of MSA patients significantly complained of sleep disorders when compared to 51% of patients with PD. Sleep fragmentation was reported by 53% of patients as the most frequent complaint followed by early waking (33%) and insomnia (20%) with no significant difference in PD patients. Excessive daytime sleeping has also been reported according to Ghorayeb et

al. [41] in half of the MSA patients, while Moreno-Lopez et al. [42] has recently reported it in 28% of patients with MSA, weakly correlated with disease severity and not correlated with the amount of dopaminergic treatment.

Sleep Structure

Polysomnographic studies reported that the total sleep time and sleep efficiency reduced and wake after sleep onset increased [43–47]. Vetrugno et al. [44] found that sleep stages 1 and 2 were increased, while stages 3 and 4 decreased; however, REM sleep was normal. Plazzi et al. [46] found sleep stage percentages unchanged with respect to a whole group of MSA patients. But individual variations in sleep stage percentages were described by Nam et al. [43] in a study designed to eliminate the major confounding variables of sleep such as obstructive sleep apneas (OSA), periodic limb movements during sleep (PLMS) and the influence of anti-parkinsonian medications. These authors conclude that MSA by itself does not affect the sleep structure because even the analysis of the microstructure (i.e., sleep instability) compared with controls shows no differences in every aspect, including cycling alternating pattern (CAP rate, CAPs A and B, and non-CAP). However, this topic is still a matter of debate because Vetrugno et al. [48] had shown a significantly lower CAP rate in a group of MSA patients compared to a group of patients with primary restless legs syndrome.

Sleep-Related Respiratory Abnormalities

Nocturnal stridor and OSA have been extensively reported as the most common sleep-related breathing disorders in MSA patients [40, 41, 44, 46, 47]. The prevalence of nocturnal stridor (a strained, high-pitched, harsh respiratory sound) varies from 13% to 69% [49, 50]. In one study, stridor was more frequently detected in MSA-C than in MSA-P patients [44], but the contrary was also shown [41]. OSA ranges from 15% to 37% [44–46] and may contribute to mild O₂ desaturation occurring during sleep in MSA. However, the relationship between nocturnal respiratory abnormalities and cognitive performance has not been specifically investigated yet.

Periodic Limb Movements during Sleep

PLMS are frequently reported in polysomnographic studies on MSA [43–46, 48]. They are significantly increased respect to control [45, 46, 48], and may contribute to sleep fragmentation and reduced sleep efficiency. Restless legs syndrome, in a questionnaire-based study, occurred in 28% of patients with MSA, doubling the fre-

quency occurred in PD patients (14%) and 4 times more frequent than in the control group (7%) and unrelated to the amount of dopaminergic treatment [44].

RBD

RBD is the most common sleep-related disorder in MSA [40, 41, 44, 46, 51, 52] and may precede the development of parkinsonism by years [45, 52–54]. Current knowledge indicates that up to 81–82% of patients with idiopathic RBD develop a parkinsonian disorder [55, 56]. Ninety to 100% of MSA patients have polysomnographic-confirmed RBD, and clinical symptoms of RBD precede the onset of MSA by more than 1 year in 44% of the patients evaluated [44, 46]. Comparing RBD in MSA and PD, Iranzo et al. [57] showed that patients with MSA, compared to subjects with PD, had a higher REM sleep without atonia percentage, and, if compared with those with idiopathic RBD, an onset of RBD at a younger age with a less awareness of their abnormal sleep behaviours. Authors suggest that in MSA there could be a more severe dysfunction in the structures that modulate REM sleep. Vetrugno et al. [51] described similar pathogenetic mechanisms about the natural evolution of RBD in the so-called status dissociatus, a more complex and pervasive sleep disturbance with a sleep pattern disruption where the stages can no longer be identified.

The Prospective Study

Patients and Methods

Ten consecutive in-patients, fulfilling the criteria for probable MSA [1], were evaluated in our Neurological Department in a two-year period. All subjects gave their informed consent to the study according to the Declaration of Helsinki.

All patients underwent a detailed interview, checked with interviews of close relatives, and a general and neurological examination, including the application of the UMSARS [58]. Patients were also investigated by blood tests, cerebral MRI scans, and by means of a cardiovascular reflexes study. An extensive battery of neuropsychological tests, standardized in the Italian population, exploring global cognition and different cognitive functions was administered (table 1) [59–72]. We evaluated depression with the Beck Depression Inventory (BDI) [73] and anxiety using the State-Trait Anxiety Inventory-Form Y (STAI) [74]. An all-night video-polysomnography recording (VPSG) was acquired and sleep was scored according to the American Academy of Sleep Medicine

(AASM) criteria [75]. RBD, defined according to International Classification of Sleep Disorders [76], was checked against the video-recordings. Sleepiness was assessed by Epworth Sleepiness Scale [77].

All patients were re-evaluated (T1) in a mean of 16.1 ± 5.5 (range: 12–28) months after the initial evaluation (T0). At the second evaluation (T1), the neuropsychological assessment and video-polysomnography were repeated.

Statistical Analysis

Data were analyzed using the SPSS statistical analysis software, version 19.0. We performed a descriptive analysis of the various parameters of patients, considering the normal values of the normative data. Some variables being non-normally distributed, non-parametric tests were employed: test U of Mann-Whitney for comparison of patients' performance between groups (MSA-P versus MSA-C, no depressed versus depressed patients, shorter duration versus longer duration patients), Wilcoxon test for correlated samples for comparisons between T0 and T1 performance, Kendal Tau for correlation among cognitive performances, clinical variables and polygraphic data.

Results

Seven men and 3 women were enrolled. Six had probable cerebellar type MSA (MSA-C) (4 men) and four had probable parkinsonian type MSA (MSA-P) (3 men). The overall mean age was 57.8 ± 6.4 (range: 47–64) with a mean education of 10.7 ± 4.5 years (range: 5–17). The mean age at disease onset was 53.2 ± 7.1 (range: 43–61) and symptoms duration at T0 was 60 ± 48 months (range: 12–144). MSA-P in respect to MSA-C had a higher age (61.75 ± 0.94 vs. 55.17 ± 2.94 years), lower education (8.75 ± 2.83 vs. 12.00 ± 1.41 years) and shorter symptoms duration (27.00 ± 7.55 vs. 82.00 ± 20.64 months). Only symptoms duration is significantly different ($p = 0.03$). RBD was present in all patients with a mean age at onset of 53.4 ± 7.3 (range: 40–61).

Neuropsychological and Affective Results

At the initial evaluation (T0), 7 patients showed no cognitive deficits, while 2 patients (MSA-C) had a long-term verbal memory deficit and 1 patient (MSA-P) had deficit in visuospatial tasks (table 2). Considering the global cognitive indexes for each patient (MMSE and BMDB Final Result) and daily living activity, no patient could be stated demented. At T0, the mean values of all tests in the whole group were within normal range, while the mean values of

Table 1. Neuropsychological tests and assessment of anxiety and depression

Cognitive functions	Test
Global cognitive functions indices	MMSE (range: 0–30) (Folstein et al., 1975), MMSE corrected for age and education (range: 1.93–35.24; cut-off: <23.8) (Measso et al., 1993) Brief Mental Deterioration Battery (BBDM) with Final Result (FR) (cut-off: <0) (Gallassi et al., 1986, 2010)
Memory	Rey's 15 Words: immediate recall (range: 0–75; cut-off: <28.53); delayed recall (range: 0–15; cut-off: <4.69) (Carlesimo et al., 1996) Paired-associated Word Learning Test (range: 0–22.5; cut-off: <8.73) (De Renzi et al., 1977) Immediate Visual Memory (range: 0–22; cut-off: <13.85) (Carlesimo et al., 1996) Digit Span Forward (range: 0–9; cut-off: <3.75) (Orsini et al., 1987) Corsi Block-tapping Test (range: 0–infinite; cut-off: <3.75) (Spinnler and Tognoni, 1987) Rey-Osterrieth Complex Figure Test: delayed recall (range: 0–36; cut-off: <6.20) (Caffarra et al., 2002)
Attention	Barrage Test (time cut-off: ≥90; score cut-off: ≤9; errors cut-off: ≥2; result cut-off: >2.5) (Gallassi et al., 1986, 2002) Stroop Test (time cut-off: >27.5; errors cut-off: >7.5) (Caffarra et al., 2002) Trail Making Test (A cut-off: >93; B cut-off: >283; B-A cut-off: >187) (Giovagnoli et al., 1996)
Language	Verbal Fluency: phonemic (range: 0–infinite; cut-off: <17.35) (Carlesimo et al., 1996); semantic (range: 0–infinite; cut-off: <25) (Novelli et al., 1986)
Constructional praxis	Copy Design: simple (range: 0–12; cut-off: <7.18) (Carlesimo et al., 1996) Rey-Osterrieth Complex Figure Test: direct copy (range: 0–36; cut-off: <28) (Caffarra et al., 2002)
Visuospatial functions	Judgment of Line Orientation Test (range: 0–30; cut-off: <19) (Ferracuti et al., 2000)
Executive functions	Wisconsin Card Sorting Test (global score cut-off: <90.50; perseverations cut-off: <42.60; non-perseverative errors cut-off: <29.90; failure to maintain the set cut-off: <3) (Laiacona et al., 2000)
Abstract/concrete thinking – intelligence	Raven Coloured Progressive Matrices (range: 0–36; cut-off: <18.96) (Carlesimo et al., 1996) Analogies (range: 0–20; cut-off: <15.1) (Gallassi et al., 1986, 2002) Test di Intelligenza Breve derived from the National Adult Reading Test by Nelson H.E., 1982 (raw score cut-off: ≥19.8; total IQ cut-off: ≤93.1) (Colombo et al., 2002)
Anxiety	State and Trait Anxiety Inventory–Y (range: 20–80; cut-off: >50 T points) (Spielberger et al., 1980)
Depression	Beck Depression Inventory (range: 0–63; cut-off: >9) (Beck et al., 1961)

the scales for depression and trait anxiety were slightly increased (table 3). Slight/moderate depression was present in half of the patients, in those with isolated cognitive deficits, without a difference in respect to the type of MSA (P or C), and also in those not cognitively impaired. Comparing depressed patients with those who were not depressed, no significant differences emerged in neuropsychological tasks, clinical and sleep parameters (table 2).

Comparing MSA-P and MSA-C, although MSA-C had a longer illness duration, any significant differences were detected in neuropsychological, affective and sleep variables (table 2).

Comparison between patients who had a shorter illness duration (within two years) and those who had longer ones (≥48 months) showed that patients with a longer duration had longer RBD duration ($p = 0.03$), better per-

formance in MMSEc ($p = 0.02$) and in Rey 15 words short-term ($p = 0.04$).

At the second evaluation (T1), after a mean of 16 ± 5 months (range: 12–28) after T0, 6 patients still showed no cognitive deficits and 3 patients were cognitive unchanged, respectively showing deficits in long-term verbal memory in 2 (MSA-C) and in constructional praxis and visuospatial functions in 1 (MSA-P). Only 1 patient's (MSA-P) (patient 2) condition worsened by the development of multiple cognitive deficits from a not cognitive impaired condition (table 3). In this patient, global cognitive indexes were still unchanged and within normal limits. At T1, the mean values of all tests in the whole group were still within the normal range.

The comparisons between neuropsychological and affective evaluation at T1 and T0 (table 3) showed a signif-

Table 2. Clinical and neuropsychological data at T0 and T1

Patient/ sex	Age at examination, years (T0/T1)	Education, years	MSA type (C/P)	Symptoms duration, years (T0/T1)	Cerebral MRI	Depression (yes/no)	Impaired cognitive functions (T0/T1)
1/f	52/54	8	C	2/4	cerebellar atrophy	yes	T0/T1: long-term verbal memory
2/m	59/60	5	P	2/3	cerebellar atrophy	no	T0: no deficit T1: long-term verbal memory; short-term spatial memory; visual attention; constructional praxis; visuospatial tasks; verbal fluency
3/m	47/50	13	C	2/4	cerebellar atrophy	yes	T0/T1: long-term verbal memory
4/m	64/65	8	P	2/3	normal	yes	T0/T1: no deficit
5/m	62/63	13	C	13/15	normal	yes	T0/T1: no deficit
6/m	48/49	13	C	6/7	normal	no	T0/T1: no deficit
7/m	62/63	17	P	1/2	cerebellar atrophy	no	T0/T1: no deficit
8/f	63/64	5	P	5/6	bilateral putaminal atrophy	yes	T0/T1: visuospatial tasks
9/m	58/59	17	C	12/13	normal	no	T0/T1: no deficit
10/f	64/65	8	C	4/5	normal	no	T0/T1: no deficit

icant worsening in two tests of attention: Barrage Test (score), and Trail Making Test (A). A comparison between functional autonomy and motor performances scales disclosed a significant worsening in ADL, IADL and UMSARS (table 3).

A significant positive correlation was found between the duration of MSA and RBD ($p = 0.004$) without any other correlations of each with the neuropsychological, affective results or sleep variables. IADL negative correlated with UMSARS ($p = 0.002$).

Findings on VPSG

No significant differences were found comparing T1 and T0 all VPSG parameters. Nevertheless, the following findings were detected (table 4):

Sleep Structure. Sleep efficiency was reduced (n.v. >85%) and REM latency increased (n.v. 60–90 min). Sleep structure was characterized by a slight increase of NREM sleep stages 1–2 (n.v. 45–55%).

Sleep-Related Complaints. Eighty percent of patients complained about sleep fragmentation at T0 and T1. Excessive daytime sleepiness was not referred to by patients and Epworth Sleepiness Scale was within normal limits in all patients.

Respiratory Abnormalities. Snoring was detected in 3 out of 10 patients and paradoxical breathing in 6 out of 10. Only in 2 patients, the apnea index was higher than 10

compatible with a diagnosis of OSAS. Stridor was detected in 7 out of 10 patients. For the whole group of patients, mean SaO_2 throughout sleep remained at 93%, with the lowest mean values at 89%.

PLMS. PLMS were present in all patients and 9 out of 10 patients showed PLMS index >10.

RBD. All patients had a history of RBD that preceded the onset of the disease in 6 out of 10 (range: 1–3 years, respect the onset of the disease), coincided with the onset in 2 and followed in 2 (4 and 7 years after the onset). All patients showed continuous EMG activity and repetitive motor unit potential discharges in the submental mylohyoid muscle while awake and when asleep, with phasic or tonic increase during REM sleep. RBD in the form of complex motor behaviors such as limb and body jerks or complex vigorous movements was recorded in 9 out of 10 patients.

Discussion

Neuropsychological and Affective Findings

At the first evaluation, the majority of our ten patients did not show any cognitive deficits, while only three had selective deficits (two patients in long-term verbal memory and one in visuo-spatial tasks). However, the clinical, behavioral and functional autonomy data did not indi-

Table 3. Neuropsychological, affective and functional evaluation (mean $\pm$ SD)

Test	T0	T1
MMSE	28.10 $\pm$ 2.07	28.26 $\pm$ 1.73
Brief mental deterioration battery final result	2.23 $\pm$ 0.93	2.46 $\pm$ 1.02
Rey's 15 Words		
Immediate recall	45.4 $\pm$ 10.64	47.42 $\pm$ 10.28
Delayed recall	9.08 $\pm$ 3.06	9.82 $\pm$ 3.59
Barrage Test		
Time	56.4 $\pm$ 24.2	61 $\pm$ 32.5
Score	12.2 $\pm$ 1.03	10.4 $\pm$ 1.77*
Errors	0.1 $\pm$ 0.31	0.3 $\pm$ 0.67
Result	-0.22 $\pm$ 0.88	0.3 $\pm$ 1.82
Copy Design simple	11.17 $\pm$ 1.04	9.8 $\pm$ 2.89
Immediate Visual Memory	20.3 $\pm$ 2.03	20.8 $\pm$ 1.29
Analogies	18.4 $\pm$ 1.32	18.6 $\pm$ 2.02
Verbal Fluency		
Phonemic	30.29 $\pm$ 8.05	26.12 $\pm$ 7.35
Semantic	48.1 $\pm$ 6.38	44.2 $\pm$ 7.33
Stroop Test		
Time	16.16 $\pm$ 7.4	23.34 $\pm$ 28.03
Errors	-0.4 $\pm$ 0.68	0.28 $\pm$ 1.5
Rey-Osterrieth Complex Figure Test		
Direct copy	33.3 $\pm$ 6.38	29.42 $\pm$ 9.71
Delayed recall	17.67 $\pm$ 3.97	16.57 $\pm$ 5.63
Digit Span Forward	6.28 $\pm$ 1.18	6.18 $\pm$ 1.08
Corsi Block-tapping Test	5.96 $\pm$ 1.04	5.56 $\pm$ 1.19
Trail Making Test		
A	35.5 $\pm$ 17.87	60.75 $\pm$ 43.82**
B	62.45 $\pm$ 48.17	93.15 $\pm$ 76.7
B-A	27 $\pm$ 41.04	31.85 $\pm$ 35.85
Paired-associated word learning test	13.22 $\pm$ 5.65	12.7 $\pm$ 4.37
Judgment of line orientation test	26 $\pm$ 5.22	25.30 $\pm$ 4.99
Raven colored progressive matrices	31.16 $\pm$ 4.19	31.40 $\pm$ 5.14
Test di Intelligenza Breve		
IQ verbal	107.2 $\pm$ 9.5	107.2 $\pm$ 9.5
IQ performance	109.6 $\pm$ 8.55	109.6 $\pm$ 8.55
IQ global	108.7 $\pm$ 9.63	108.7 $\pm$ 9.63
Wisconsin Card Sorting Test		
Perseverations	5.3 $\pm$ 8.32	1.67 $\pm$ 4.9
Non-perseverative errors	6.12 $\pm$ 4.2	5.28 $\pm$ 4.32
Failure to maintain the set	0.7 $\pm$ 2.21	0.6 $\pm$ 1.57
Global score	18.34 $\pm$ 21.53	11.48 $\pm$ 21.17
State and Trait Anxiety Inventory-Y		
State	49.6 $\pm$ 8.59	51.6 $\pm$ 11.38
Trait	50.1 $\pm$ 9.08	53.2 $\pm$ 8.5
Beck Depression Inventory	12.3 $\pm$ 7.33	14.2 $\pm$ 7.56
Epworth scale	5.3 $\pm$ 2.7	4.9 $\pm$ 3.1
Activities of daily living (ADLs)	5.6 $\pm$ 0.69	4.8 $\pm$ 1.31*
Instrumental activities of daily living (IADLs)	5.2 $\pm$ 1.61	4.1 $\pm$ 2.07**
Unified multiple system atrophy Rating Scale (UMSARS)	19.8 $\pm$ 4.54	28.3 $\pm$ 6.91***

* p = 0.02; ** p = 0.01; *** p = 0.005.

Table 4. Video-polysomnographic recordings at T0

Sleep parameters	Pt. 1 MSA-C	Pt. 2 MSA-P	Pt. 3 MSA-C	Pt. 4 MSA-P	Pt. 5 MSA-C	Pt. 6 MSA-C	Pt. 7 MSA-P	Pt. 8 MSA-P	Pt. 9 MSA-C	Pt. 10 MSA-C	Mean $\pm$ SD
Total sleep time, min	312	249	341	293	194	291	283	335	343	215	285.6 $\pm$ 51.96
Sleep efficiency, %	82	79	87	75	49	67	70	83	79	56	72.7 $\pm$ 12.3
Phase											
1, %	4	5	3	6	6	20	7	2	16	3	7.2
2, %	40	43	27	72	35	56	56	42	51	41	46.3
3, %	19	14	38	14	41	12	18	5	11	42	21.4
REM, %	37	38	32	9	18	12	19	51	22	14	25.2
WASO (%)	13	18	11	23	48	30	22	17	21	43	24.6
Sleep latency, min	24	14	10	15	25	22	47	2	2	12	17.3 $\pm$ 13.22
REM latency, min	74	95	56	140	120	135	114	67	21	254	107.6 $\pm$ 63.7
PLMS index	79	191	11	10	105	134	10	101	5	6	65.2 $\pm$ 66.47
Arousal index	7	6	7	20	7	6	8	13	10	6	9 $\pm$ 4.44
Apnea index	0	0	3	8	6	3	11	8	50	1	9 $\pm$ 14.88
SaO ₂ , min	93	80	92	91	90	94	90	91	81	91	89.3

cate the presence of dementia in any of our patients. Also considering the follow-up, after a mean of 16 months, cognitive performance of all patients remained unchanged, except for one of the seven previously not impaired who developed multiple cognitive deficits. Nevertheless, the global cognitive indexes of this patient were still within normal limits; therefore, he should not be considered demented. The significant worsening of ADL/IADL of the entire group between T0 and T1 could be related to a motor impairment increase. We did not find significant differences in cognitive performance between MSA-P and MSA-C patients, according to recent findings [17].

Depression was present in half of our MSA patients as in the Kao et al. study [8]. Since depression was present both in patients with or without cognitive deficits, and neither were there differences between cognitive performance in depressed and not-depressed patients nor a significant worsening from T0 to T1, its effective role on cognition is probably marginal as recently supposed by others [17].

To our knowledge, only a study [6], analyzed the longitudinal follow-up of cognitive functions in MSA, evaluating for a mean of 21 months, 14 striatonigral degeneration patients classified by Quinn's criteria [36]. These authors disclosed a verbal fluency deficit at the first examination and a significant worsening on a visual search test at the follow-up. No patients were clearly demented during both the evaluations.

In our study, comparing the cognitive results between T0 and T1, a significant worsening was found in two tests

exploring attention (Barrage Test score and Trail Making Test-A), while global cognitive indexes or tests exploring other cognitive domains, showed no significant difference. Although Barrage Test and Trail Making Test mainly explore attention, other cognitive functions such as ability to inhibit contrasting responses, speed of cognitive processing and visual searching capacity are implied. However, it's noteworthy that results at the Wisconsin Card Sorting Test, which explores the cognitive flexibility, which is an aspect of executive functions, were within normal limits in all our patients at both evaluations. Thus, it's conceivable that a selective deficit of attention may occur in a minority of MSA patients, especially along the evolution of the disease. A longer follow-up of our patients should allow a more detailed characterization of their cognitive evolution; nevertheless, the dramatic worsening of motor and dysautonomic functions, often makes very difficult, if not impossible, to perform the formal neuropsychological assessment.

Sleep Structure, Sleep-Related Respiratory Abnormalities and PLMS

Polygraphic data of our patients confirmed a reduced sleep efficiency, slight increase of the NREM stages, and increase of REM latency without significant difference between the first and the second polygraphic recordings. Our patients showed a frequency of stridor and OSA comparable with those previously reported, respectively of 70 and 20%, with a mild O₂ desaturation. PLMS are significantly increased as reported in literature [43–45, 47].

RBD

In idiopathic RBD, visuoconstructional and visuospatial deficits had been detected with a pattern similar to the neuropsychological profile of LBD [3–5]. In our sample, RBD preceded the onset of the disease in 6 patients (four who showed cognitive deficits and two who were cognitive normal). Visuoconstructional and visuospatial deficits were found only in two and a uniform neuropsychological profile was not detected. Moreover,

as in idiopathic RBD [3], in our patients, the RBD duration did not correlate with the neuropsychological performance. Overall, considering these data in our small MSA sample, we found that RBD does not correlate with the neuropsychological findings and this disorder, although present in all our patients, does not appear as a clear early marker of cognitive impairment. Future longer-term studies with a larger patient sample are thus encouraged.

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