Improving Cognition in people with Progressive Multiple Sclerosis: A Multi-Arm, Randomized, Blinded, Sham-Controlled Trial of Cognitive Rehabilitation and Aerobic Exercise (CogEx)

CogEx
Improving cognition in people with progressive multiple sclerosis

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Background

Cognitive dysfunction affects up to 70% of people with progressive MS (PMS). It can exert a deleterious effect on activities of daily living, employment and relationships. Preliminary evidence suggests that impairments can improve with cognitive rehabilitation (CR) and aerobic exercise, but data come predominantly from people with relapsing-remitting MS. There is a need to investigate these approaches in people with progressive forms of the disease.

Study hypotheses

1. CR and aerobic exercise are effective treatments for people with PMS who have cognitive impairment, in particular processing speed deficits, and that a combination of these two treatments is more effective than each individual treatment given alone.
2. Improvements in processing speed are associated with magnetic resonance imaging (MRI) modifications of functional and/or structural plasticity within specific brain networks/regions involved in information processing speed.

Methods

Randomized, double-blinded, four armed, controlled clinical trial of CR and exercise. 360 subjects will be randomly assigned to one of four groups: CR plus aerobic exercise; CR plus non aerobic exercise; passive CR plus aerobic exercise and passive CR plus non aerobic exercise. Subjects will receive one of these treatments for 12 weeks, twice a week. One in three subjects will undergo structural and functional MRI to investigate the mechanisms underlying the response.

Following screening (Table 1), all eligible subjects will have a cognitive and physical assessment at baseline, 12 weeks and 6 months. The primary outcome measure is the symbol digit modalities test (SDMT – oral version) which measures processing speed. Secondary outcome measures include: indices of non-verbal memory, a range of Patient Reported Outcomes (Table 2), walking speed and a dual cognitive-motor task.

Table 1. Initial Screening Measures

Age	25-65
Cognition	Exclude persons who score within 1.282 SD of SDMT country specific normative data
Ambulation	Exclude persons who are wheelchair dependent (EDSS ≥ 7.0).
Medical History	Exclude persons with a nervous system disease other than PMS
Medications	Exclude persons who have used steroids within the past 3 months
Exercise activity	Exclude persons doing regular aerobic training (eg. bicycling, running, swimming or rowing) at >60% of the maximal heart rate, for > 1day/week for > 30min/session for past 3 months. Assessment based on a customized telephone interview and the Borg scale.
Medical contraindications	Exclude persons with more than a single "yes" response on all items of the Physical Activity Readiness Questionnaire (PAR-Q) or two "yes" responses along with a physician's approval.
Transport	Exclude persons unable to travel to the centre or requires ambulance transportation.

Table 2 Patient Reported Outcomes

Anxiety and depression	Hospital Anxiety and Depression Scale Beck Depression Inventory-revised
Fatigue	Modified Fatigue Impact Scale
Subjective cognitive difficulties	Perceived Deficits Questionnaire
Subjective impact of walking	12-item Multiple Sclerosis Walking Scale
Impact of Multiple Sclerosis	29-item Multiple Sclerosis Impact Scale
Quality of Life (generic)	European Quality of Life-5 Dimensions
Assessment of Global Function	Functional Assessment of Multiple Sclerosis

Discussion

The study is being undertaken in 6 countries (11 centres) in multiple languages (English, Italian, Danish, Dutch); with testing material validated and standardized in these languages. The rationale for this approach is to obtain a robustly powered sample size and to demonstrate that these two interventions can be given effectively in multiple countries and in different languages.

Funding Agency: MS Society of Canada