Post exertional malaise, a starting point to investigate and understand myalgic encephalomyelitis/chronic fatigue syndrome.

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To explore the pathophysiology of post-exertional malaise (PEM). Investigate the changes occurring in cardiovascular parameters, cognitive capacity, physical capacities, brain activation and perfusion, and metabolites in patients with ME/CFS...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON56626

Source
ToetsingOnline

Brief title
PEM

Condition

- Other condition

Synonym
chronic fatigue syndrome; post exertional malaise

Health condition

Myalgic encephalomyelitis, chronic fatigue syndrome

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Chronic fatigue syndrome (CFS), Myalgic encephalomyelitis (ME), Post-exertional malaise (PEM)

Outcome measures

Primary outcome

Cardiovascular measures:

- Values obtained during T1 and T2 during prone and standing conditions of

Heart rate (HR), Blood pressure (BP), Oxy- and deoxygenated hemoglobine

concentration (oxy-Hb, deoxy-Hb)

Neuromuscular measures

- Absolute values and changes over time during T1 and T2 of maximal index

finger abduction force, voluntary activation of the index finger abductor

- Absolute values and changes over time during T3, and T4 of maximal index

finger abduction force

Cognitive measures:

- Absolute values and changes over time during T1 and T2 of reaction times and

percentage of correct responses

-Absolute values and changes over time during T3 and T4 of reaction times and

percentage of correct responses

MRI measures during T3 and T4:

-BOLD activation at rest and during a cognitive and physical tasks.

-Arterial spin labelling (ASL) at rest and during physical task.

Secondary outcome

- Changes over time, during physical and cognitive task performance of heart rate, blood pressure, oxygen and deoxygenated hemoglobin concentration

- Metabolites

- Patient-reported outcome measures (PEM questionnaires, Chalder fatigue scale, SSS questionnaire, EQ-5D questionnaire, DPEMQ, SF-36, HADS, Bell_CFDIS scale, COMPASS-31, PSQI, MFIS

- Scores of daily activity and sleep patterns:

o time spent at different activity intensities and sedentary time.

o sleep parameters such as time in bed, sleep time, waking up after sleep onset, waking time.

o Heart rate variability (HRV) measured during cognitive and physical tasks in the lab and for 7 days during daily activities

- Number of repetitions in the two 30 chair to stand tests (30CST)

- Handgrip strength

- Knee extensor force

Neuromuscular measures

- Absolute values and changes over time during T1 vs T2 and T3 vs T4 of the

index finger abductor force decline (fatigability) during sustained contraction

Study description

Background summary

Exercise is an important contributor to general health and is considered a potential remedy for chronic diseases. This is in strong contrast with the observation that in most ME/CFS patients exercise aggravates their symptoms. Recently, post-exertional malaise (PEM) is defined as the key symptom of ME/CFS. The etiology and pathophysiological mechanisms underlying ME/CFS are still unknown and objective diagnostic criteria are not available. Various hypotheses are postulated including disorders of several organ systems but the heterogenous presentation of symptoms in patients, and the multisystem deficits complicate reaching an all-encompassing hypothesis. It seems therefore reasonable to focus on the key symptom, i.e., PEM. PEM can be induced by minor cognitive or physical exertion and can be assessed with questionnaires. Acute physical activity triggers complex cardiovascular, metabolic, and molecular responses and for ME/CFS, it is important to understand the relation between these acute processes and the prolonged presentation of aggravated symptoms. We therefore want to measure metabolites, cardiovascular responses, cognitive performance, muscle force and fatigability in 50 controls matched on group level for sex, age, and activity. To follow changes in these parameters over we perform time-series analysis, before, during and after recovery of task performance. Besides understanding these interactions, it is also essential to understand how these acute and prolonged responses affect behaviour and perception. To obtain objective and subjective measures of perception we include advanced brain activation analysis (measures of brain activity and network analysis), together with effort and PEM-related questionnaires.

Study objective

To explore the pathophysiology of post-exertional malaise (PEM). Investigate the changes occurring in cardiovascular parameters, cognitive capacity, physical capacities, brain activation and perfusion, and metabolites in patients with ME/CFS compared with sex, age, and activity matched controls

before and after physical and cognitive fatiguing tasks on two consecutive days. Secondary objectives are to investigate the differences in sleep patterns, activity levels and heart rate variability in ME/CFS patients and their matched controls as well as to find associations between patient report outcomes and changes in the response of organ systems.

Study design

A single centre, cross-sectional, experimental study in which effects of cognitive and physical tasks are followed.

Study burden and risks

Participants will be asked to perform physical and cognitive fatiguing tasks while measuring cardiovascular parameters as well as brain activation and perfusion and various blood samples will be taken. Regarding the experimental protocol it is anticipated that after performing our protocol ME/CFS patients will perceive a temporary worsening of their symptoms (e.g. fatigue, muscular and joint pain, headaches, brain fog), but no serious adverse events are expected. The importance of investigating worsening of symptoms in detail and on so many different levels, allows us to identify and better understand the parameters involved in the mechanisms of the disease. Possible additional burdens that all our participants may experience during our study are the following:

Collection of 8 blood samples over three days

Determination of voluntary muscle activation with the superimposed twitch technique may feel a bit painful but for less than one second.

Standardized vascular occlusion test of the thigh muscle can feel uncomfortable

Time investment: 5 times 2.5 hours of measurements as well as the filling in of the questionnaires at home (90 min* + 4*3 min), total= ca. 14.5 hours.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Age > 18 years but <65.
- Willing and be able to complete all study procedures.
- Able to provide informed consent

Additional inclusion criteria for ME/CFS patients:
- ME/CFS patients must meet international concensus criteria (ICC) or Canadian consensus criteria (CCC).
- A self-reported illness narrative of the development of persistent fatigue.
- Existence of post-exertional malaise according to the DSQ-2.
- The persistent fatigue may have an acute onset or become progressively worse over 6 months.

Exclusion criteria

Exclusion criteria for all subjects:
- Use of immune-modulating drugs in the past 3 months.
- A serious medical condition that may explain symptoms similar to ME/CFS, such as cancer, coronary artery disease, uncontrolled diabetes, chronic infection (hepatitis B and C, tuberculosis, HIV), inflammatory diseases, autoimmune diseases (e.g. such as rheumatoid arthritis, lupus or polymyositis), severe COPD or other severe persistent respiratory disease, severe anaemia, renal failure, Addison's or Cushing's disease or severe neurological disease (such as

Parkinson's disease).
- History of head injury with loss of consciousness or amnesia lasting greater than a few seconds within last five years or lasting greater than 5 minutes at any point during their lifetime.
- Suspected, probable, or confirmed Lyme disease.
- Current or substance use disorder within last 5 years.
- A mood disorder or other psychiatric diagnosis (prior to a diagnosis of ME/CFS).
- Pregnant, actively seeking to become pregnant or breastfeeding in the past 12 months.
- BMI >35.
- having cognitive or communication problems which reduces the capacity to understand instructions.
- planned a change in medication during the testing period.
- Use of medication that affects the blood pressure (e.g., Beta-blockers, fludrocortisone, vasoconstrictors).
- Participation in a clinical protocol (e.g., anti-inflammatory drug intervention study) which includes an intervention that may affect the results of the current study.
- Having claustrophobia
- Current (within 1 week) use of prescription or over-the-counter medications, herbal supplements, or nutraceuticals that may influence brain excitability. Examples of medications that influence brain excitability include tricyclic antidepressants, hypnotic, antiepileptic, antipsychotic medication, stimulants, antihistamines, muscle relaxants, dopaminergic medications, and sleep medications.
- Use of B12 high dosage injections
- colour blindness

Additional exclusion criteria for control subjects:
- performing high intensity or moderate intensity activities more than 30 minutes per week
- substantial fatigue as determined using MFIS fatigue questionnaire >30 .

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2024
Enrollment:	100
Type:	Anticipated

Ethics review

Approved WMO

Date:	13-03-2024
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	10-12-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	ClinialTrails.gov
CCMO	NL85693.042.23