Journal of the Neurological Sciences 362 (2016) 251–257

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

High-intensity resistance training in multiple sclerosis — An exploratory study of effects on immune markers in blood and cerebrospinal fluid, and on mood, fatigue, health-related quality of life, muscle strength, walking and cognition

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ARTICLE INFO

Article history:
Received 22 October 2015
Received in revised form 7 January 2016
Accepted 29 January 2016
Available online 3 February 2016

Keywords:
Multiple sclerosis
Exercise
Resistance training
Immunology
Fatigue
Quality of life

ABSTRACT

Background: High-intensity resistance training is unexplored in people with multiple sclerosis.
Objectives: To evaluate effects of high-intensity resistance training on immune markers and on measures of mood, fatigue, health-related quality of life, muscle strength, walking and cognition. Further, to describe participants' opinion and perceived changes of the training.
Methods: Twenty patients with relapsing–remitting multiple sclerosis performed high-intensity resistance training at an intensity of 80% of one-repetition maximum, twice a week for 12 weeks. Blood and optional cerebrospinal fluid samples, and data on secondary outcome measures were collected before and after intervention. A study-specific questionnaire was used for capturing participants' opinion.
Results: Seventeen participants completed the study. Plasma cytokine levels of tumor necrosis factor were significantly decreased post-intervention ($p = 0.001$). Exploratory cytokine analyses in cerebrospinal fluid ($n = 8$) did not reveal major changes. Significant and clinically important improvements were found in fatigue ($p = 0.001$) and health-related quality of life ($p = 0.004$). Measures of mood ($p = 0.002$), muscle strength ($p \leq 0.001$), walking speed ($p = 0.013$) and cognition ($p = 0.04$) were also improved. A majority of participants evaluated the training as very good and perceived changes to the better.
Conclusion: High-intensity resistance training in persons with relapsing remitting multiple sclerosis with low disability had positive effects on peripheral pro-inflammatory cytokine levels, led to clinically relevant improvements in measures of fatigue and health-related quality of life, and was well tolerated. These results provide a basis for a larger randomized trial.

1. Introduction

Multiple sclerosis (MS) is an autoimmune chronic inflammatory and neurodegenerative disease of the central nervous system (CNS). A majority of patients initially display relapses of focal neurological deficits followed by a variable degree of recovery, so called relapsing–remitting MS (RRMS) [1]. This phase is likely driven by a systemic immune response with enrichment of activated cytokine producing T cells to the CNS [2–3]. Cytokines play an important role in the MS pathogenesis and are therefore targets for treatment interventions. It is believed that pro-inflammatory and anti-inflammatory effects occur over time

Abbreviations: CIS, checklist individual strength; CNS, central nervous system; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; HADS, hospital and anxiety depression scale; HRQL, health-related quality of life; IL, interleukin; MS, multiple sclerosis; MSIS-29, MS impact scale; 1RM, one-repetition maximum; RRMS, relapsing–remitting multiple sclerosis; RCT, randomized controlled trial; TNF, tumor necrosis factor; TST, timed-stands test; VAS, visual analog scale.

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http://dx.doi.org/10.1016/j.jns.2016.01.063
0022-510X/

in the progression of the disease. Disease progression and clinical outcome in MS is usually monitored by the expanded disability status scale (EDSS) [4] with scores ranging from 0 (no signs) to 10 (death).

MS has a vast impact on health, leads to activity limitations and may lead to reduced health-related quality of life (HRQL) [5–6]. Exercise is suggested to be important to retain motor and ambulatory functions. There is robust evidence for positive effects of exercise on aerobic capacity, muscle strength and mobility-related activities, and weaker evidence for positive effects on mood, fatigue and HRQL [7–8]. In most cases effects of aerobic exercise have been studied. Resistance training, although less evaluated, seems to be well tolerated at low-to-moderate-intensity in MS patients with mild-to-moderate disability [7]. Notably, some results also suggest that resistance training may have direct effects on MS disease processes by modulating blood cytokine levels [9]. This is in line with recent research identifying skeletal muscles as a secretary organ that produce and release a contraction dependent variety of cytokines mediating both direct and indirect anti-inflammatory effects [10–12]. It may be speculated that higher intensity exercise will have a more profound effect on the inflammatory processes [13].

Studies of high-intensity resistance training where loads correspond to 80% of one-repetition maximum (1RM), i.e. 7–8RM, are practically non-existing in MS. When the present study was planned, only two studies reporting such loads were found, and both involved solely lower extremity muscles. One reported enhanced neural drive after 4×4 repetitions (85–90% of 1RM) of dynamic leg press and plantar flexion 5 days a week for 3 weeks in seven patients attending a rehabilitation program [14]. The other, a randomized controlled trial (RCT) of 38 patients with mild-to-moderate MS, reported improved muscle strength, functional capacity, fatigue, mood and HRQL after 12 weeks with twice a week lower extremity progressive resistance training [15–16]. However, the high-intensity load of 8RM was only applied during the last four weeks of the training period [15–16]. Notably, none of the above mentioned studies included analyses of the effects on cytokine levels. Thus, there is a lack of studies evaluating the effects on inflammatory markers in MS after exercise regimes using high loads involving major muscle groups of the whole body. The primary exploratory aim of the present study was to test the hypothesis that high-intensity resistance training in people with MS would have a positive effect on the inflammatory process by lowering markers of immune activation in blood and cerebrospinal fluid (CSF). Secondary aims were to explore effects on measure of mood, fatigue, HRQL, muscle strength, walking and cognition. Further, we wanted to describe participants' opinion on the form and intensity of the training, as well as their perceived changes in fitness, strength, flexibility and fatigue.

2. Material and methods

2.1. Participants

Possible participants were identified in January 2013 through a MS registry held at the Department of Neurology, Karolinska University Hospital, Stockholm, Sweden. Inclusion criteria were; RRMS, EDSS score ≤4, age 18–50 years and clinically stable on first line therapy with once weekly intramuscular interferon beta-1a (AVONEX®) since at least six months. The latter inclusion criterion was chosen in order to rule out potential differences in exercise effects due to differences in disease-modifying drug treatment. Exclusion criteria were; people practicing high-intensity training, inability to understand Swedish and other conditions or diagnoses judged to potentially interfere with the study, e.g. severe cardiorespiratory or renal disease.

An invitation letter was sent out to 91 eligible patients, of which 22 declined, 47 did not answer and 22 were interested in participating. Two were excluded for insufficient knowledge of Swedish and ongoing regular high-intensity training, respectively, leaving 20 participants for the study. Ten were enrolled in the study in March 2013 and the remaining 10 in September 2013. Information was given both orally and written, and all participants gave their signed consent before enrolment. All participants completed, for safety reasons, a general somatic evaluation including blood pressure measures and heart and lung auscultations before enrolment. Further, a new EDSS evaluation was performed to check for the accuracy of EDSS scores in the MS registry. The study was approved by the Regional Ethical Review Board (2013/11-31/4) in Stockholm. Procedures were conducted in accordance with the Helsinki Declaration. The study was not registered before participant recruitment due to the exploratory pilot design. A specific power analysis was not preformed given the exploratory nature of the study. However, based on previous experience in the research group of studies in inflammatory diseases, a sample size of 15–20 patients was considered necessary for a pilot-study. Accordingly, this was the number we applied and received ethical approval from the Regional Ethical Review Board in Stockholm to include in the study (register number 2013/11-31/4).

2.2. Measures

Sampling of blood and CSF (optional) as well as assessments by EDSS and the cognitive symbol digit modalities test [17] were conducted at the Neurology Department, Karolinska University Hospital, Sweden. The remaining data was collected by an experienced physiotherapist, not involved in the training, at the hospital's Physiotherapy Department. Data was collected before, i.e. within two weeks before the first training session, and after the 12 week intervention, i.e. within three weeks after the last training session.

Mood was assessed by the hospital anxiety and depression scale (HADS) [18], which consists of two subscales ranging from 0 to 21. A score of eight or greater in MS patients indicates a generalized anxiety disorder or depression, respectively [19]. Fatigue was assessed with a 100 mm visual analogue scale (VAS), with 0 = no fatigue and 100 = worst imaginable fatigue, and the checklist individual strength (CIS) [20]. The CIS consists of 20 items concerning different aspects of fatigue experienced during the last two weeks. The fatigue subscale (8 items) gives a score from 8 to 56, where ≥35 is considered as severe fatigue [21], and a 21% change in scores is regarded clinically relevant in ambulatory MS patients [22]. The MS impact scale (MSIS-29) [23] was used as a disease specific measure of HRQL. The MSIS-29 consists of 29 items concerning the impact of MS on daily life in the last two weeks. A physical and a psychological subscale are calculated and converted to a 0–100 number, where higher scores indicate a worse health impact. A change in scores of 24% and 37% in the physical and psychological subscales, respectively, is considered clinically relevant [24].

Muscle strength was assessed by calculation of 1RM for each included exercise in the intervention, see description under Section 2.3 below. Further, maximal concentric knee extension and flexion were assessed using a Biodex dynamometer. Participants performed, after a standardized warming-up session, four isokinetic knee extensions/flexions first at 60 degrees/s and after a minute's rest at 90 degrees/s. The right leg was tested first and then the left. The highest peak torque value from the four trials, i.e. the maximal peak torque in Newtonmeter (Nm), was recorded for each condition (extension and flexion and speed) and side (right and left). The mean value of the maximal peak torques from the right and the left leg was calculated for each speed and movement direction and used in analyses of isokinetic muscle strength. The timed-stands test (TST) [25] was used as a functional measure of lower limb strength and the time for performing 10 stands was recorded after a practice trial. The timed 10 m walk test [26] was used for calculation of walking speed. The test was performed with a static start and rolling finish and participants walked at their maximum speed, the mean of three trials was recorded and used in analyses.

Cognition was assessed by the symbol digit modalities test [17], a test where a person is asked to substitute geometric symbols into