Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

European Journal of Experimental Biology, 2014, 4(2):271-276

ISSN: 2248 –9215
CODEN (USA): EJEBAU

Physical performance and myelination factors in female patients with multiple sclerosis

Mehrzad Moghadasi[1]*, Amir Rahimi[2], Rahim Shirazi Nezhad[1], Fariba Alipour[2], Somayeh Rashidfar[2], Marzieh Noruzpour[2] and Aida Moeini[2]

[1]*Department of Exercise Physiology, Shiraz branch, Islamic Azad University, Shiraz, Iran*
[2]*Department of Exercise Physiology, Fars Science & Research Branch, Islamic Azad University, Fars, Iran*

ABSTRACT

Physical performance has been reported to be reduced among multiple sclerosis (MS) patients; however the mechanisms that affected physical performance in these patients no well known. The aim of the present study was to examine the physical performance and myelination factors in female patients with MS. Twenty seven female MS patients (32.3 ± 6.9 years of old; mean ± SD) with expanded disability status scale (EDSS) 1– 4.5 participated in this study as the subject. The subjects divided into three groups: Group A: EDSS <1.5, Group B: EDSS 1.5 – 2 and Group C: EDSS> 2. Each participant was assessed with standing balance test and 500-meter walking test and fasted blood sample was taken during the follicular phase of the menstrual cycle. The time of leg balance were higher in MS patients with lower EDSS and they completed the 500-meter walking test faster that those with higher disability status (P<0.05). The results showed that although BDNF concentration was higher in MS patients with lower disability (P<0.05), no significant changes were observed in NGF, IL-6, TNF-α, IL-10, IL-1β, IL-17, Prolactin, DHEA sulfate, ACTH and Cortisol levels among MS patients with different disability. Finally, the present study demonstrated a positive relationship between DHEA sulfate with leg balance of the patients (P<0.05) and no significant relationships were observed between neurotrophin concentrations, inflammatory markers and other hormonal levels with physical performance of the subjects. According to these finding, it seems that hormonal disorders may the most important factors that affected physical performance in female MS patients.

Key words: Multiple Sclerosis, Balance, Aerobic performance, Myelination factors

---

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that causes demyelinated plaques with glial scar formation [22]. In MS, naive CD4 T cells differentiate in the CNS into T_H1 and T_H2 cells, which produce different cytokines and have different effector mechanisms [26]. T_H1 cells produce pro-inflammatory cytokines, such as interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), and interferon (IFN)-γ. In contrast, T_H2 cells produce anti-inflammatory cytokines, such as IL-4, IL-5, IL-10, and IL-13. These cytokines regulate humoral immunity, down regulate local inflammation, promote T_H2 differentiation, and inhibit T_H1 differentiation. The inflammation seen in MS appears to be largely due to a misguided and overactive T_H1 response [26,13]. Blood and cerebrospinal fluid levels of IL-1β, IL-2, IL-6 and TNF-α are shown to be

increased in MS with respect to healthy controls [4,33]. On the other hand, the function of hormones has expanded to include immunomodulation and neuroprotection in addition to their classic roles. The story of how hormones influence inflammation and neuron and glial function is being slowly unraveled. There is increasing evidence that hormones such as prolactin [34,38], cortisol [11], hypothalamo-pituitary-adrenal (HPA) axis [35] and testosterone [34,17] may influence diseases such as MS or may be used therapeutically to modulate the immune response. Several studies in patients with MS have investigated whether HPA axis dysfunction is involved in the pathogenesis of this disease. Numerous investigators have shown hyperactivity of the HPA axis in MS patients [21]. Michelson et al. [27] have also shown that basal levels of plasma cortisol are significantly elevated in patients with MS, despite a normal HPA response these patients. Hyperprolactinemia [38] and testosterone levels significantly below the normal range [17,12] also more common in MS patients.

On the other hand, functional deficits and impairments, such as muscle weakness, fatigue, and impaired ventilation, have long been recognized as major causes of morbidity and mortality in individuals with advanced MS [30]. Deficit in balance control is a common and often an initial disabling symptom of MS [20] and previous studies demonstrated that aerobic performance is significantly reduced in persons with MS [8,32], which may suggest an increased risk of mortality and limited mobility. There are limited data on physical performance in individuals with MS and determining factors that contribute to aerobic performance and balance in people with MS will assist therapists in planning treatment for these individuals. We hypothesized that increase in inflammatory factors and hormonal dysfunction may attributed to impaired physical performance in MS patients; therefore, we examine the physical performance and myelination factors levels in MS patients with different disability status. We also investigated the relationship between physical performance and myelination factors such as hormonal, inflammatory and anti-inflammatory markers in MS patients.

MATERIALS AND METHODS

Subjects

The participants in this study were 27 female between 18 and 48 years of age. All participants were volunteers from the MS Center of Shiraz, Iran. The inclusion criteria for the subjects with MS were diagnosis with relapsing-remitting MS by modified McDonald criteria, presenting any type of orthopedic, any cardiovascular or pulmonary disease, pregnancy, cancer, bone fracture of less than 6 months, use of prostheses, any serious nervous system disorder, any health problems to prevent effort on the physical test and taking part in regular physical activities before this study and age between 18 and 50 years. Their mean Expanded Disability Status Scale (EDSS) score was 2, with a range of 1 to 4.5.

Study design

This was a cross-sectional study, and each subject was tested during a single session lasting approximately 60 min. The study protocol was approved by the Islamic Azad University, Shiraz branch, Iran and all study participants provided written informed consent before testing. Before the examinations a neurologist assessed EDSS and participants divided into three groups: Group A: EDSS <1.5, Group B: EDSS 1.5 – 2 and Group C: EDSS> 2.

Measurements

Anthropometric and body composition measurements

Height and weight were measured, and body mass index (BMI) was calculated by dividing weight (kg) by height (m^2). Waist circumference was determined by obtaining the minimum circumference (narrowest part of the torso, above the umbilicus) and the maximum hip circumference while standing with their heels together. The waist to hip ratio (WHR) was calculated by dividing waist by hip circumference (cm). Body fat mass, body fat percentage and lean body mass were assessed by bioelectrical impedance analysis using a Body Composition Analyzer (BoCA x1, Johannesburg, South Africa).

Balance Assessment

To assess Balance and monitor mobility, the standing balance test was used [6]. The subjects stood on one leg for as long as possible. The subject was permitted to practice their balancing before starting the test for one minute. The timing stopped, when the elevated foot touched the ground or the subjects lost their balance position. The best of three attempts was recorded. The test was repeated on the other leg.

Aerobic performance measurement
The 500-meter walking test was used to examine the aerobic performance. Each participant walked 500 meters as above as fast possible and the time of performance was recorded.

Biochemical analyses
Fasted, resting morning blood samples (10 ml) were taken at the same time after familiarization. For menstrual status, all the participants were menstruating regularly and defined as eumenorrheic (28- to 32-day menstrual cycles during the previous year); all testing was performed during the follicular phase of the menstrual cycle. All the subjects fasted at least for 12 hours and a fasting blood sample was obtained by venipuncture. Plasma obtained was frozen at -80 ^{o}C for subsequent analysis. The plasma brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), IL-6, IL-10, IL-17, IL-1β (Boster Biological Technology Co., Ltd, Hubei, China), prolactin (Pishtaz teb, Tehran, Iran), cortisol (AccuBind^{TM} Monobind Inc, USA), Adrenocorticotropic hormone (ACTH) (Enzo Life Sciences GmbH, Germany), TNF-α (Orgenium Laboratories Business Unit, Finland) and Dehydroepiandrosterone sulfate or DHEA sulfate (Demeditec Diagnostics GmbH, Germany) were measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kits. The sensitivity of kits for BDNF, NGF, IL-6, IL-10, IL-17, IL-1β, prolactin, cortisol, ACTH, TNF-α and DHEA sulfate was < 2 pg/ml, < 1 pg/ml, < 0.3 pg/ml, < 0.5 pg/ml, <1 pg/ml, < 0.15 pg/ml < 15 mIU/l, < 0.25 µg/dl, < 27 pg/ml, < 7pg/ml and < 44 ng/ml respectively.

Statistical analysis
Results were expressed as the mean ± SD. One-way ANOVA was used to evaluate time-course change in variables. Post hoc analyses (Bonferroni) were then performed when warranted. The relationships between variables were determined using Spearman correlation test. The level of significance in all statistical analyses was set at P≤0.05. Data analyses were performed using SPSS software for windows (version 17, SPSS, Inc., Chicago, IL).

RESULTS

Anthropometric and body composition characteristics of the subjects are presented in Table 1. The results showed that there were no significant differences in body mass, BMI, WHR, body fat mass, body fat percentage and lean body mass among the three groups. One-Way ANOVA, also demonstrated that there are significant differences in RLB (F= 8.9, P= 0.001), LLB (F= 3.8, P= 0.03) and 500-meter walking test (F= 7.4, P= 0.003) between the groups (Table 1). The time of RLB and LLB were higher in MS patients with lower EDSS and they completed the 500-meter walking test faster that those with higher disability status.

Table 1. Anthropometric, body composition and physical performance (mean ± SD) of the subjects

	Group A (EDSS< 1.5, n= 8)	Group B (EDSS 1.5 – 2, n= 9)	Group C (EDSS> 2, n= 10)
Body mass (kg)	58.8 ± 18.7	68.9 ± 6.2	72.3 ± 16.09
BMI (kg/m^2)	22.8 ± 6.8	26.2 ± 2.6	29.3 ± 7.2
WHR	0.79 ± 0.06	0.81 ± 0.03	0.83 ± 0.03
Body fat mass (kg)	18.8 ± 11.4	24.8 ± 4.7	28.4 ± 10.8
Body fat (%)	29.3 ± 9.6	35.7 ± 4.2	38.1 ± 8.0
Lean body mass (kg)	37.6 ± 7.2	41.4 ± 3.5	40.9 ± 6.2
EDSS	0.6 ± 0.5	1.7 ± 0.2 ‡†	3.4 ± 1.1*
RLB (s)	55.4 ± 38.2	25.2 ± 19.6	6.1 ± 11.2 *
LLB (s)	63.5 ± 81.9	22.8 ± 16.9	4.3 ± 10.8 *
500-meter walking test (s)	370.5 ± 85.4	386.2 ± 51.6 †	616.7 ± 227.02 *

Data are the mean ± SE of values of the anthropometric, body composition and physical performance in each group. (‡) Statistical significance for Group A vs. Group B, (*) Statistical significance for Group A vs. Group C and (†) Statistical significance for Group B vs. Group C.

Neurotrophin concentrations, inflammatory markers and hormonal levels of the subjects are presented in Table 2. One-Way ANOVA showed that there is a significant difference in BDNF between groups (F= 5.7, P= 0.009). Post hoc analyses demonstrated that BDNF concentration was higher in group A than group B and C, while no significant differences were observed between group B and C. For NGF, inflammatory (IL-6, TNF-α, IL-17 and IL-1β) and anti-inflammatory (IL-10) markers and hormonal concentrations (prolactin, Cortisol, ACTH and DHEA sulfate) no significant differences were observed between groups.

As shown in Table 3, there is a positive relationship between DHEA sulfate with LLB (r = 0.69, P= 0.001) and RLB (r = 0.58, P= 0.001). Spearman correlation test demonstrated that no significant relationships between neurotrophin concentrations, inflammatory markers and other hormonal levels with physical performance of the subjects.

Table 2. Neurotrophin concentrations, inflammatory markers and hormonal levels (mean ± SD) of the subjects

	Group A (EDSS< 1.5, n= 8)	Group B (EDSS 1.5 – 2, n= 9)	Group C (EDSS> 2, n= 10)
BDNF (pg/ml)	1228.7 ± 253.05	950.0 ± 99.04‡	982.9 ± 176.4*
NGF (pg/ml)	31.6 ± 37.8	7.3 ± 6.3	13.05 ± 14.9
IL-6 (pg/ml)	10.7 ± 2.7	13.9 ± 7.7	19.2 ± 22.3
TNF-α (pg/ml)	7.5 ± 3.9	18.05 ± 27.9	19.8 ± 25.6
IL-10 (pg/ml)	84.9 ± 119.7	60.08 ± 34.1	67.01 ± 61.6
IL-1β (pg/ml)	13.9 ± 18.5	6.9 ± 11.3	3.8 ± 4.3
IL-17 (pg/ml)	527.7 ± 407.1	466.4 ± 603.6	463.1 ± 554.4
Prolactin (mIU/l)	267.6 ± 138.5	339.8 ± 100.8	339.5 ± 127.8
Cortisol (µg/dl)	17.1 ± 8.08	19.08 ± 7.3	19.8 ± 11.2
ACTH (pg/ml)	3.1 ± 1.4	6.7 ± 7.9	4.03 ± 4.2
DHEA sulfate (ng/ml)	1.4 ± 0.5	0.98 ± 0.4	1.3 ± 1.07

Data are the mean ± SE of values of the neurotrophin concentrations, inflammatory markers and hormonal levels in each group. (‡) Statistical significance for Group A vs. Group B and (*) Statistical significance for Group A vs. Group C.

Table 3. Correlation coefficients of physical performance with neurotrophin concentrations, inflammatory markers and hormonal levels of the subjects

	RLB		LLB		Aerobic performance	
	r	P	r	P	r	P
BDNF (pg/ml)	0.33	0.09	0.23	0.2	0.36	0.07
NGF (pg/ml)	- 0.15	0.4	- 0.23	0.2	0.01	0.9
IL-6 (pg/ml)	- 0.19	0.3	- 0.15	0.4	0.02	0.9
TNF-α (pg/ml)	- 0.17	0.3	- 0.2	0.3	0.01	0.9
IL-10 (pg/ml)	- 0.15	0.4	- 0.13	0.5	- 0.02	0.9
IL-1β (pg/ml)	- 0.07	0.7	- 0.1	0.6	0.3	0.09
IL-17 (pg/ml)	- 0.01	0.9	- 0.01	0.9	0.2	0.3
Prolactin (mIU/l)	0.20	0.2	0.22	0.2	0.14	0.4
Cortisol (µg/dl)	0.12	0.5	0.09	0.6	0.06	0.7
ACTH (pg/ml)	0.07	0.7	0.18	0.3	0.05	0.7
DHEA sulfate (ng/ml)	0.58	0.001*	0.69	0.001*	0.34	0.08

(*) Correlation is significant at the 0.001 level.

DISCUSSION

The present study demonstrated that MS patients with lower EDSS were better in physical performance. The results showed that the time of RLB and LLB were higher in MS patients with lower EDSS and they completed the 500-meter walking test faster that those with higher disability status. It is well known that MS patients have a lower daily activity level than matched healthy people [28] and inactivity-related health problems such as an increased incidence of osteoporosis, depression, fatigue and death from cardiovascular diseases have been shown in MS patients [7,10,39]. Fatigue, often severe, affects about 85% of MS patients which causes decreased mobility, leads to impaired functional capacity and subsequently reduced physical activity and sporting [25,36]. Some studies have indicated a loss of muscle mass in MS patients [14,15] that is due to decreased muscle strength [14], and may affect balance defect [9]. Maintaining dynamic balance relies on intact visual, somatosensory and vestibular input [1] combined with coordinated righting reflexes. The increased risk of falls in MS is complicated by poor judgment and compromised muscle strength and motor control [5]. Risk of fracture from falls in MS patients is 2- to 3.4-times higher than for a healthy control. Changes in mental status may lead to poor judgment and slowed response time that contribute to fall risk [31]. Furthermore, aerobic capacity, in terms of maximal oxygen consumption (VO_{2max}), has been reported to be reduced among MS patients [8,32]. Other cardiovascular parameters like resting heart rate and diastolic blood pressure have been shown to be elevated in MS patients [2]. Savci et al. [32] noted that the shorter distance covered during a 6 minute walking test is determined by the limitations in activities of daily living, resting heart rate and subjective symptomatic fatigue in patients with MS, while respiratory muscle weakness, lung function and level of neurological impairment do not contribute to impaired functional exercise capacity in these patients.

Our results showed that although BDNF concentration was higher in MS patients with lower disability (P<0.05), no significant changes were observed in inflammatory, anti-inflammatory and hormonal levels among MS patients with different disability. Neurotrophins like BDNF and NGF are thought to play an important role in neuronal repair and plasticity. Recent experimental evidence suggests neuroprotective effects of these proteins in MS [16]. BDNF is a neurotrophin; it is integral in the maintenance of the healthy neuronal phenotype. Additionally, BDNF has been shown to acutely modulate presynaptic neurotransmitter release [18] and evoked excitatory postsynaptic currents via TrkB receptors [23] and to directly induce neuronal depolarization [19]. It is becoming widely recognized that exercise is directly beneficial to brain health and function, probably via a BDNF-mediated mechanism. BDNF is found and made in many locations throughout the body [24] in addition to its namesake source of production, the brain. Traditionally, it was believed in MS that axonal loss occurred in chronic lesions. However, new findings suggest that axonal transection can begin very early in the course of MS and axonal damage was found in active and chronic active MS lesions, particularly in areas of acute inflammation and demyelination. The mechanisms of axonal loss are uncertain, but may involve axonal degeneration secondary to demyelination, the action of inflammatory mediators and immune attack directed at axonal components. Axonal destruction and it's progression, is the major cause of irreversible damage in the CNS and the increase of disability in MS patients [3]. Research results demonstrated that blood levels of inflammatory markers such as IL-1β, IL-6, IL-17 and TNF-α increased [4,33], while anti-inflammatory markers such as IL-10 decreased [29] in MS with respect to healthy controls. Our results also showed that inflammatory markers such as IL-1β, IL-6, IL-17 and TNF-α level were higher and IL-10 concentration was lower than normal range however no significant changes were observed among MS patients with different EDSS.

Hormonal disorders are one of the most important compliant of MS patients. The results are in agreement with previous reports showing that plasma cotrisol, prolactin, and ACTH were higher than normal range, however no significant differences were observed between three groups of MS patients. Previous studies have shown hyperactivity of the HPA axis and increase in ACTH in MS patients [21,37]. Michelson et al. [27] and Ysrraelit et al. [37] have also shown that basal levels of plasma cortisol and ACTH are significantly elevated in patients with MS. Researchers indicated that hyperprolactinemia also more common in MS patients [38]. HPA axis dysfunction, hyperprolactinemia and increased in plasma cortisol and decrease in DHEA sulfate suggesting a possible preclinical endocrine insufficiency in MS patients. In conclusion, our results showed that balance and aerobic performance were higher in MS patients with lower EDSS and BDNF concentration was higher in these patients. On the other hand, the present study demonstrated a positive relationship between DHEA sulfate with leg balance of the patients and no significant relationships were observed between neurotrophin concentrations, inflammatory markers and other hormonal levels with physical performance of the subjects.

CONCLUSION

The results of this study indicate that MS patients with lower EDSS were better in physical performance. On the other hand, our results showed that hormonal disorders may the most important factors that affected physical performance in female MS patients; however additional research is needed

Acknowledgment
The work was supported by grants from the Islamic Azad University, Shiraz branch. The authors gratefully acknowledge the all subjects whom cooperated in this investigation.

REFERENCES

[1] Anacker SL, Di Fabio RP, *Phys Ther*, **1992**, 72, 575.
[2] Anema JR, Heijenbrok MW, Faes TJ, Heimans JJ, Lanting P, Polman CH. *J Neurol Sci*, **1991**, 104, 129.
[3] Bartosik-Psujek H, Stelmasiak Z. *Neurol Neurochir Pol*, **2002**, 36, 505.
[4] Bielekova B, Martin R. *Brain*, **2004**, 127, 1463.
[5] Black FO, Shupert CL, Horak FB, Nashner LM. *Prog Brain Res*. **1988**, 76, 263.
[6] Bohannon RW. *Age Ageing*, **1997**, 26, 15.
[7] Bronnum-Hansen H, Koch-Henriksen N, Stenager E. *Brain*, **2004**, 127, 844.
[8] Chetta A, Rampello A, Marangio E, Merlini S. *Respir Med*, **2004,** 98, 522.
[9] Claerbout M, Gebara B, Ilsbroukx S, Verschueren S. *Mult Scler*, **2012**, 18, 498.
[10] Cosman F, Nieves J, Komar L, Ferrer G, Herbert J. *Neurology*, **1998**, 51, 1161.

[11] Fischer A, Otte C, Krieger T, Nicholls RA, Krüger S, Ziegler KJ, et al. *Psychoneuroendocrinology*, **2012**, 37, 1712.
[12] Foster SC, Daniels C, Bourdette DN, Bebo BF Jr. *Neuroimmunol*. **2003**, 140, 78.
[13] Fox EJ. *Neurology*. **2004**, 63, S3.
[14] Garner DJ, Widrick JJ. *Muscle Nerve*, **2003**, 27, 456.
[15] Gloeckl R, Heinzelmann I, Baeuerle S, Damm E, Schwedhelm AL, Diril M, et al. *Respir Med*, **2012**, 106, 75.
[16] Gold SM, Schulz KH, Hartmann S, Mladek M, Lang UE, Hellweg R, et al. *Neuroimmunol*, **2003**, 138, 99.
[17] Gold SM, Voskuhl RR. *Prog Brain Res*, **2009**, 175, 239.
[18] Jovanovic JN, Czernik AJ, Fienberg AA, Greengard P, Sihra TS. *Nat Neurosci*, **2000**, 3, 323.
[19] Kafitz KW, Rose CR, Thoenen H, Konnerth A. Nature, **1999**, 401, 918.
[20] Kanekar N, Lee YJ, Aruin AS. *Gait Posture*, **2013**, S0966, 135.
[21] Kern S, Schultheiss T, Schneider H, Schrempf W, Reichmann H, Ziemssen T. *Psychoneuroendocrinology*, **2011**, 36, 1505.
[22] Lassmann H. *Pathology of multiple sclerosis*. In: Compston A, Ebers G, Lassmann H, McDonald I, Matthews B, Wekerle H, editors. McAlpine's multiple sclerosis. London: Churchill Livingstone, **1998**.
[23] Levine ES, Dreyfus CF, Black IB, Plummer MR. *Proc Natl Acad Sci USA*, **1995**, 92, 8074.
[24] Lommatzsch M, Braun A, Mannsfeldt A, Botchkarev VA, Botchkareva NV, Paus R, et al. *Am J Pathol*, **1999**, 155, 1183.
[25] MacAllister WS, Krupp LB. *Phys Med Rehabil Clin N Am*, **2005**, 16, 483.
[26] Martino G, Furlan R, Brambilla E, Bergami A, Ruffini F, Gironi M, et al. *J Neuroimmunol*, **2000**, 109, 3.
[27] Michelson D, Stone L, Galliven E, Magiakou MA, Chrousos GP, Sternberg EM, et al. *J Clin Endocrinol Metab*, **1994**, 79, 848.
[28] Ng AV, Kent-Braun JA. *Med Sci Sports Exerc*. **1997**, 29, 517.
[29] Ozenci V, Kouwenhoven M, Huang YM, Xiao B, Kivisäkk P, Fredrikson S, et al. *Scand J Immunol*, **1999**, 49, 554.
[30] Redelings MD, McCoy L, Sorvillo F. *Neuroepidemiology*, **2006**, 26, 102.
[31] Sandyk R. *Int J Neurosci*, **1997**, 92, 95.
[32] Savci S, Inal-Ince D, Arikan H, Guclu-Gunduz A, Cetisli-Korkmaz N, Armutlu K, et al. *Disabil Rehabil*, **2005**, 27, 1365.
[33] Seven A, Aslan M. *Turk J Biochem*, **2007**, 32, 112.
[34] Shuster EA. *Curr Top Microbiol Immunol*, **2008**, 318, 267.
[35] Then Bergh F, Kümpfel T, Grasser A, Rupprecht R, Holsboer F, Trenkwalder C. *J Clin Endocrinol Metab*, **2001**, 86, 1610.
[36] White LJ, Dressendorfer RH. *Sports Med*, **2004**, 34, 1077.
[37] Ysrraelit MC, Gaitán MI, Lopez AS, Correale J. *Neurology*, **2008**, 71, 1948.
[38] Zhornitsky S, Yong VW, Weiss S, Metz LM. *Mult Scler*, **2013**, 19, 15.
[39] Zorzon M, de Masi R, Nasuelli D, Ukmar M, Mucelli RP, Cazzato G, et al. *J Neurol*, **2001**, 248, 416.