Official Title: Preventive Complex Program for Newly Diagnosed
People With Multiple Sclerosis
Brief Title: Preventive Program in Multiple Sclerosis
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Methods

1.1. Study design

The study Preventive Complex Program for Newly Diagnosed

People With Multiple Sclerosis (NCT04355663) was realized between October 2017 and October 2019. This study monitor the immediate and persistent impact of a preventive complex six-month program specifically developed for newly diagnosed people with multiple sclerosis on fatigue, mental and physical fitness, and quality of life. The study determined whether changes in clinical function are related to changes in neurohormones, and whether the effect of therapy is dependent on the active approach of study participants.

1.2. Participants

The study included 22 newly diagnosed MS patients who met the study entry criteria (definitively confirmed diagnosis of MS, maximum similarity of clinical manifestations and disease course, stability of the clinical condition over the last 3 months, Expanded Disability Status Scale (EDSS) ≤ 6, no changes in pharmacotherapy. The evaluation of the entry criteria was performed by an independent neurologist of the MS Center of the Neurological Clinic of the FNKV in Prague. All subjects signed an informed consent form approved by the Ethics Committee of Kralovske Vinohrady University Hospital in Prague (full trial protocol EK-VP/25/0/2014 is available there).

1.3. Examination

All 22 participants were examined three times - before the start of the physiotherapy program, immediately after its end and six months apart. The effect on physical fitness (activity) (spiroregometric examination), fatigue (Modify Fatigue Impact Scale, Fatigue scale for motor and cognitive functions), depression (Beck's scale for assessing depression), acceptance of MS (Inventory of Adoption of Multiple Sclerosis), quality of life (Scale life satisfaction) and selected neurohormones (cortisol, cortison, 7β-OH-DHEA, 7-oxo-DHEA, DHEA). Inclusion Criteria:

• definite MS

• stable clinical status in the preceding 3 months

• imuno-modulatory treatment for at least two years (including glatiramer acetate, interferon beta-1a, 1b, mitoxantrone, fingolimod, natulizumab)

• Expanded Disability Status Scale (EDSS)≤6

• predominant motor impartment

• six months or more without any physiotherapy

• ability to undergo ambulatory physiotherapy

Exlusion criteria:

•   other neurological disease or conditions disabling movement

1.3.1.

Basic characteristics

The study collected some sociodemographic data, disease and treatment data: age, gender, height, weight, Body Mass Index (BMI), disease duration, type of disease, current pharmacological treatment, EDSS.

1.3.2.

Spiroergometric parameters

The following parameters were measured during spiroergometric examination: ventilation capacity - Forced vital capacity (FVC),

metabolic utilization (maximal muscle performance Watt kg^{-1} = Rmax), maximal oxygen uptake VO2 kg^{-1} = VO2max.kg-1), maximal oxygen pulse VO2 HR^{-1} kg^{-1} = VO2max.TF-1), relative ventilation (VEmax.kg-1), and overall fitness compared to the population of the same age in percent.

It was used for P / O (flow-volume) spirometry automatic breathing gas analyzer Kardiospirox-W1. Instrumentation was used for spiroergometry on a bicycle ergometer, Vita maxima method: bicycle ergometer Sana Bike 350 GE, electrodes for restless conditions Cardio-Vac type Vacuboy D, monitor for continuous monitoring of exercise electrocardiogram DELL REV A02, USA, monitor for continuous monitoring of spiroergometric values Benq FP 72E, Taiwan, mercury tonometer Sphygmomanometer Global 660, automatic respiratory gas analyzer Kardiospirox-W1.

1.3.3.

Endocrine parameters

A blinded assessor (unaware of the intervention assigned to the assessed participant) examined primary and secondary outcomes immediately before the beginning (Pre-assessment), immediately after (Post-assessment) and 8 weeks after the cessation of the two months' PT program (Washout-assessment).

The levels of serum hormones were assessed in continuous-flow left ventricular assist device (CF-LVAD) recipients between 7 to 8 a.m. in the morning before lumbar drainage test. Samples were collected in plastic tubes, frozen and stored at -79 °C. Levels of cortisol, cortisone, 7α-OH-DHEA, 7β-OH-DHEA, 7-oxo-DHEA, DHEA were measured by LC-MS/MS method described in Sosvorova et al., 2015.

1.3.4.

Questionnaires

The study monitored fatigue, depression, acceptance of MS and quality of life using a questionnaire survey. The following questionnaires were used to assess the degree of fatigue:

1) Modified Fatigue Impact Scale. This scale consists of 21 statements that describe how often fatigue has affected a person during last four weeks. Each statement is ranged from 0 (never) to 4 (almost, always). The maximum value of the scale is 84, which represents very frequent fatigue in the person. (Ritvo et. al., 1997).

2) The Fatigue scale for motor and cognitive functions: FSMC is an assessment of MS-related cognitive and motor fatigue. A Likert-type 5-point scale (ranging from 'does not apply at all' to 'applies completely') produces a score between 1 and 5 for each scored question. Thus minimum value is 20 (no fatigue at all) and maximum value is 100 (severest grade of fatigue). Two subscales (mental and physical fatigue) can be made. Items included in the subscale mental are 1-4-7-8-11-13-15-17-18-20 and items included in the subscale physical are 2-3-5-6-9-10-12-14-16-19. (Penner et al.,2009).

3) Questionnaires were used to assess the mental state and acceptance of MS:

The Satisfaction With Life Scale measures the current level of satisfaction with one's own life. Investigators express the extent to which they agree or disagree with the five statements. The rating scale contains 7 points (1- "strongly

disagree" and 7 - "strongly agree"). The maximum number of points on the scale is 35 (maximum satisfaction with your life) and the minimum number of points is 5 (dissatisfaction with your life). (Diener et al., 1985).

4) Multiple Sclerosis Acceptance Questionnaire focuses on the method of adaptation to the diagnosis of MS. This questionnaire consists of 20 statements that relate to the lives of patients with MS. The rating scale has seven points (1- "never pays" to 7 - "always pays"). The minimum value is 20 (minimum adaptation to the diagnosis of MS for a large limitation of the normal life of MS) and the maximum value is 140 points (maximum adaptation to the diagnosis of MS - without the limitation of the normal life of MS) (Ferenbach et al., 2011).

5) Beck Depression Inventory Score. This questionnaire is divided into thirteen categories and patients select a statement in each category which best fits their current feelings on the scale ranged from 0 (the best feelings) to 3 (the worst feelings). The maximum value of the total scale is 39 and shows the worst feeling of the person. (Beck et al.,1961).

1.4 Therapy

The program included information on the possibilities of physiotherapy (seminar, brochure), influencing fatigue (recommending lifestyle changes, learning movement strategies, regular controlled aerobic training), psychotherapy, treatment of psychosomatic, somatovisceral and visceromotor functional disorders using computer kinesiology, and individual therapy for neurophysiological basis Motor programs activating therapy.

1) Providing information about the possibilities of physiotherapy (seminar, brochure, Řasová et. Al., 2017). At the beginning of the program, an introductory lecture was organized, in which participants were introduced to the possibilities of physiotherapy in the treatment of multiple sclerosis (Řasová et. Al., 2017). We focused on fatigue management - recommending lifestyle changes.

2) Individual therapy dealt with the treatment of psychosomatic, somatovisceral and visceromorotic functional disorders by reflexively poor connection through the locomotor system using computer kinesiology. The patients received a total of four individual therapies. This therapy was performed by a trained physiotherapist by manual contact according to the usual procedures in the field

of rehabilitation and physical medicine, ie it examines the range of motion in individual limb segments, examines the spine in the basic planes, examines reflex changes in soft tissues and actively searches for trigger points. All tests are evaluated according to the required criteria and the obtained data are entered into special software. EIS Computer Kinesiology Profi The Start Complex compares the obtained data with the reflection contexts of Western and Eastern medicine. EIS Computer Kinesiology Profi Complex Start software processes information on feedback relationships of "horizontal" functions, ie segmental (meaning spinal segments, reflex relationships to visceral organs and endocrine glands) as well as "vertical relationships" (myofascial chains and chaining of functional disorders, muscle pathways from classical acupuncture).

EIS Computer Kinesiology Profi Start Complex in therapy uses:

• kinesiological analysis algorithm

• algorithm for searching for reflex changes in soft tissues

• currently individually adequate selection of exercises (patient education for homework) (Jandová et. Al., 2013).

3) Group psychotherapy: The program participants completed a total of six group psychotherapies. Psychotherapy used psychological means such as words, conversation, nonverbal behavior, working with emotions and awareness, creating a therapeutic relationship. During group psychotherapy, self-knowledge expands and deepens and leads to a reduction in self-destructive behavior, effective management of problems, conflicts and life tasks. It helps patients better adapt to life situations, gain insight (understanding the context and unconscious motives), gain new information, learn to solve their problems effectively (Schubertova, 2013). The main goal of psychotherapy was to accept a new life situation, change attitudes, improve self-awareness, persuade to take an active approach to treatment, create a new healthier lifestyle with respect for illness and oneself, and thus to increase the overall quality of life.

4) A series of three workshops in which participants became actively introduced to how they can control momentum using Motorized Therapy Activating Programs (MPAT).

In MPAT therapy, partial motor functions are induced, which mature during postural development. Motor programs that can only be activated at the

subconscious level are activated. Postural stabilization is induced and supported in the sagittal plane, stabilizing functions while sitting, when getting up, standing and stepping. The whole body is activated, there is an interaction between the postural system, the upright system and the system of phasic movements. During therapy, the joints of the whole body are functionally centered, the spine is straightened and the dynamic reaction of the whole body is activated (Řasová et. Al., 2017). The workshop was attended by all participants in the study at once. The elements of sensorimotor learning and motor control were individually shown to everyone and the motor program was activated (during the first workshop the motor program for sitting, the second for standing and the third step). The programs were individually activated during the two-hour workshop (the workshop was also attended by eight postgraduate students, thanks to whom it was possible to correct the activated postural positions for all workshop participants).

1.5.

Primary outcome measures:

Questionnaires: *Modified Fatigue Impact Scale, The Fatigue scale for motor and cognitive functions, The Satisfaction With Life Scale, Multiple Sclerosis Acceptance Questionnaire, Beck Depression Inventory Score.*

Secondary outcome measures:

Spiroergometric parameters - ventilation capacity - *Forced vital capacity* (FVC), *metabolic utilization* (maximal muscle performance Watt kg^{-1} = Rmax), *maximal oxygen uptake* (VO2 kg^{-1} = VO2max.kg-1), *maximal oxygen pulse (*VO2 HR^{-1} kg^{-1} = VO2max.TF-1), *relative ventilation* (VEmax.kg-1).

Endocrine parameters - levels of cortisol, cortisone, 7β-OH-DHEA, 7-oxo-DHEA, DHEA.

1.6.

Statistical analysis:

All measured spiroergometric values as well as all the measured spirometric values were compared with the Czech population norm. (Seliger V, Bartůněk Z,

Roth Z. Physical fitness of the Czech population aged from 12 to 55 years . Praha: Karolinum, 1977 (in Czech).