MR Imaging in Spinal Muscular Atrophy (SMA) as a biomarker for disease progression

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To investigate the feasibility and usefulness of various MR techniques as a quantitative biomarker for SMA severity and disease progression. Two different MR protocols will be used. The first to investigate muscle tissue in the upper leg of both SMA...

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

Summary

ID

NL-OMON47876

Source
ToetsingOnline

Brief title
MRI as a biomarker in SMA

Condition

- Neurological disorders congenital
- Neuromuscular disorders

Synonym
Spinal Muscular Atrophy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: subsidie van het Prinses Beatrix Spierfonds

Intervention

Keyword: Biomarkers, Magnetic Resonance Imaging, Muscular Atrophy, Spinal

Outcome measures

Primary outcome

1. Muscle fat fraction as quantified with DIXON method (based on a chemical shift method for water-fat separation.

2. Changes in tissue composition of muscle, as quantified with T2 mapping (based on the transverse relaxation time of water in tissue).

3. Tissue architecture visualized using Diffusion Tensor Imaging (DTI), further enabling 3D reconstruction of tissue and quantification of microstructural properties (based on fiber tractography (FT) and fractional anisotropy (FA) together with mean diffusity (MD)).

4. Structures of spinal cord and nerve roots visualized with MR images and DTI for qualitative and quantitative assessment.

Secondary outcome

The structural and functional changes will be regarded in relation to genotype (= SMN2 copynumber, a disease modifier) and clinical parameters.
Clinical parameters include: age, gender, age at onset of disease, Forced Vital Capacity, disease severity (as measured by the SMA-FRS questionnaire and clinical scores; MRC and dynamometry score and HFMSE combined with upper limb

module) and disease duration.

Study description

Background summary

Hereditary proximal spinal muscular atrophy (SMA) is caused by the homozygous deletion of the survival motor neuron (SMN) 1 gene resulting in progressive weakness in proximal and axial muscles. A second SMN gene (SMN2) highly homologous to SMN1 is present in humans and is responsible for the production of residual SMN protein amounts that prevent lethality of SMN deficiency, but are insufficient to prevent degeneration of spinal cord *-motor neurons. The presence of the SMN2 gene has allowed the development of experimental treatment strategies that aim at increasing full length SMN mRNA and SMN protein. The preliminary development of therapeutic options call for sensitive biomarkers for disease progression and treatment efficacy. In this study, we will explore the value of innovative and non-invasive techniques as quantitative MRI biomarkers of SMA severity. We hypothesize that multi-parametric MRI can serve as an important and sensitive biomarkers of diseases severity and progression in patients with SMA.
These developments have led to the introduction of a fist-ever therapy for SMA, altering the natural disease course and giving way to emerging phenotypes. MRI techniques will be explored in this cohort of patients under therapy, during their treatment for its ability to capture this altered disease course.

Study objective

To investigate the feasibility and usefulness of various MR techniques as a quantitative biomarker for SMA severity and disease progression. Two different MR protocols will be used. The first to investigate muscle tissue in the upper leg of both SMA patients type 2 and type 3 and age-matched healthy control subjects. The second aims at visualizing the cervical spinal cord and nerve roots using a protocol that was established in a previous pilot study. Findings will be correlated to clinical scores to explore the sensitivity to detect disease progression.
Main objective of this imaging study is to investigate the value of various MR techniques such as DIXON, T2 mapping and DTI as a quantitative biomarker for SMA severity and its progression over time.

Key objectives are:
- The development of a protocol for muscle MR imaging for techniques as DIXON, T2 mapping and DTI in healthy subjects.
- To explore muscle alterations in SMA-patients compared to healthy controls using the MR techniques DIXON, T2 mapping and DTI.

- To establish the aspects of cervical spinal cord and nerve roots in SMA-patients in relation to healthy control subjects.
-To investigate the correlation of these alterations with established clinical scores, in particular motor function scales.
- To investigate the sensitivity of these MR techniques to detect SMA disease progression, with and without therapy.

Study design

Cohort study at the UMC Utrecht.

SMA patients will be recruited using the Dutch SMA database. Consent will be asked from patients with SMA who participate in this study. We aim to enrol patients with SMA type 2 and type 3.

Healthy subjects for the optimization of MR scanning protocol of muscle and of spine will be recruited prior to the research protocol.

The healthy control subjects that serve as the cohort group for the SMA-patients will be age-matched because of age-dependent changes in muscle volume and development of spinal cord. Healthy subjects will be examined for the establishment of baseline for SMA patients, the cohort of SMA patients will be followed for a period of 1 year. Only the healthy controls in the adolescent period between 12 and 18 years paired to the adolescent SMA patients will be followed again after 1 year because of spinal and muscular changes accompanying ongoing development and growth in this period.

The study aims to enrol subjects for the muscle protocol first. After completion of the first visit of the muscle protocol, the motivation for participating in the second scanning protocol of spine will be explored. Subsequently, SMA patients and their controls can be included for the spine protocol.

Total study duration is 3 years.

Study burden and risks

MRI is considered a generally safe technique. The MRI procedure produces no pain and causes no known short-term or long-term tissue damage of any kind. Risks are primarily related to the magnetic fields used in MRI. The most important known risk is the projectile effect, which involves the forceful attraction of ferromagnetic objects to the magnet. This risk is assessed prior to participation in the study through the screening procedures of the radiology department. Common side-effects of the MRI include headache, dizziness, nausea and fatigue; these are all temporary side-effects. Therefore, the risk associated with participation can be considered a minimal exceeding of

negligible risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1 a. SMA patients
i. Patients with SMA from the treatment naive cohort will be included following the predefined criteria:
1) a diagnosis of SMA type 2 or 3, diagnosed on clinical grounds and confirmed by homozygous deletion of the SMN1 gene;
2) given oral and written informed consent

ii. Patients with SMA eligible for therapy will be included following the predefined criteria:
1) a diagnosis of SMA type 1-4, diagnosed on clinical grounds and confirmed by homozygous deletion of the SMN1 gene;
2) given oral and written consent by:
- patient and parents or legal guardians when patient is between 12-15 years
- parents or legal guardians when patient is under 12 years
iii. Aged 6 years and older
b. Healthy control subjects without manifest diagnosis of motor neuron disease or myopathy
i. given oral and written informed consent
2. Capable of thoroughly understanding the study information given

Exclusion criteria

1. Tracheostomy, tracheostomal ventilation of any type, (non)-invasive ventilation
2. Any intoxication or medication known to have an association with motor neuron dysfunction, which might confound or obscure the diagnosis of motor neuron disease.
3. Presence of pronounced swallowing disorders or orthopnoea (which make it dangerous to lie supine in the MRI scanner)
4. Contra-indication for 3 Tesla MRI (as established by the radiology department)
5. Pregnancy
6. Forced Vital Capacity >15% postural change between sitting and supine or symptoms of nocturnal hypoventilation (recurrent morning headaches, nightsweats, orthopneu).
7. Presence of non-MRI compatible material in the body
8. Claustrophobia

Study design

Design

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

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	03-10-2017
Enrollment:	85
Type:	Actual

Ethics review

Approved WMO Date:	31-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL61066.041.17

Study results

Date completed:	01-07-2020
Results posted:	23-12-2020

Actual enrolment: 63

First publication
01-01-1900