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Mild and motivational exercise in social supporting environment for over passing primary fatigue in patients with multiple sclerosis

Abstract

The most common symptom displayed in patients with multiple sclerosis (MS) is a pronounced sense of fatigue that can have negative effect on functional ability and quality of life (QOL). An important goal of researchers and clinicians involves improving the QOL of individuals with MS and the exercise therapy represents potentially modifiable behavior that positively impacts on pathogenesis of MS and thus the QOL.

However, the main barrier for its application is low motivational level that MS patients experience due to fatigue with adjacent reduced exercise tolerability and mobility, and muscle weakness. Getting individuals with MS motivated to engage in continuous physical activity may be particularly difficult and challenged, especially those with severe disability (Expanded Disability Status Scale; EDSS 6-8). Till now, researchers have focused their attention mainly on the moderate or vigorous intensity of exercise and on cardio respiratory training in MS patients to achieve improvements in daily life quality and less pointed on exercise content, and most importantly, on breathing exercise. We assume that MS patients experience more stress with aerobic exercise or moderate to high intensity program exercise and hardly keep continuum including endurance exercise, or treadmill. It is important to make exercise more applicable and accessible, motivational and easy to handle, and most of all productive for everyone with MS. We propose that specific exercise content, including breathing exercise in a group led by physiotherapist at first, efficiently reduces primary MS fatigue and brings more motivation for this patients to support personal continuous exercise at home by themselves.

Keywords: exercise, fatigue, motivation, multiple sclerosis, quality of life

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Introduction

Multiple sclerosis (MS) is chronic and progressive disease which involves unpredictable episodes of inflammatory demyelination and axonal transaction that result in lesions along axons of nerve fibers in the central nervous system (CNS). These lesions disturb smooth and rapid conduction of electrical potentials along neuronal pathways. The interference with neuronal conduction causes many symptoms which people with MS experience. Ultimately, this disease process can result in functional limitations, disability and thus reduced QOL. Fatigue is the most common and often contributor to disability in MS, and more than any other symptom, determines the QOL in MS patients.[1]

MS fatigue is defined as a lack of physical and mental energy, which interferes with usual and every day activities. When fatigue is a direct consequence of MS it is termed „primary" fatigue. A term secondary" fatigue is cause of MS-related conditions like infection, poor sleep, spasticity, pain and drug side effects.[2]

The cause of the primary fatigue in MS remains unclear. Inflammation and neurodegeneration are basic processes that lead to the damage of CNS structures in MS. Dysgulation of the inflammatory balance in favor of a pro-inflammatory state is characteristic of MS, which underlies MS-related fatigue.[3,4] As well, the MS patients very low levels of serum Brain Derived Neurotropic Factor (BDNF), normally the most abundant neurotrophic factor in our CNS, unlike those found in the healthy controls suggest that main neuron repair factor was hardly present. BDNF regulates the growth of nerve axons, neuron differentiation, proliferation and survival, promotes neurogenesis and neuro plasticity and mediates central and peripheral myelination. In CNS, it enhances the capacity of oligodendrocytes to myelinate nerve axons (brain and spinal cord).[5–7] In addition, it regulates the myelin structural proteins.[8,9] It is possible that low levels of the neuron repair protein–BDNF can cause „weakened nerves" and ''central and peripheral nervous system exhaustion" and thus primary fatigue.

Exercise therapy is an efficient rehabilitation strategy, and during the past decades, studies on exercise therapy in MS have shown promising effects. It has been documented that exercise in general possesses the potential to reduce MS fatigue.[2]

The possible mechanisms that exercise leads to, is decrease of pro-inflammatory cytokines expression and increase of serum and cerebrospinal fluid BDNF concentration that may underlie MS-related fatigue.

There are evidences that acute and moderate exercises induce a Th1 response with creating pro-inflammatory cytokines such as IL1β and TNF-α (associated with fatigue in individuals with MS)[10–12] while chronic exercise appeared to suppress these pro-inflammatory cytokines and increase anti-inflammatory cytokines including IL-4, IL-10 and TGF-β.[13]

It is obvious that the combination between modality, intensity and duration of exercise determines the type of synthesized cytokines.[14] High levels of circulating cytokines in serum are known to negatively affect the circulating levels of BDNF in MS.[3,12]

The down-regulation of BDNF leads to neuronal atrophy in the brain structures including hippocampus, the important region for motivation.[12] accordingly, exercise will promote increase of BDNF and thus hippocampal neurogenesis which in turn improves mood,

memory, cognition and motivation.[16–18] So, motivation for continuous exercise gets stimulated through decrease of depression symptoms with exercise itself.[18]

However, the BDNF response to exercise in MS-patients is poorly understood and demands further investigation.[19–21] Also, some studies have reported that, despite increased concentrations, BDNF levels in blood returned to baseline 30 min after cessation of exercise. These results have increased the interest to investigate the potential effects of circulatory BDNF induced by continuous exercise in MS and the fate of locally produced BDNF in CNS tissue as well.[14,15,22,23]

On the one hand, BDNF-gene is a stress sensitive gene that responds to glucocorticoid hormones, secreted during stress reactions like in exercise. That interplay is mechanism that shows important effect on disease because it is well known that small amounts of glucocorticoids support normal brain function, and the opposite, stimulation excess by these hormones causes stress-related affective disorders. Thus, corticosteroids may act in unpredictable ways in the autoimmune conditions like MS. For that reason, it is important the precise timing, dosage and duration of exercise and thus corticosteroids exposure which can likely give to heterogeneity of exercise outcome.[24]

Discussion

The fatigue in MS patients represents leading initial motivational barrier for further exercise at home alone by themselves and, we assume, it could be easily over passed with continuous mild and stress less exercise program providing more motivation for MS patients.[25] Regarding fatigue, MS individuals are characterized by reduced exercise tolerability and muscle weakness, often leading to decreased motivation and physical inactivity.[26] This was the main reason to see was there any improvement in MS patients fatigue, especially in those with Expanded Disability Status Scale (EDSS) from 6-8, after mild stress less exercise but with an accent on breathing exercise in a short time.

Muscle strengthening in general is important for MS patients because of stimulated secretion of certain myokines with anti-inflammatory effect and stimulation of brain structures associated with increase of neurotrophic factors.[2,15,16] Furthermore, by improving the strength of the respiratory muscles in MS patients, it is likely that the exercise capacity and overall physical functioning will also improve and fatigue will be reduced.[27]

The effect of physical activity on fatigue happens mainly through interplay of BDNF and pro-inflammatory cytokines.[3,4,14,28] However, there are controversial findings about serum BDNF concentration after certain exercise program. For example, studies have reported no changes in exercise- induced serum BDNF levels in MS individuals following moderate aerobic training program. Other studies reported increase of serum BDNF levels in MS after 30 min of moderate exercise but with following decrease to baseline 30 min after cessation of exercise. Some authors indicated that the increase magnitude of the serum BDNF levels during exercise is dependent on the intensity of exercise.[22,28,29]

Many of the clinical trials have examined the effect of exercise on fatigue in people with MS using moderate to high exercise intensity and endurance exercise (cycle ergometry, resistance training) to achieve improvements in daily life quality. Some of them had positive outcomes or improvements, whereas other trials reported no beneficial changes in fatigue after exercise.[30] Also, thede studies concentrated mainly on MS patients with good mobility or minimal-to-moderate disability who mostly need no assistance in walking (EDSS<6,5).[30] We assume that moderate intensity exercises could be harmful for CNS in certain group of MS patients, especially in those with EDSS from 6-8. It is possible that forced exercises induce bigger stress response that in turn leads to negative effects in the body of MS patients, especially in CNS.[23,30]

Further, Motl and Gosney identified length and amount of exercise as significant exercise effect moderators on QOL of MS patients.[31] However, detailed reporting of disability status scale of MS subjects is needed, involved in exercise program.[32]

Getting MS individuals with low mobility motivated to engage in physical activity may be particularly difficult and challenged. Thus, we also want to make a point on importance of physiotherapists role as "motivational leader" in helping overpass this psychophysical barrier that primary fatigue makes on motivation in MS patients. To maintain this motivation for exercise continuum at home we emphasize exercise in a social supporting surrounding with MS individuals (range of EDSS from 0-8). We assume that this is an important segment of motivational struggle regarding primary fatigue.

Based on our preliminary positive results in a pilot study with MS individuals (EDSS 0-8) we can assume that content of exercise program and its duration pro session is important to carry out this goal.[25] The pilot study was designed to verify feasibility of an upper limbs and breathing exercise and to explore possible effects on fatigue and the QOL in a group of ambulatory and nonambulatory individuals with MS for the future larger trial. Ambulatory and non-ambulatory individuals could successfully complete this exercise program without exacerbation of MS.

The pilot study involved exercise program with respiratory muscle involvement for 10 minutes in the beginning and in the end of each session, exercise for coordination and amplitude, and combination of strengthening exercise for upper limbs, 2 times a week for 1 hour in a group led by the physiotherapist in the MS Center, and at home alone in between. The precise exercise protocol can be found in reference from Grubić Kezele et al.[25] For measuring fatigue and psychophysical functioning before and after exercise we propose Modified Fatigue Impact Scale (MFIS) and RAND Medical outcomes study 36-item short-form health survey (SF-36).

Our preliminary results showed decreased fatigue followed by better psychophysical functioning. As well, we noticed that continuous exercise is important to achieve better QOL. We assume that this exercise program could be quite enough to achieve positive results regarding MS-fatigue as motivational barrier and thus QOL in MS individuals with all ranges of EDSS.

However, our research needs further evaluation in a bigger group of subjects. Besides measuring QOL, determining BDNF and cytokine profile is necessary. We can assume that serum BDNF levels don't reflect the intensity than continuity of specific strengthening exercise. To test this hypothesis, we propose to determine BDNF serum level and compare it with cytokine profile in MS patients before and after recommended exercise program. We also propose that maintenance of increased BDNF levels in brain tissue.[23] rather than in serum, determinate final psychophysical state in these patients.

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Conflicts of interest

The authors report no conflicts of interest.

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