A prospective, multi-centre study investigating the incidence and prognosis of relapses, pseudo-relapses and other causes of (sub)acute neurological symptoms in patients with relapsing-remitting multiple sclerosis.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Demyelinating disorders
Study type	Observational invasive

Summary

ID

NL-OMON55562

Source
ToetsingOnline

Brief title
RELAMS study

Condition

- Demyelinating disorders

Synonym
Multiple sclerosis

Research involving

Human

Sponsors and support

Primary sponsor: Sint Elisabeth Ziekenhuis
Source(s) of monetary or material Support: Nationaal MS Fonds

Intervention

Keyword: Multiple sclerosis, Neurofilament light, Pseudo-relapses, Relapses

Outcome measures

Primary outcome

The percentage of patients with neurological deterioration based on relapse, pseudo-relapse or other mimics. The cause of deterioration is determined by the treating neurologist, based on history taking, neurological examination, laboratory results and if available MRI and when in doubt on the panel's opinion.

Secondary outcome

* The duration, severity (measured on the EDSS/physical examination, comparison based on available information on previous neurological examination and history taking to determine FSS prior to relapse, and patient reported outcomes on the impact on daily activities) and prognosis (no, partial or complete recovery, based on available information on previous neurological examination and patient*s judgement) of relapses/pseudo-relapses/mimics
* The diagnostic tools (history taking, EDSS, MRI, laboratory tests) which guide a neurologist to diagnose the cause of the deterioration
* Serum NFL

Study description

Background summary

Relapses in patients with multiple sclerosis (MS) are common. Relapses have a considerable impact on patients; they can lead to residual symptoms and uncertainty and have considerable impact on daily life. It is important to recognize relapses because the present treatment strategy aims for NEDA (No Evidence of Disease Activity), which means no relapses, no progression of disability and no change in MRI MS white matter lesions. A relapse indicates activity of the disease and will lead to decision making such as start of methylprednisolone treatment and/or change in immunomodulating therapy.
In daily practice it is however not always easy to determine whether there is a real relapse. A possible other cause is a pseudo-relapse during a period with infection or fever, however true relapses can also be provoked by infections. Other possible mimics are for example other neurological conditions, complications of treatment, heat intolerance, orthopaedic conditions, metabolic disturbances or functional disturbances. These mimics / pseudo-relapses ask for different care and support than relapses.
Magnetic resonance imaging (MRI) for diagnosing a relapse is not a very sensitive test. A gadolinium-enhancing lesions which correlates with the new clinical symptoms supports the diagnosis of a real relapse, however, new lesions may not always be apparent on imaging and new lesions can also appear without clinical symptoms (the clinic-radiological paradox). There are no studies correlating the location of the lesion with the clinical localisation.
A potential biomarker to make it more easy to distinguish a relapse from a pseudo-relapse could be serum neurofilament light protein (NFL). No research has been done on NFL as marker to distinguish relapse from pseudo-relapse.
Hardly any literature exists on the incidence of relapses versus pseudo-relapses in patients with (sub)acute new symptoms in MS. In this prospective study we want to assess the cause of neurological deterioration (relapse, pseudo-relapse, mimic) and their incidence and outcome. Also we would like to find out if serum NFL is a good marker to distinguish relapse from pseudo-relapse.

Study objective

The primary objective of this study is to assess whether the cause of neurological deterioration in patients with RRMS/CIS is a real relapse, a pseudo-relapse or mimic and compare these groups on baseline characteristics.

Secondary objectives:
* To determine the duration, severity and prognosis of documented relapses measured on the Expanded Disability Status Scale (EDSS) and patient reported outcomes on impact on daily activities and degree of recovery and compare these

parameters between groups.
* To describe which data, derived from anamnesis, neurological examination, MRI and laboratory tests, guide a neurologist to diagnose the cause of the deterioration
* To determine if serum NFL differs between patients with a clear relapse, a clear pseudo-relapse and patients in who the neurologist is in doubt between these two causes

Tertiary (exploratory) objectives:
* To investigate the diagnostic potential of serum NFL to distinguish relapse from pseudo-relapse
* To determine the location of the relapse (optic nerve, cerebellum, brainstem, cerebral hemispheres or spinal cord) (in case of real relapse) and the prognosis of a relapse in that region
* To determine if the location of the current relapse is associated with the location of the previous relapse
* The requirement for treatment with glucocorticoids due to the relapse
* Degree of certainty about the cause of deterioration

Study design

This is a prospective, multi-centre, study. Eligible subjects with a possible relapse with onset less than 14 days are included. The subjects will be examined clinically at baseline, after 6 and 12 weeks. As per standard care laboratory tests and urinary screening will be performed at baseline if necessary. In a subgroup an extra blood sample is taken at baseline and week 12 to assess on neurofilament light chain levels (only in patients with relapse, pseudo-relapse or when in doubt). The MRI of the brain and/or spinal cord is performed (T1-weighted, T2-weighted, FLAIR (fluid attenuated inversion recovery) and gadolinium enhanced) at baseline depending on the judgement of the treating neurologist. After each visit patients will receive an e-mail with 1 or 2 questions on impact on daily activities and degree of recovery.

Study burden and risks

For each subject this study covers for a period of approximately 12 weeks. During this period subjects will visit the hospital 3 times, which is 1 extra visit than during regular care. During these visits a physical and neurological examination will be performed. During the first visit a blood sample and urinary screening will be taken (as per standard care). The visits will take approximately 30 minutes per visit. According to standard care, in some cases a MRI will be performed. The MRI takes about 20 minutes. At baseline and week 12 an extra blood sample will be taken in a subgroup. Risks associated with the visits and investigations are considered minimal as these are routine activities. After each of the 3 visits patients will receive an e-mail with 1 or 2 questions on impact on daily activities and degree of recovery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* The subject must give written informed consent
* The subject is between the age of *18 and *55 years
* The subject suffers from RRMS or CIS
* The subject has an EDSS of 5.5 or less prior to baseline (e.g. ambulatory without aid for about 100 meters)
* The subject has experienced (sub)acute neurological symptoms within 14 days before visit
* The subject must be prepared to and considered able to follow the protocol during the whole trial period and to attend the planned visits

Exclusion criteria

* The subject has received treatment with glucocorticoids within one month prior to the inclusion in the study
* The subject has experienced a relapse within one month prior to inclusion in the study
* The subject has already been included in this study during a previous episode of symptoms

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-02-2020
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO Date:	23-08-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-09-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
CCMO	NL68078.028.19

Study results

Date completed: 16-05-2023

Actual enrolment: 125

Summary results
Trial is onging in other countries