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LONGITUDINAL EVOLUTION OF COGNITIVE FUNCTIONS IN PATIENTS WITH MULTIPLE SYSTEM ATROPHY: A PROSPECTIVE STUDY

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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 absent response to levodopa, and pathologically by cell loss, gliosis, and glial cytoplasmic inclusions in several neural cell systems (striatonigral, olivopontocerebellar, autonomic) [1]. Bladder dysfunction, and in males erectile dysfunction, usually are the first symptoms of the disease. The presenting motor symptoms can be of parkinsonian type with bradykinesia, rigidity, and gait instability or of cerebellar type with ataxia. Indeed, the clinical terms MSA-P and MSA-C were introduced to classify cases according to the predominant motor disorder (parkinsonian or cerebellar). MSA is considered a synucleinopathy along with Parkinson's disease (PD) and dementia with Lewy bodies (LBD) [2]. Diagnostic categories of possible, probable and definite MSA were introduced, with a diagnosis of definite MSA requiring neuropathological confirmation [1].

The analysis of cognitive functions in MSA has gained interest. Nevertheless the related profile and degree of cognitive impairment is still debated. Indeed, the presence of dementia, particularly at onset, is an exclusion feature by current consensus criteria [1,3]. To our knowledge, there is only one study on the longitudinal evolution of cognitive functions in MSA [4]. We therefore investigated cognitive functions longitudinally in a group of probable MSA patients, matching data with sleep parameters.

Review on cognitive impairment in MSA

Cognitive deficits

Heterogeneous cognitive dysfunctions in MSA have been reported by many authors [4-29]. The executive functions are described as the most frequent impaired abilities but other cognitive domains can be involved as memory, visuospatial, and constructional functions. Brown et al [6] in a large cohort of MSA patients found that approximately two-thirds of subjects showed no significant

cognitive impairment. Impairment in a single domain was found in 28.6%, while impairment in two or more domains was present in 13.5% and significant cognitive impairment was observed in 11-32% of patients. Cognitive impairment was predicted by greater motor disability, fewer than 10 years of education, male gender, and presence of cardiovascular dysautonomia. It is however noteworthy that in the cognitive impaired group of patients, the diagnosis was further pathologically confirmed in 64.4% of cases while a final diagnosis of progressive supranuclear palsy, LBD or amyotrophic lateral sclerosis was ascertained in the other ones. In the unimpaired group, diagnosis of multiple system atrophy was confirmed in 94.6% of cases.

Wenning et al [30] in a pathologically confirmed case study, showed that dementia was detected in a 15.7% of a sample of 38 MSA cases and in none of them dementia was reported within the first 5 years onset. In another study [31], 14% of a sample of 83 pathologically confirmed cases were identified as demented.

Evolution of cognitive deficits

To our knowledge, only one study [4] analyzed the longitudinal evolution of cognitive functions in a group of 14 patients affected by striatonigral degeneration-type of MSA (SND), according to Quinn's criteria [32]. At first evaluation, MSA patients showed a significant deficit in a test of verbal fluency if compared with a group of patients affected by PD. 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.

Difference of cognitive deficits between MSA-P and -C

Kawai et al [13] compared 21 MSA-P with 14 MSA-C patients. In respect to controls, MSA-P patients showed involvement of visuospatial and constructional function, verbal fluency, and executive functions while 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 [11,16,26] obtained heterogeneous and even conflicting data. Bak et al [16], in fact, found no visuospatial impairment in a group of MSA patients that included subjects with long disease duration, high levels of physical disability, and evidence of other cognitive domain impairment. These data are consistent with those of Robbins et al [26] on a group of MSA-P patients and with those of Bürk et al [15] on a MSA-C sample that did not show any visuospatial functions impairment. On the contrary, Kao et al [11] confirmed the presence of visuospatial deficits in a group of MSA patients.

Neuropsychiatric symptoms

Kao et al [11] described depression in the 50% of patients of a small group of MSA subjects, anxiety in the 33.3% and disinhibition in 10%. Schrag et al [8] confirmed these data while Kawai et al [13] and Brown et al [6] found a smaller prevalence of depression (about 21-22%) and Chang et al [12] confirmed a significantly presence of anxiety in a group of MSA-C patients. Balas et al [7] made also the analysis of the impact effect of mood, anxiety and depression, on cognitive functions of a MSA group of subjects compared with controls and a group of patients affected by PD. The comparison of depression and anxiety levels showed that the MSA-P and PD patients reported significantly greater state anxiety, trait anxiety, and depression than controls as well as MSA-C patients reported a significantly increased state anxiety compared to controls. Authors conclude that anxiety and depression are related to cognitive decline.

Pathogenetic mechanisms of cognitive deficits

The pathogenetic mechanisms of cognitive deficits in MSA are debated. When compared with others parkinsonian syndromes, MSA patients display a milder degree of cognitive impairment respect to corticobasal degeneration (CBD), progressive sopranuclear palsy (PSP) and LBD. In respect to PD without dementia, not definite differences seem emerge [4,6,11,16-19,24-26].

A SPECT study by Kaway et al [13] shows that frontal lobe involvement can be responsible for cognitive dysfunction in patients with MSA. Hypoperfusion in the medial frontal cortices and dorsolateral prefrontal cortex is detected in MSA-P patients and the severity of cognitive impairment is correlated with the hypoperfusion in the dorsolateral prefrontal cortex. Frontal cortical atrophy has been also detected bilaterally in MSA-C by means of a voxel-base morphometry study together with bilateral cerebellum gray matter reduction [12]. This suggests that cognitive tasks in patients with MSA-C are influenced by various lesions: cerebellum, cerebellocortical circuits, and the frontal lobe. Complex interactions between frontal cortex and basal ganglia have to be considered influencing cognitive performances in MSA. Lyoo et al [14], analyzing the progression of MSA by PET examination, found that hypometabolism started from the frontal and cerebellar regions, sparing the basal ganglion in a group of patients with a shorter disease duration (less than one year). Patients with longer disease duration showed hypometabolism in more widespread cerebral cortical areas involving the frontal, temporal, parietal and cingulate cortices. Patients with shorter disease duration had executive and verbal memory dysfunctions, while patients with longer disease duration had multiple domain cognitive impairment, including visuospatial deficits. Furthermore, comparing functional with morphologic data of these patients, the authors suppose that the hypometabolism observed is more likely caused by the widespread and distribution of glial cytoplasmatic inclusions than by cortical loss, especially in the first phases of the disease. An alternative hypothesis could be the progressive alteration of the afferent cortical inputs arising from the subcortical nuclei (e.g. locus coeruleus and substantia nigra), thus linking together subcortical and cortical structures. Finally, the influence of orthostatic hypotension on cognitive function in MSA is still controversial [9,33-35].

Review on sleep disturbances in MSA

Sleep related complaints

A clinical questionnaire based study by Ghorayeb et al [36] showed that 70% of MSA patients complains of sleep disorders compared to 51% of patients with PD. Sleep fragmentation is reported by 53% of patients as the most frequent complaint followed by early waking (33%) and insomnia (20%). Excessive daytime sleepiness has been also referred by Ghorayeb et al [37] in half of MSA patients while Moreno-Lopez et al [38] 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-disordered breathing and sleep efficiency predict excessive daytime sleepiness in MSA [38].

Sleep structure

Polysomnographic studies reported total sleep time and sleep efficiency reduced and wake after sleep onset increased [39-43]. Plazzi et al [42] found sleep stage percentages unchanged as a whole group of patients but individual variations were described. Vetrugno et al [40] found stages 1 and 2 increased, 3 and 4 decreased while REM sleep was normal. On the contrary, in a study by Nam et al [39], designed to eliminate the major confounding variables of sleep such as obstructive sleep apneas (OSA) and periodic limb movements during sleep (PLMS) and the influence of anti-parkinsonian medications, no alteration of the stage distribution of sleep was found. These authors conclude that MSA by itself does not affect the sleep structure since even the analysis of the microstructure (i.e. sleep instability) compared with controls shows no differences in every aspect, including CAP rate, CAPs A and B, and non-CAP. However, this topic is a matter of debate since Vetrugno et al [44] had shown in a group of MSA patients a significantly lower CAP rate compared to a group of patients with primary restless legs syndrome.

Sleep-related respiratory abnormalities

Nocturnal stridor and OSA as the most common sleep-related breathing disorders in MSA patients have been extensively reported [36,37,40,42,43]. The prevalence of nocturnal stridor (a strained, high-pitched, harsh respiratory sound) varies from 13% to 69% [45,46]. In one study, stridor was more frequently detected in MSA-C than in MSA-P patients [40], but the contrary was also shown [37]. OSA ranges from 15% to 37% [40-42] and may contribute to mild O2 desaturation occurring during sleep in MSA. The relationship between nocturnal respiratory abnormalities and cognitive performance in MSA has not been specifically investigated yet.

Periodic limb movements (PLMS)

PLMS are frequently reported in polysomnographic studies on MSA [39-42,44]. They are significantly increased respect to control [41,42,44], and may contribute to sleep fragmentation and reduced sleep efficiency. Restless legs syndrome, a condition often correlated with PLMS, in a questionnaire based study, occurred in 28% of patients with MSA, doubling the frequency occurred in PD patients (14%) and 4 times more frequent than in the control group (7%) and unrelated to the amount of dopaminergic treatment [38].

REM sleep behavior disorder (RBD)

REM sleep behavior disorder, a REM sleep parasomnia, is the most common sleep-related disorder in MSA [36,37, 40,42,47,48] and may precede the development of parkinsonism by years [42,49,50]. Indeed, up to 81% of patients with idiopathic RBD develop a parkinsonian disorder [51]. Ninety to 100% of MSA patients have polysomnographic confirmed RBD and clinical symptoms of RBD precede the onset of MSA by plus than 1 year in 44% of the patients evaluated [40,42].

Comparing clinical and video-polysomnographic characteristics of idiopathic RBD vs the RBD seen in MSA and PD, Iranzo et al [52] showed that patients with MSA, compared to subjects with

PD, had a significantly shorter duration of disease, a higher REM sleep without atonia percentage, a greater PLMS index, and less total sleep time. Furthermore, subjects with MSA, compared to those with idiopathic RBD, had an onset of RBD at a younger age, were less likely to be aware of their abnormal sleep behaviours, had reduced total sleep time, and higher PLMS index. Authors suggest that in MSA there could be a more severe dysfunction in the structures that modulate REM sleep. This hypothesis could also explain the natural evolution of RBD in MSA. Indeed, Vetrugno et al [47] analyzed RBD in two MSA patients showing its evolution in a more complex and pervasive sleep disturbance with possible associated confused arousals and hallucinations. In these patients sleep quality and quantity severely decreased and the sleep pattern gradually disrupted, with stages no longer identifiable (the so-called Status Dissociatus). Authors hypothesize that this condition may be due to the progressive degeneration of the neuronal structure responsible for the origin of the RBD, in agreement with findings by Iranzo et al [52]. Furthermore, they remarked that these two patients did not develop any global intellectual decline suggestive of dementia.

General aspects on RBD and related cognitive deficits

Cognitive deficits in idiopathic RBD have been reported [53,54]. Neuropsychological data in 34 patients with idiopathic RBD showed deficits of short- and long-term verbal visual memory in about 40% patients and 25% of these patients were also impaired on executive functions or verbal associative fluency [53]. Ferini-Strambi et al [54], in a longitudinal healthy controls matched study, disclosed visuospatial constructional dysfunction and altered visuospatial learning in idiopathic RBD. These neuropsychological deficits were not correlated to RBD duration or to selected video-polysomnography data such as sleep efficiency, stage 3 and 4 NREM and REM sleep percentages, and PLMS index. Since in LBD there is evidence of perceptual dysfunctions, i.e. visuoconstructional and visuospatial deficits [55-57], Authors suggest idiopathic RBD as a possible early marker of LBD. Indeed, in a group of 37 patients with RBD affected by degenerative dementia, Boeve et al found that 34 met clinical criteria for possible or probable LBD [58]. This

hypothesis was recently confirmed based on the neuropsychological pattern similarity between idiopathic RBD and LBD detected in a selected group of RBD patients matched with a group of healthy controls [59]. Finally, in a recent prospective study, RBD confers a 2.2-fold increased risk of developing Mild Cognitive Impairment (MCI) within 4 years [60] and in this population MCI patients convert to dementia at twice the rate of those without [60]. Summarizing, clinicopathologic data show that patients with RBD and MCI, regardless of the MCI subtype, are likely to evolve a LBD [49,59,61-64].

Prospective study

Patients and Methods

Consecutive patients, fulfilling criteria for probable MSA [1], were evaluated in our Neurological Department from January 2009 to June 2011. Patients with significant current or previous neurological or psychiatric comorbidity likely to confound the test results (history of strokes, severe depression, active psychosis), alcoholism or other substance abuse, use of neuroleptics or other antipsychotics and tricyclic antidepressants and advanced disease causing significant physical debility (making cooperation for neuropsychological testing difficult) were excluded. Low doses of selective serotonin reuptake inhibitors antidepressants or dopaminoagonists/levodopa were allowed. Ten patients responding to inclusion/exclusion criteria were enrolled. 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 application of the UMSARS for assessing disease severity [65]. Patients were also investigated by blood tests (haemachrome, thyroid function, vitamin B12, folates, cholesterol, triglycerides, syphilis serology), by MRI scans to exclude space occupying and neoplastic lesions or major atrophic and vascular lesions, according to exclusion criteria, and by means of a cardiovascular reflexes study. An extensive battery of neuropsychological tests exploring different cognitive functions was administered and video-polysomnographic recording acquired.

All patients were revaluated (T1) a mean of 16±5 (range: 12-28) months after the initial evaluation (T0). At the second evaluation (T1), the neuropsychological assessment and video-polysomnography were repeated.

Neuropsychological and affective evaluation

The tests and scales employed are standardized in the Italian population and listed in Table 1. These tests were standardized for age, years of education and sex in the Italian population [66-75]. We evaluated global cognition by Mini Mental Status Examination (MMSE) [76,77], and Brief Mental Deterioration Battery (BMDB) [78-81]. BMDB consists of verbal and visuospatial tasks which are scored using a method of equivalent points. Pathological tasks are those in which the subject's performance is below the lower limit of the tolerance interval of 95% for a confidence level of 95%. BMDB is derived from Mental Deterioration Battery [82] by discriminant function analysis's procedures, allowing inclusion of the smallest tasks with the highest correct classification and with a Final Result allowing a classification for each subject with respect to the threshold value of zero with negative scores considered as pathological. We also investigated learning, verbal, visual, spatial memory, attention, language, constructional praxis, visuospatial and executive functions, abstract and concrete thinking (Table 1). We evaluated depression with the Beck Depression Inventory (BDI) [83] and anxiety by the State-Trait Anxiety Inventory—Form Y (STAI) [84].

Video-polysomnographic recording

Patients underwent an all-night video-polysomnography (VPSG) which included EEG (C3-A2, O2-A1, Cz-A1), right and left EOG, surface EMG from submental, right and left extensor carpi radialis and tibialis anterior and intercostalis muscles, microphone, oro-nasal airflow, thoracic and abdominal respirogram, ECG, systemic arterial blood pressure by means of Finapress and oxyhaemoglobin saturation (SaO_2). Sleep was scored according to American Academy of Sleep Medicine (AASM) criteria [85].

The tonic and phasic components of REM sleep were scored separately, according to AAMS criteria. Each 30-second epoch was arbitrarily defined as tonic if tonic chin EMG activity was present for more than 50% of the epoch. Phasic EMG REM activity was evaluated for mini-epochs of 3 seconds; a phasic EMG event was defined as any burst of EMG activity lasting 0.1-5.0 seconds

in duration with an amplitude exceeding and at least 4 times the background EMG activity. Each 30-second epoch of REM sleep was defined as phasic if at least 5 mini-epochs (50% of the epoch) contain bursts of transient muscle activity.

The arousal index (number of arousals per hour of sleep), apnoea–hypopnoea index (number of obstructive/central/mixed apneas/hypopneas per hour of sleep) and PLMS index (number of PLM per hour of sleep), were evaluated for each patients according to AASM criteria. RBD, defined according to International Classification of Sleep Disorders [86], was checked against the video recordings.

Statistical analysis

Data were analyzed using the SPSS statistical analysis software, version 18.0. We performed a descriptive analysis of the various parameters of patients. Considering that some variables were non-normally distributed, statistical analysis was done with non-parametric tests (Wilcoxon test for correlated samples). Cognitive performances were correlated with both clinical variables and polygraphic data using Pearson's correlation and non-parametric Kendal Tau correlation.

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 mean age was 57.8±6.4 years (range: 47-64) with a mean age at disease onset of 53.2±7.1 years (range: 43-61) and symptoms duration at T0 of 60±48 months (range: 12-144) (Table 2).

Neuropsychological findings

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 deficits in constructional praxis and visuospatial functions (Table 3). Considering global cognitive indexes for each patient (MMSE and BMDB Final Result) and daily living activities, no patient could be stated demented. At T0, mean values of all tests in the whole group were within normal range while mean values of scales for depression and trait anxiety scales were slightly increased (Table 4). Nevertheless, none of the patients had major depression, according to DSM IV criteria.

At the second evaluation (T1), after a mean of 16±5 months (range: 12-28) after T0, 6 patients still showed no cognitive deficits, 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 (MSA-P) worsened developing multiple cognitive deficits (long term verbal memory; short term spatial memory; attention; constructional praxis; language; visuospatial functions; abstract thinking) from a non impaired cognitive condition. In this patient, global cognitive indexes (MMSE and BMDB Final Result) were still unchanged and within normal limits. At T1, mean values of all tests in the whole group were still within normal range. Slightly increased mean values of scales for depression, state and trait anxiety were confirmed.

Comparisons between neuropsychological and affective evaluation at T1 and T0 showed a significant worsening in two tests of attention: Barrage Test (score) ($p = 0.02$) and Trail Making Test (A) ($p = 0.01$). A comparison (T1/T0) between motor performances and functional autonomy

scales disclosed a significant worsening in IADL (p= 0.01) and UMSARS (p = 0.005). No significant correlation was found between the neuropsychological results and clinical variables (e.g. symptoms duration, MSA type).

Findings on VPSG

No significant differences were found between T1 and T0 VPSG parameters. No significant correlation was found between the neuropsychological results and VPSG findings or RBD duration. In particular:

Sleep structure: Sleep efficiency was reduced (n.v. > 85%) and REM latency increased (n.v. 60-90 min) (Table 5). Sleep structure was characterized by a slight increase of NREM sleep stages 1-2 (n.v. 45-55%).

Sleep related complaints*:* 80% of patients complained about sleep fragmentation at T0 and T1. Excessive daytime sleepiness was not referred by patients as assessed by Epworth Sleepiness Scale [87].

Respiratory abnormalities: snoring was detected in 3/10 patients and paradoxical breathing in 6/10. Only in 2 patients the apnea index was higher than 10 compatible with a diagnosis of OSAS and 1 of these displayed nocturnal stridor. Stridor was detected in 7/10 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 with abnormal PLMS index in 9/10 patients (n.v. ≥10).

RBD*:* All patients referred a history compatible with RBD that preceded the onset of the disease in 6/10 patients (range: -3,-1 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 mylohyoideus muscle while awake and during sleep, with phasic or tonic increase during REM sleep. RBD in the form of complex motor

behaviours such as limb and body jerks or complex vigorous movements was recorded in 9/10 patients.

Discussion

Neuropsychological findings

At first evaluation, the majority of our patients had not any cognitive deficits while only three had selective cognitive deficits (two patients in long-term verbal memory and one in visuo-spatial tasks). Our findings are consistent with those of the majority of previous reported ones [4-30]. Considering the follow-up of our patients, after a mean of 16 months, the above mentioned three patients were unchanged, whereas one of the seven previously not impaired ones developed non amnesic multiple cognitive deficits. In this last patient, the global cognitive indexes were still within normal limits, therefore this patient should not be considered as demented. Moreover, the clinical problem of the majority of MSA patients is related with the severe motor disability that could induce a bias in attempting to judge the impact of functional autonomies on daily living.

The majority of our patients (80%) disclosed a mild degree of depression and anxiety, confirming the prevalence of known data [8,11]. Depression and anxiety were present in all four patients with isolated cognitive deficits, without a difference in respect to the type of MSA (P or C). In our study, we did not find relevant differences in cognitive performance between MSA-P and MSA-C patients, although some authors signalized a greater degree of cognitive deficits in MSA-P patients [13].

Soliveri et al [4], analyzing the evolution of cognitive functions in a group of MSA patients, disclosed a verbal fluency deficit and a significant worsening on a visual search test. No patients were clearly demented at either evaluation. In our study, a significant worsening was found in two tests exploring attention (Barrage Test and Trail Making Test-A) while global cognitive indexes 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 (WCST) were within normal limits in all our patients at either evaluations, except for the patient who developed multiple deficits at the second evaluation. WCST explores mainly the cognitive flexibility that is an aspect of executive functions and is

frequently altered in PD and parkinsonian syndromes [15,17]. Thus, it's conceivable that a selected deficit of attention may occur in a minority of MSA patients, especially along the evolution of the disease, probably as an expression of a functional cognitive impairment of frontal type. Indeed, cerebral SPECT and PET studies in MSA have shown that hypometabolism is observable in frontal lobes, even in the first phases of the disease [13,14]. Frontal lobes hypometabolism is thought to be the consequence of both cortical and subcortical atrophy and their associated cortical pathophysiological changes. Lyoo et al [14] suggest that these functional changes could be the consequence of the spread and distribution of glial cytoplasmatic inclusions and related neuronal cortical loss and/or the consequence of the alteration of the afferent cortical inputs arising from the subcortical nuclei (e.g. locus coeruleus and substantia nigra). This last pathogenetic hypothesis could explain the complex relations that occur in MSA between the progressive degeneration of cortical-subcortical anatomical structures, the pattern and evolution of the deficits of cognitive functions and the possible subtle alterations of sleep. In fact, in MSA, subcortical anatomical structures, especially brainstem nuclei, are firstly altered leading to a functional modification of the afferent cortical inputs that could impair attention and execution. Subsequently, after some years, cognitive functions may worsen, probably as a consequence of a widespread of cortical glial cytoplasmatic inclusions and related neuronal loss. Moreover, it's noteworthy that RBD, as an early modification of sleep that may precede the onset of the disease by years, is significantly related to anatomical alterations of subcortical nuclei of the brainstem, especially locus coeruleus [63].

Sleep structure, sleep-related respiratory abnormalities and PLMS

Polygraphic data of our patients confirm a mild alteration of sleep structure, with sleep efficiency reduced, slight increase of the NREM stages, and increase of REM latency without significant difference between the first and the second polygraphic recording. Our patients show a frequency of stridor and OSA comparable with those previous reported, respectively of 70% and 20%, with a

mild O2 desaturation [40-42,45,46]. PLMS are significantly increased as reported in literature [40-42,44], and may probably contribute to sleep fragmentation, reducing its efficiency.

RBD and related cognitive deficits

RBD was present in all our patients and preceded the onset of the disease in 6 (3 MSA-C and 3 MSA-P). Of this last group, 4 patients showed or developed isolated cognitive deficits. In idiopathic RBD, visuoconstructional and visuospatial deficits had been detected with a pattern similar to the neuropsychological profile of LBD [54,58,59]. In our sample, visuoconstructional and visuospatial deficits were detected in two patients while the other two patients showed a long-term verbal memory deficit. So, all our patients with isolated cognitive deficits had a RBD that preceded the onset of the disease of a few years but a homogeneous neuropsychological pattern was not detected. Moreover, as in Ferini Strambi et al [54], neuropsychological deficits did not correlate to RBD duration or to selected VPSG data.

Idiopathic RBD confers a 2.2-fold increased risk of developing MCI within 4 years [60]. In our sample, the patient who developed multiple cognitive deficits from a normal condition after about three years of disease had RBD that started one year before the onset of the disease. In the other three patients who showed stable cognitive deficits, RBD started few years before the onset of the disease. Moreover, cognitive deficits were not found in the remaining two patients with RBD that preceded the onset of the disease. So, even if a correlation between neuropsychological deficits and RBD duration was not found, the majority of our patients (4/6) with a RBD onset prior the beginning of the disease showed isolated cognitive deficits. Probably, statistical correlation was not evidenced as a result of a small sample size. A follow-up of our patients should allow a more detailed characterization of their cognitive evolution; nevertheless the dramatic worsening of motor and dysautonomic functions make very difficult, if not impossible, performing formal neuropsychological assessment.

Conclusions

The majority of our patients affected by MSA do not show any cognitive deficits at the first neuropsychological evaluation neither at the follow-up, while isolated cognitive deficits (verbal memory, visuospatial functions and constructional praxis) are present in the remaining patients. Attention is the cognitive function which significantly worsened after a mean of 16 months follow-up. Our data confirm the previous findings concerning the prevalence, type and the evolution of cognitive deficits in MSA. Regarding the developing of a condition of dementia, our data did not show a clear-cut diagnosis of dementia. We confirmed mild alteration of sleep structure and frequency of stridor, OSA and PLMS. In our MSA patients, we found that RBD duration does not correlate with neuropsychological findings.

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Tables

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, 2002)
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)

Table 2. Clinical data

Sex (m/f)	7/3
Age (years, mean±s.d.)	57.8±6.4 (47-64)
Education (years, mean±s.d.)	10.7±4.5 (5-17)
Age at onset (years, mean±s.d.)	53.2±7.1 (43-61)
Symptoms duration at T0 (months, mean±s.d.)	60±48 (12-144)
MSA type (C/P)	6/4
RBD (n. of patients)	10/10
RBD age at onset (years, mean±s.d.)	53.4±7.3 (40-61)

Table 3. Neuropshycological findings: T0/T1evolution

Patient/sex	Age at examination (years) (T0/T1)	Education (years)	MSA type (C/P)	Symptoms duration (years) (T0/T1)	Impaired cognitive functions (T0/T1)
1/f	52/54	8	C	2/4	T0/T1: Long term verbal memory
2/m	59/60	5	P	2/3	T0: No deficit T1: Long term verbal memory; Short term spatial memory; Attention; Constructional praxis; Language; Visuospatial functions; Abstract thinking; Executive functions.
3/m	47/50	13	C	2/4	T0/T1: Long term verbal memory
4/m	64/65	8	P	2/3	T0/T1: No deficit
5/m	62/63	13	C	13/15	T0/T1: No deficit
6/m	48/49	13	C	6/7	T0/T1: No deficit
7/m	62/63	17	P	1/2	T0/T1: No deficit
8/f	63/64	5	P	5/6	T0/T1: Constructional praxis; Visuospatial functions
9/m	58/59	17	C	12/13	T0/T1: No deficit
10/f	64/65	8	C	4/5	T0/T1: No deficit

Table 4. Neuropsychological, affective and functional evaluation

Neuropsychological, affective and functional tests and scales	I evaluation (T0) (mean±s.d.)	II evaluation (T1) (mean±s.d.)
MMSE	28.1±2.07	28.26±1.73
Brief Mental Deterioration Battery Final Result	2.23±0.93	2.46±1.02
Rey's 15 Words		
immediate recall	45.4±10.64	47.42±10.28
delayed recall	9.08±3.06	9.82±3.59
Barrage Test		
time	56.4±24.2	61±32.5
score	12.2±1.03	10.4±1.77*
errors	0.1±0.31	0.3±0.67
result	-0.22±0.88	0.3±1.82
Copy Design simple	11.17±1.04	9.8±2.89
Immediate Visual Memory	20.3±2.03	20.8±1.29
Analogies	18.4±1.32	18.6±2.02
Verbal Fluency		
phonemic	30.29±8.05	26.12±7.35
semantic	48.1±6.38	44.2±7.33
Stroop Test		
time	16.16±7.4	23.34±28.03
errors	-0.4±0.68	0.28±1.5
Rey-Osterrieth Complex Figure Test		
direct copy	33.3±6.38	29.42±9.71
delayed recall	17.67±3.97	16.57±5.63
Digit Span Forward	6.28±1.18	6.18±1.08
Corsi Block-tapping Test	5.96±1.04	5.56±1.19
Trail Making Test		
A	35.5±17.87	60.75±43.82*
B	62.45±48.17	93.15±76.7
B-A	27±41.04	31.85±35.85
Paired-associated Word Learning Test	13.22±5.65	12.7±4.37
Judgment of Line Orientation Test	26±5.22	25.30±4.99
Raven Coloured Progressive Matrices	31.16±4.19	31.40±5.14
Test di Intelligenza Breve		
IQ verbal	107.2±9.5	107.2±9.5
IQ performance	109.6±8.55	109.6±8.55
IQ global	108.7±9.63	108.7±9.63
Wisconsin Card Sorting Test		
perseverations	5.3±8.32	1.67±4.9
non-perseverative errors	6.12±4.2	5.28±4.32
failure to maintain the set	0.7±2.21	0.6±1.57
global score	18.34±21.53	11.48±21.17
State and Trait Anxiety Inventory–Y		
state	49.6±8.59	51.6±11.38[§]
trait	50.1±9.08[§]	53.2±8.5[§]
Beck Depression Inventory	12.3±7.33[§]	14.2±7.56[§]
Epworth scale	5.3±2.7	4.9±3.1
Activities of daily living (ADLs)	5.6±0.69	4.8±1.31
Instrumental activities of daily living (IADLs)	5.2±1.61	4.1±2.07*
Unified Multiple System Atrophy Rating Scale (UMSARS)	19.8±4.54	28.3±6.91*

* $p<0.05$; [§] pathological score

Table 5. Video-polysomnographic recordings at T0

Sleep parameters	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6	Pt. 7	Pt. 8	Pt. 9	Pt. 10	mean±s.d.
Total sleep time (min)	312	249	341	293	194	291	283	335	343	215	285.6±51.96
Sleep efficiency (%)	82	79	87	75	49	67	70	83	79	56	72.7±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±13.22
REM latency (min)	74	95	56	140	120	135	114	67	21	254	107.6±63.7
PLMS index	79	191	11	10	105	134	10	101	5	6	65.2±66.47
Arousal index	7	6	7	20	7	6	8	13	10	6	9±4.44
Apnea index	0	0	3	8	6	3	11	8	50	1	9±14.88
SaO_2 (min – max)	93 - 99	80 - 98	92 - 97	91 - 98	90 - 95	94 - 97	90 - 96	91 - 95	81 - 98	91 - 99	89.3 – 97.2