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Hair cortisol concentration, cognitive, behavioral, and motor impairment in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease that is characterized by the demyelinated inflammatory processes that occur within the central nervous system. Hypothalamus–pituitary–adrenal axis (HPA axis) dysfunctions have been associated with the triggering or increase in MS symptoms. We thus aimed at evaluating motor and behavioral functions, planning skills, processing speed, and their relationship with stress through measuring hair cortisol concentration from patients with MS. The sample was composed of 40 volunteers that were clinically diagnosed with MS, along with 33 healthy adults. Evaluations included: Clinical Evaluation Form, Mini-Mental State Exam, Hamilton Depression Rating Scale, Multiple Sclerosis Functional Composite Measure, Expanded Disability Status Scale, Berg Balance Scale, Perceived Stress Scale, Zoo Map task, and a hair sample to analyze cortisol levels in the last 30 days. MS patients showed highly elevated hair cortisol levels in comparison to the control group ($p = 0.048$). All groups presented some degree of depressive and anxiety symptoms, aside from considerable perceived stress levels. The MS group presented deficits in gait, balance, manual skills and processing speed, and this was particularly so in individuals with moderate impairments when compared to control group ($p < 0.001$). Individuals with MS spent less time planning on ZooMap1 ($p = 0.024$) and made more mistakes ($p < 0.001$). No correlation was found between hair cortisol and the symptoms we assessed. However, depressive symptoms and anxiety were related to perceived stress, and higher hair cortisol suggests a change in levels in the HPA axis in MS. Nevertheless, future studies will be necessary to further understand how basal hair cortisol is related to MS symptoms.

Keywords Autoimmune disease · Perceived stress · Hair cortisol · Symptoms · Neurodegenerative disease

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Introduction

Multiple sclerosis (MS) is a degenerative, demyelinated, and inflammatory disease that affects the central nervous system (CNS) (Lassmann et al. 2007; Loma and Heyman 2011; Altowaijri et al. 2017). Aside from its biological effects, it is also characterized by relapses and insidious progression with extensive heterogeneous clinical course, symptoms and severity of disease (Krieger et al. 2016). Due to its large number of possible lesion sites, symptoms can vary widely and differ from one patients to another, with symptoms including sensorial disorders, visual problems, urinary dysfunctions, fatigue, cognitive dysfunctions, emotional disorders, such as anxiety and depression, along with balance and gait changes (Brassington and Marsh 1998; Sakai et al. 2011; Pilutti et al. 2013; Minden et al. 2014; Gunn et al. 2015; Pearson et al. 2015; Phé et al. 2016; Ortiz et al. 2017; Coric et al. 2018; Penner and Paul 2017). As MS progresses, cognitive, behavioral and physical changes impact the lives of patients through a large number of problems (Yozbatiran et al. 2006). Furthermore, motor dysfunctions are present in all stages and forms of MS (Lipp and Tomassini 2015).

Individuals with MS have been presented to have a higher risk of developing emotional disorders as compared to the general population (Minden et al. 2014). Around 54% of the population that have MS experience some extent of anxiety or depression disorder at a certain stage in the disease; 13% present bipolar disorder, and 22% present adjustment disorders (Joffe et al. 1987; Sullivan et al. 1995; Jones et al. 2012). In addition, cognitive dysfunctions are present in up to 70% of the MS cases (Paul 2016). Roughly 19% of the MS cases present deficits in executive functions, although these occurrences are less frequent than deficits in memory and processing speed (Guimarães and Sá 2012).

While the causes for MS are still unknown, its etiology is considered as being multifactorial, and involving genetic and environmental mechanisms which affect some mechanisms in immunological response, the main triggers of the disease (Ebers 2008; Kümpfel et al. 2014). Evidences have shown that stress has been associated with triggering or an exacerbation of MS symptoms (Artemiadis et al. 2011). In MS, HPA dysfunctions have been related with the progression of the disease (Huitinga et al. 2004). Studies in humans also show that patients with active lesions in the Hypothalamus present an impaired activation of CRH neurons and are exposed to a more severe course of the disease, and this might lead a decrease of cortisol secretion and reduced capability of controlling inflammation (Huitinga et al. 2004). According to that assumption, low cortisol levels were related to higher number of lesions in white matter in post-mortem brains (Melief et al. 2013).

Conversely, studies in humans with MS have shown a chronic activation of the HPA axis (Huitinga et al. 2004). Studies have observed that basal cortisol levels are elevated in the cerebrospinal fluid (CSF) and in the blood, aside from having an increased cortisol awakening response (CAR) if measured in saliva (Kern et al. 2011; Powell et al. 2015; Melief et al. 2013; Baranowska-Bik et al. 2015; Ysrraelit et al. 2008; Erkut et al. 2002). Furthermore, this HPA axis hyperactivity seems to be involved with the progression of the disease and with associated cognitive disorders (Gold et al. 2005). Higher cortisol levels can be observed in behavioral symptoms as anxiety and depression, especially among patients with RRMS (Gold et al. 2011; Kern et al. 2011; Fassbender et al. 1998).

Furthermore, hyperactivity in the HPA axis has been also described in pharmacological studies that utilized corticotrophin releasing hormone/dexamethasone (CRH), and showed that patients with MS presented significantly higher plasmatic cortisol expression than healthy subjects, and that PPMS and SPMS had more elevated cortisol levels than in RRMS (Then Bergh et al. 1999). Moreover, patients with MS had increased adrenal size and rise in number of CRH neurons, co-expressing vasopressin in the hypothalamus (Reder et al. 1994; Erkut et al. 1995). Regarding the current knowledge on cortisol levels change in patients with MS, we observed that there is still a divergence in the results among several studies. This study was thus developed with the aims of contributing to the field by presenting new findings about cortisol levels and its role on symptoms present in MS. Consequently, its main objective was to assess motor and behavioral functions, planning skills, processing speed, and their relation with stress through hair cortisol in patients with MS.

Methods

This study was approved by the Committee of Ethics in Research in Human Beings of UFRGS—CEP/UFRGS. All participants provided written consent and their anonymity was kept during the whole study.

Patients

Forty patients that were clinically diagnosed with MS were recruited in accordance with McDonald's criteria (Thompson et al. 2018) and 33 healthy subjects were accordingly paired with the former by age and sex. MS group was non-probabilistic by accessibility and recruited between March 2017 and March 2018 from the ambulatory of neuroimmunology at São Lucas Hospital of Pontificia Universidade Católica do Rio Grande do Sul, Brazil. A total of 350 patients received clinical treatment and are accompanied in

this ambulatory, and of those, forty-six patients accepted participation in this study. One patient was excluded as they had a neurological comorbidity, while others were excluded by lack of the hair sample. All patients received immunomodulatory treatment during the period of recruitment. Immunomodulatory drugs included: fingolimod, natalizumab, fampridine, interferon beta 1-alpha, glatiramer acetate, and azathioprine.

Participants from the control group were recruited by local divulgation, and the exclusion criteria for both groups were as follows: having any associated neurological comorbidity; having physical limitations due to trauma orthopedic or rheumatologic conditions; presenting severe non-corrected visual conditions; using alcohol or other psychoactive drugs; having taken any corticoids in the last month; have a score > 24 points in MMS; and individuals with less than 1-cm hair length. In addition, individuals in MS group were excluded if their score in EDSS were higher than 6.0 or if they were on a relapse.

Assessment of hair cortisol concentration

Hair strands of approximately 3–5 mm in diameter and of 1-cm in length were cut from the posterior vertex position of subjects' heads with surgical scissors. After collection, the scalp end of the sample was identified, and hair samples were stored at room temperature for up to 12 months. Subsequently, 1-cm hair sections (representing 1-month period) were cut and minced into 1 mm pieces with clean and fine-tipped surgical scissors. Based on an average hair growth rate of 1-cm per month (Wennig 2000), each hair segment should reflect the cumulative cortisol secretion for last month.

Hair cortisol extraction followed a protocol that was described in the literature (Kirschbaum et al. 2009) with an adaptation that was previously tested in our lab (Boeckel et al. 2016; Buchweitz et al. 2019). We implemented a slight alteration in the extraction procedure due to absence of a mixer mill for hair pulverization. At least 10 mg of hair per 1-cm section was weighed and manually milled with surgical scissors into different clean centrifuge tubes (mean ± SEM = 29.22 mg ± 1.01). Powdered hair was prepared in 1.5 mL methanol and incubated in a water bath for 16–24 h at 50 °C. After incubation, ~ 1.0 mL of supernatant methanol (containing cortisol extract) was removed to a clean microtube and evaporated under a constant stream of nitrogen at 50 °C using TurboVap® Classic LV (Biotage, Sweden).

The residues were reconstituted with 200 µL of phosphate-buffered saline (pH 8.0) and vortexed for 15 s. Samples were frozen at 20 °C until needed for further analysis. For a double-blinded measurement of cortisol in the extracts, we used a commercially available high-sensitivity salivary cortisol enzyme-linked immunosorbent assay (ELISA) (Enzo Life Sciences, AD-901-071, Farmingdale, USA), which was implemented according to the manufacturer's instructions. All samples were run in duplicates.

Assessment instruments

Neurological measures

Expanded Disability Status Scale (EDSS) (Kurtzke 1983) was applied for patients with MS. EDSS assesses the neurological impairment, and follows the alteration of disabilities through time, providing a score from 0 to 10 points. Scores from 1.0 to 4.5 refer to people with no or little impairment in deambulation; scores from 5.0 to 9.5 mainly indicate deambulation inability; and 10 indicate death due to MS. EDSS scores were provided by a certified neurologist.

Cognitive, behavioral, and motor assessment

Global cognitive function was assessed by mini-mental state examination (MMSE) (Folstein et al. 1975). To measure depression and anxiety, we used the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960) and Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959).

To assess planning skills, we used ZooMap Task subscale from the behavioural assessment of the dysexecutive syndrome (BADS) (Wilson et al. 1996). We also used the paced auditory serial addition task, a 3-s version (PASAT 3′) subtask from the multiple sclerosis functional composite measure (MSFCM), which assesses auditory information processing speed, flexibility, and calculation skills (Fischer et al. 1999). To measure stress, we applied the Perceived Stress Scale—PSS (Cohen et al. 1983), which was validated for the Brazilian Portuguese segment (Luft et al. 2007).

Berg Balance Scale (BBS) was used (BERG et al. 1989). To assess gait and manual skills, timed 25-foot walk task (T25W) and 9-hole peg test (9-HPT) were applied, respectively. Both are subtasks from MSFC (Fischer et al. 1999).

Statistical analysis

We analyzed the normality of data distributions for each variable using the Shapiro–Wilk test. The test for hair cortisol concentration showed that the data were not normally distributed. Statistical difference in cortisol levels, along with cognitive and behavioral variables between groups were measured by Mann–Whitney *U* tests for independent samples. Correlational analyses were made using Spearman's correlation. According to severity of MS that was measured by the EDSS, patients with MS were divided into two groups: low severity (EDSS ≤ 3.5) and moderate

severity (EDSS > 3.5). Comparisons between cortisol means of MS subgroups (according EDSS score) and control was made using the Kruskal–Wallis test with pairwise multiple comparisons. All statistical analyses were performed using SPSS software 20th version (SPSS, Chicago, USA). A p value < 0.05 was considered statistically significant.

Results

MS group was composed of 40 patients, with a mean age of 39.82 ± 10.57 years, mean EDSS of 2.5 (1.5–5.0), and were paired by age, schooling, and sex with corresponding healthy adult subjects. Most patients were female (87.5%) and were clinically diagnosed with RRMS (92.5%). The average time after the diagnosis was at 7.06 ± 5.26 years. Results about subgroups are described in Table 1.

Hair cortisol

Mean hair cortisol concentration that was found in MS group was 51.20 ± 4.61 pg/mg and 38.91 ± 3.78 in control group. Patients with MS showed higher cortisol levels when compared to the control group ($p = 0.048$; $z = -1.97$) (Fig. 1). When controlled by EDSS score, there was significant difference between MS subjects with little impairment and moderate impairment ($p = 0.373$; $z = -1.44$), even when compared to control subjects ($p = 0.099$; $x^2(2) = 4.613$) (Fig. 2).

Table 1 Sociodemographic and clinical characteristics of the participants

Groups	Control ($n = 33$)	MS ($n = 40$)
Age (years)[a]	38.03 ± 1.68	39.82 ± 1.67
Sex (%)		
Female	90.9 (30)	87.50 (35)
Male	9.10 (3)	12.50 (5)
Years of education[a]	13.78 ± 0.47	11.32 ± 0.49
MMSE[a]	29.12 ± 0.23	27.97 ± 0.29
EDSS[a]	–	3.01 ± 0.28
EDSS[b]		2.5 (1.5–5.0)
Time after diagnosis	–	7.2 ± 0.81
RRMS (%)	–	92.5 (37)
SPMS (%)	–	5 (2)
PPMS (%)	–	2.5 (1)
Number of relapses[a, c]	–	3.4 ± 0.29

MS multiple sclerosis, *EDSS* Expanded Disability Status Scale, *MMSE* mini mental state examination, *RRMS* remitting relapsing multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis

[a]Data expressed in number (n) and mean ± standard error

[b]Median (tercis)

[c]Total number of relapses over the disease course

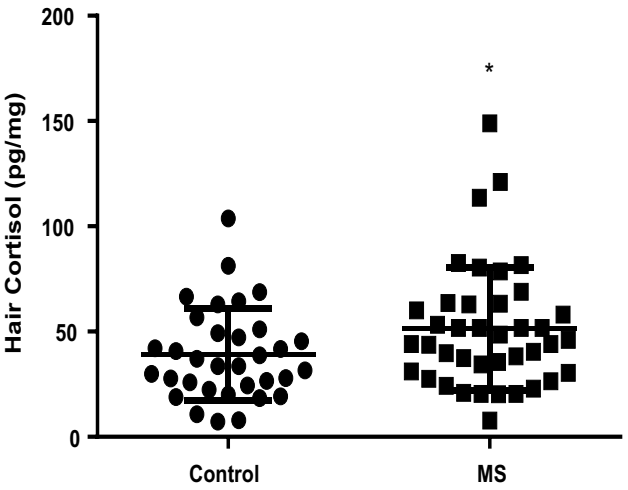

Fig. 1 Hair cortisol concentration between groups. Comparison between MS groups and control. Error bars represent mean standard errors *Significant difference, $p < 0.05$

Cognitive, behavioral, and motor impairments in MS

Regarding the behavioral aspects, there were no statistically significant differences between the control and the MS group for anxiety, depression and perceived stress. Nonetheless, both group presented depressive and anxiety symptoms levels, as well as high score in PSS (Table 2). In relation to the motor aspects, MS group presented a worse performance in static balance ($z = -6.958$; $p < 0.001$), had a longer walking time ($z = -7.160$; $p < 0.001$), and took longer to perform fine motor skills task (MD: $z = -5.897$; ME: $z = -5.642$; $p < 0.001$) when compared to the control group (Table 2).

With regards to the cognitive components, MS group presented statistically significant shorter planning time in the ZooMap test ($z = -2.250$; $p = 0.024$) when compared to the Control group, yet no difference was found in the total execution time of the task between groups. Mean number

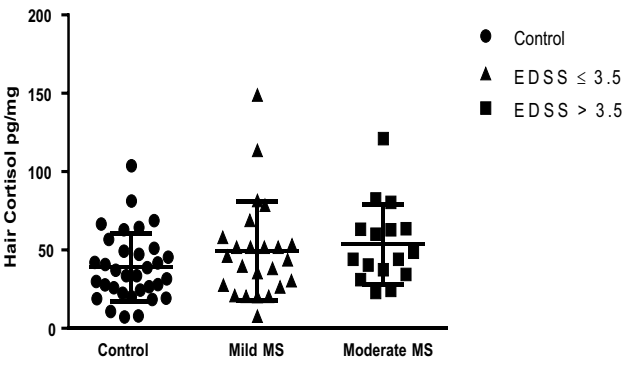

Fig. 2 Hair cortisol concentration between groups. Comparison between MS subgroups according to the EDSS score and control group. Error bars represent mean standard errors

Table 2 Behavioral, cognitive, and motor characteristics for MS patients and healthy controls

Characteristics	MS	Control	*z*-score	*p* value
Behavioral				
HAM-A	23.92 ± 1.35	23.78 ± 1.92	−0.061	0.951
HAM-D	15.02 ± 0.95	13.90 ± 1.12	−0.361	0.718
PSS	30.55 ± 0.72	30.42 ± 0.79	−0.133	0.894
Cognitive				
PASAT 3′	27.05 ± 2.09	39.45 ± 1.78	−3.887	0.0001
ZooMap (s)				
ZooMap—P	32.54 ± 5.85	54.14 ± 8.59	−2.250	0.024
ZooMap—T	202.89 ± 14.65	182.10 ± 10.86	−0.344	0.731
Number of errors	2.25 ± 0.27	0.96 ± 0.20	−3.197	0.001
Motor				
EBB	48.05 ± 1.21	55.72 ± 0.78	−6.958	0.0001
T25W	9.69 ± 0.63	5.06 ± 0.12	−7.160	0.0001
9-HPT-D	32.93 ± 1.94	21.31 ± 0.65	−5.897	0.0001
9-HPT-E	33.28 ± 2.14	22.01 ± 0.61	−5.642	0.0001

Data expressed by mean ± mean standard error. Mann–Whitney *U* test. Significance level for $p < 0.05$

of errors in execution was higher in MS group ($z = -3.197$; $p = 0.001$) (Table 2).

With respect to the processing speed that was measured by PASAT 3′, MS group subjects presented lower scores ($z = -3.887$; $p < 0.001$) (Table 2). In relation to the EDSS score, individuals with moderate impairment MS presented a worse performance in motor and processing speed tasks ($p < 0.001$).

Correlations

Symptoms related to anxiety ($r = 0.476$; $p = 0.002$) and depression ($r = 0.476$; $p = 0.002$) were positively correlated with perceived stress in MS patients, while hair cortisol concentration did not correlate with any assessed symptom (Table 3).

Discussion

This study aimed to assess hair cortisol concentration and verify the relation between motor, cognitive, behavioral aspects, and stress levels in MS with low and moderate impairments. Through a comparison with the control group, we were able to verify that the MS group presented deficits in motor and cognitive functions, with a worse performance in participants with a moderate degree of disability. Perceived stress levels did not differ between the groups. However, Scores were considered high if 17.8 was to be

Table 3 Correlations among hair cortisol concentration, cognitive, behavioral, and motor aspects in MS

	EDSS	Diagnostic time	Number of relapses	PSS	HAM-D	HAM-A	EBB	T25W	9-HPT		PASAT	ZooMap1		Cortisol
									Right	Left		Planning	Total	
PSS														
r	−0.267	0.122	−0.087	–	0.476**	0.491**	−0.091	0.002	−0.037	−0.052	−0.131	−0.171	0.079	−0.077
p value	0.096	0.452	0.594	–	0.002	0.001	0.577	0.988	0.822	0.750	0.419	0.293	0.629	0.635
Cortisol														
r	0.116	0.034	0.118	−0.077	0.098	0.006	−0.107	−0.031	0.041	−0.024	0.031	0.202	0.083	–
p value	0.475	0.835	0.468	0.635	0.546	0.972	0.509	0.849	0.800	0.881	0.849	0.212	0.609	–

9-HPT nine hole peg test, *BBS* Berg Balance Scale, *EDSS* Expanded Disability Status Scale, *HAM-A* Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression Ranting Scale, *PASAT* paced auditory serial addiction task, *PSS* Perceived Stress Scale, *r* = Spearman's rank correlation coefficient, *T25W* timed 25-foot walk

considered as the threshold for people with same age and sex (Reis and Petroski 2004).

Results found in this study showed that hair cortisol levels were different among groups, with MS patients presenting higher levels. However, no difference was found with regards to cortisol levels and the severity of the disease, as seen by the EDSS score. Furthermore, no correlation was found between perceived stress and hair cortisol. Hair cortisol is regarded as a potential biomarker for stress exposure (Van Der Meij et al. 2018). Besides representing long-term exposure to stress in humans, hair cortisol concentration could denote balance with blood cortisol levels (Sauvé et al. 2007). However, little is known about hair cortisol samples when investigating cortisol levels in MS (Pereira et al. 2018; Scheffer et al. 2019). Nevertheless, evidence has indicated a change in cortisol levels in other biological analysis from individuals with MS, such as saliva, blood, cerebrospinal fluid (CSF), and urine (Akcali et al. 2017; Powell et al. 2015; Melief et al. 2013; Baranowska-Bik et al. 2015; Ysrraelit et al. 2008).

High cortisol levels have been associated with different degrees of impairment in MS, particularly when compared with healthy subjects (Ysrraelit et al. 2008; Gold et al. 2011; Kern et al. 2011, 2013; Powell et al. 2015; Baranowska-Bik et al. 2015; Akcali et al. 2017). They might also be associated with different symptoms that are present in MS, and indicate dysfunction in the HPA axis, which might be influenced by comorbidities. In this sense, patients with MS who presented higher scores of depressive symptoms which were measured by Beck Depression Inventory (BDI) have a higher saliva CAR than the control group (Kern et al. 2011). Patients with depressive symptoms and/or major depression disorder (MDD) in RRMS presented hyperactivity in the HPA axis that was associated with higher cortisol levels at night (Gold et al. 2010, 2011). On the other hand, higher cortisol levels in plasma and urine were found in patients with SPMS, PPMS, and RRMS in the active stage of the disease, but there was no correlation with the depressive symptoms in that particular population (Ysrraelit et al. 2008). Moreover, patients with RRMS presented higher saliva CAR than healthy subjects on a 9 months' follow-up with progression on EDSS ≥ 0.5. However, no correlation was found with depressive symptoms and stress (Kern et al. 2013). Additionally, stress-induced brain activity might increase clinical disability and brain atrophy in MS (Weygandt et al. 2016).

In our study, all MS patients received a disease modifying treatment (DMT) and we did not control cortisol concentration for untreated patients versus patients under DMT. However, a previous study showed that there was a higher adrenal activation in untreated patients than those on DMT, which presented a more stable HPA system (Kümpfel et al. 2014), thereby demonstrating the relevance of DMT on the stability of activation on the HPA axis. However, our results suggested that even with this regulation of the HPA axis by DMT, the unbalance in the release of cortisol can still be observed in a long-term exposure of hair cortisol concentration.

Despite findings that indicate a higher levels of cortisol related to different symptoms in MS (Ysrraelit et al. 2008; Gold et al. 2010, 2011; Kern et al. 2011; Akcali et al. 2017), our data on hair cortisol did not correlate with the symptoms.

Regarding the behavioral profile of our subjects, anxiety symptoms were considered predominant in patients with MS, in spite there being no differences between the groups. Indeed, those symptoms associated with depression were frequently observed in individuals with MS and can be known to affect cognitive functioning (Arnett et al. 2001). Furthermore, as anxiety and depression can accrue in response to immunological and/or inflammatory alterations (Lotrich et al. 2011), these conditions can be said to influence MS physiopathology. Additionally, treatment of MS with glucocorticoids can trigger depression and might lead to cases of transient psychotic symptoms (Ciriaco et al. 2013).

In relation to motor skills, a worse performance in balance, manual skills and gait were related with higher degree of disability measured by EDSS. The average scores of subjects with MS indicates significant deficits in static balance, especially among individuals whose score were above 4 points on the EDSS (EBB = 43.18 ± 2.05 points), as stated by previous studies which indicated the impairment in that population set when compared against healthy subjects (Frzovic et al. 2000; Soyuer et al. 2006; Fjeldstad et al. 2009; Kasser et al. 2011). In addition, scores below 44 points lead to an increase in fall risk in this population (Cattaneo et al. 2006; Carling et al. 2016).

In the same vein, the reduction of fine motor control, as assessed by 9-HPT, is considered a predictor for the fall risk in that population (Hoang et al. 2014). In accordance with our results, which also demonstrated the loss of fine motor control in MS, studies have associated this loss with a change in the corpus callosum and white matter of the interhemispheric pathways which connect supplement motor areas and areas related to planning and motor control (Ozturk et al. 2010; Lowe et al. 2006).

Impairments in manual abilities can also be indicator for a limitation of the activities in daily life, even in early MS (Kierkegaard et al. 2012). Such impairments become more relevant in subjects with more severe impairment on gait, as upper limbs can help people to walk using locomotion helpers as canes, walkers, and wheelchairs (Kraft et al. 2014).

The limitation in gait can be found in all stages of progression in the severity, and it is considered one of the most common and incapacitating symptoms of MS (Benedetti et al. 1999; Martin et al. 2006). Additionally, from the perspective of MS patients, walking is deemed to be one of

the most important functions (Heesen et al. 2017). Walking changes can be found in patients with or without lesions on white matter of the pyramidal tracts (Martin et al. 2006). Furthermore, it can be observed in patients with higher score on EDSS, but without any trace on pyramidal tracts. Thus, treatment of these symptoms must be considered as the firsts goals of rehabilitation and for the improvement of these patients.

In line with that affirmation, participants of this study presented a longer time needed to walk than control group, even with those that had lower scores on EDSS. Previous studies that assessed patients with EDSS between 0 and 2 points and between 0 and 2.5 verified a decrease of gait speed associated with shorter steps and increase of the use of double support for the lower limps (Benedetti et al. 1999; Martin et al. 2006). Besides, there was a decrease in gait speed, with a progression of levels from 0 to 6.0, on the EDSS (Preiningerova et al. 2015).

Processing speed seems to be an important cognitive function that can be found to be altered in MS. Previous studies have shown that patients with MS who were assessed with PASAT presented deficits in processing speed when compared to the control group, an early sign that foreshadowed the disease before other deficits in cognitive functions as working memory (Forn et al. 2008; Demaree et al. 1999). A contrast enhancement of Gadolinium in MRI is observed in patients with impaired PASAT score, which indicates a diffused impairment of cerebral connectivity with a negative effect on cognitive functioning (Bellmann-Strobl et al. 2009). Additionally, processing speed can precede performance on executive tasks (Kalmar et al. 2008), as observed deficits in planning skills are also related to the efficiency of processing speed in subjects with MS. It is important to reckon that cognitive processing, above all executive processing, can also be influenced by behavioral changes such as depression. Thus, those findings seem to be inter-related and influenced by the rise of comorbidity.

On this note, a study assessed planning skill with the London Tower task showed that depressed subjects with MS took longer and made more moves before accomplishing the task (Arnett et al. 2001). Besides, researchers suggested that decreased processing speed and deficits in planning skills could be fundamental in understanding characteristic cognitive deficits of depressed patients with MS.

This study has thus presented results pertaining to the motor, behavioral, cognitive symptoms, and hair cortisol concentration in patients with MS. However, there are limitations to our study. First, the use of other cognitive tests that are more appropriate might be considered for future studies, as we have limited our assessment to PASAT. We assessed hair cortisol concentration from hair segments that were extracted at 1 cm from the scalp. Thus, our results were gleaned from cortisol exposure for 30 days before the assessment. Additionally, while hair cortisol is reportedly influenced by cumulative exposure to stress, we did not investigate the history of stressful life events that might have occurred earlier in life. Despite the patients being paired by age, sex, and schooling time, there was heterogeneity in groups, particularly in the MS group. Factors such as drug interaction (besides corticosteroids), menstrual cycle, and lifestyle can influence endocrine response on cortisol release. Furthermore, the sample size was relatively small and this made it difficult to observe the investigated factors. Finally, our main result with cortisol might have diverged in relation with the literature due to lack of previous studies that looked performing a hair cortisol analysis in that population.

Conclusion

This is the first study that aimed to investigate hair cortisol concentration and relate it to motor symptoms in MS, in addition to investigating cognitive and behavioral symptoms. Hair cortisol concentration in patients with MS indicates change in the HPA axis during the inactive stages of the disease.

Both MS and control group presented depressive, anxiety symptoms and had high levels of perceived stress. However, none of those measures correlated with cortisol. This finding indicates that behavioral perception and expression are changed in those subjects but the physiological responses do not necessarily change in tandem. Perception can be influenced by the social and cultural context by which each subject is surrounded by, along with their strategy against stress. Additionally, bodily response to cortisol changes can be a reflex for the intrinsic processes of MS physiopathology. Future longitudinal studies could bring us a step closer to getting a clearer picture on the impact of MS on neuroendocrine markers. We suggest that the following studies verify cortisol levels for periods longer than 3 months to be able to trace a trend line of cortisol levels in MS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Committee of Ethics in Research in Human Beings of UFRGS, no. 2.014.963).

Informed consent Informed consent was obtained from all individual participants included in the study.

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