Natural history and biomarker identification in Spinocerebellar Ataxia type 1

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Primary Objective- To identify (a combined set of) clinical and non-clinical markers most sensitive to disease progression in Dutch SCA1 mutation carriers. Secondary Objectives:- To quantify the annual change in disease-relevant clinical scales and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON55272

Source
ToetsingOnline

Brief title
SCA1

Condition

- Neurological disorders congenital
- Movement disorders (incl parkinsonism)

Synonym
ataxia, disorder of coordination

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ataxia, biomarker discovery, natural history study, SCA1

Outcome measures

Primary outcome

The main objective of this study is to identify (a combined set of) clinical and non-clinical markers most sensitive to disease progression in Dutch SCA1 mutation carriers. In line with this objective, the main study endpoint is defined as:

• Annual change of validated clinical scales and patient-reported outcome measures that capture the relevant disease characteristics of SCA1.

Secondary outcome

As we also want to explore the potential of novel biomarkers for disease progression in SCA1 mutation carriers, the following secondary endpoints are defined:

• Features extracted from automated speech analysis;

• Structural MRI and MR spectroscopy parameters;

• Disease protein ataxin-1 in CSF, with a to-be developed ataxin-1 assay using TR-FRET, as described for ataxin-3 (Nguyen et al., 2013);

• Total tau, neurofilament light chain (NFL) and GFAP in CSF, tear fluid, and/or blood with assays operational in the CSF lab.

• Features extracted from analysis of walk/balance performance performed

with opal-sensors.

Study description

Background summary

Spinocerebellar ataxia type 1 (SCA1) is a rare, autosomal dominant neurodegenerative disease, affecting the cerebellum and connected brain regions with devastating consequences. The cause of SCA1 is an expanded polyglutamine repeat in the ataxin-1 protein, which provides a clear target for therapy development. Previous studies showed that downregulation of mutant ataxin-1 can improve behavior and brain pathology in SCA1 mouse models.

Currently patients only receive symptomatic treatment, which is often ineffective against progressive loss of mobility and independence and an early death. Development of a gene therapy that can halt or reverse disease progression is urgently awaited, and as patients say; *there is finally hope for a treatment*. To prepare for the development of such a therapy, insights into the natural course of the disease, as well as validated biomarkers are mandatory. As it is suspected that there is already irreversible brain damage at the onset of ataxia, preclinical mutation carriers and mildly affected patients represent an appropriate target population for future interventional trials. Whereas validated clinical outcome measures for ataxia have been developed, the dynamics of these and their sensitivity to change in the Dutch SCA1 population are unknown. Also, there is an almost complete lack of biomarkers for SCA1, while the availability of validated biomarkers is an essential precondition for interventional studies, in particular of interventions that target molecular mechanisms of SCA1 and aim at modifying the disease course rather than temporarily improving ataxia symptoms. Therefore, development and validation of innovative disease biomarkers will be a major focus of this project.

Study objective

Primary Objective
- To identify (a combined set of) clinical and non-clinical markers most sensitive to disease progression in Dutch SCA1 mutation carriers.

Secondary Objectives:
- To quantify the annual change in disease-relevant clinical scales and patient-reported outcome measures in Dutch SCA1 patients.
- To establish the utility of automated speech analysis as a surrogate motor biomarker in SCA1.
- To establish the utility of structural MRI and MR spectroscopy measurements

as surrogate disease progression markers
- To develop and establish the utility of biochemical disease and progression markers
- To establish the utility of sensor measurements of walking and balance as surrogate disease progression markers.
- To generate a natural history data set of clinical parameters, MRI, speech, and biochemical biomarker measurements in SCA1 that can be exploited for further collaborative research in SCA1.
- To explore the predictive value of short-term biomarker changes (one-year) on longer term changes in clinical and patient-reported outcome measures.

Study design

This prospective cohort study will capture the natural history of Dutch SCA1 patients over the course of 2 (optionally 4) years. We will include 50 SCA1 patients (40 symptomatic and 10 preclinical) and 20 matched controls. All study participants will undergo detailed annual assessments at baseline, 1 year after baseline and 2 years after baseline, with a possible follow-up visit after 4 years.

Study burden and risks

Participants will visit the study centre once a year for two consecutive years. These three visits include a clinical assessment battery, including validated ataxia-scales and tests to assess cognitive function, mood, activities of daily living, walk/balance performance and quality of life. MRI-scans (lasting about 45 minutes to complete) and blood samples will be acquired at each visit. Patients will be asked to optionally undergo a lumbar puncture twice (baseline and after 1 year), to obtain a cerebrospinal fluid sample. Controls will receive a similar assessment protocol, with clinical assessments, MRI-scans and blood sampling, but without the lumbar puncture. 4 years after baseline an extra study visit will be planned for assessment of clinical and patient-reported outcome measures (duration 1.5 hours)

Contacts

Public
Radboud Universitair Medisch Centrum

Reinier Postlaan 4
Nijmegen 6525GC
NL
Scientific

Radboud Universitair Medisch Centrum

Reinier Postlaan 4
Nijmegen 6525GC
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Participants have to be 16 years or older;
• Patients need to have a proven mutation in the SCA1 gene (patient cohort only);
• Participant is able and willing to sign the informed consent.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Prior history of any neurological disorder, or another disease that significantly influences gait;
• General contraindications for MRI.

For those participants who consider to consent for a lumbar puncture, the following exclusion criteria, which will be checked prior to lumbar puncture, apply:
• allergy to local anesthetic agents;
• medical history of compression of spinal cord, spinal surgery, skin infection, developmental abnormalities in lower spine;
• use of blood coagulopathy and/or anticoagulant medication;
• clinical (or previous MRI) evidence of structural (space occupying) cerebral

abnormalities that are not compatible with the performance of an LP including malignancies, abscess or obstructive hydrocephalus.
• Another brain disorder, besides SCA1.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-09-2020
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	04-03-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-05-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	26-08-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL71445.091.19