MR Imaging in Spinal Muscular Atrophy; A pilot study to uncover neuronal network changes

Published: 30-01-2013
Last updated: 26-04-2024

To investigate motor connectivity in vivo in patients with SMA using MR- techniques for brain imaging.We will investigate connectivity of upper motor neurons in patients with SMA compared to disease controls (patients with myopathic disorders) and...

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

Summary

ID

NL-OMON39588

Source
ToetsingOnline

Brief title
MR Imaging in SMA

Condition

- Neuromuscular disorders

Synonym
SMA, spinal muscular atrophy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: SMA Expertise Centrum

Intervention

Keyword: Imaging, MRI, SMA

Outcome measures

Primary outcome

15 Patients with SMA type 2, 15 patients with SMA type 3 and 30 age-matched healthy controls and 15 age-related disease controls will be recruited for 3T MR imaging of the brain to determine:

1. Cortical morphology with high resolution T1 weighted images (cortical thickness, volume and surface area) (3T); 2. Structural connectivity of motor pathways with DTI and fiber tracking (3T); 3. Brain functional connectivity with resting state-fMRI (3T).

Secondary outcome

Structural and functional changes will be regarded in relation to clinical characteristics (e.g. duration of illness, disease progression), genetic factors and clinical scores.

Study description

Background summary

Spinal muscular atrophy (SMA) is a disorder characterized by degeneration of α-motor neurons, axial and proximal weakness and is caused by the homozygous deletion of human survival motor neuron (SMN) 1 gene. It is the most common genetic cause of infant mortality and causes significant disability and morbidity in survivors. The highly homologous SMN2 gene produces low amounts of functional SMN mRNA in patients with SMA, resulting in varying levels of SMN protein deficiency. SMN is important for RNA splicing and axonal transport, but the mechanisms that cause SMA are largely unknown. Recent findings in SMA animal models suggest that SMN deficiency causes abnormal connectivity of α-motor neurons with muscle at the neuromuscular junction (NMJ) and with sensory

afferents in the spinal cord. Reduced connectivity of motor neurons may therefore be an important cause for muscle weakness in SMA. We have recently confirmed that dysfunction of the neuromuscular junction is common in patients with SMA, confirming that reduced pre- and postsynaptic connectivity of motor neurons is an important characteristic of SMA. We hypothesize that reduced connectivity is not limited to lower motor neurons, but can also be found in the brain. Magnetic resonance imaging (MRI) is a powerful tool to study motor connectivity in the brain.

Study objective

To investigate motor connectivity in vivo in patients with SMA using MR-techniques for brain imaging.
We will investigate connectivity of upper motor neurons in patients with SMA compared to disease controls (patients with myopathic disorders) and healthy controls by investigating cortical thickness, structural and functional connectivity.

Study design

Observational pilot study, cross-sectional design.

Study burden and risks

Participants will undergo a clinical assessment (questionnaire (SMA FRS), FVC and muscle strength test) and MRI at the University Medical Center (UMC) Utrecht. There are no direct benefits for the individual participant.
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.
MRI in this study will be performed without medical indication for imaging of the brain. Participants will be informed of any new findings on the MR imaging of brain that need medical attention. The investigators will secure a consultation and follow up as soon as possible. Participants will be informed, before inclusion, about the possible risk of unexpected findings.
We expect that the information acquired by this research project will provide new insights in the pathogenesis of SMA.

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)
Elderly (65 years and older)

Inclusion criteria

1.
a. SMA patients
Patients with SMA will be included following the predefined criteria: 1) a diagnosis of SMA type 2 or SMA type 3, diagnosed on clinical grounds and confirmed by homozygous deletion of the SMN1 gene; 2) given oral and written informed consent
b. Disease controls with a myopathy
Patients with a myopathy will be included following the predefined criteria: 1) a diagnosis of myopathy (e.g. Becker muscular dystrophy, congenital myopathy, congenital myasthenia), diagnosed on clinical grounds and confirmed by muscle biopsy and/or genetic testing and with actual weakness defined of MRC score 1-4 of any limb; 2) given oral and written

informed consent
c. Healthy control subjects without manifest diagnosis of motor neuron disease or myopathy and given oral and written informed consent
2. Age 12 years upwards
3. Capable of thoroughly understanding the study information given

Exclusion criteria

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2013
Enrollment:	75

Type:	Actual

Ethics review

Approved WMO Date:	30-01-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-03-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-09-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2014
Application type:	Amendment
Review commission:	METC NedMec

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	NL41981.041.12