Cerebellar dysfunction and its compensation in presymptomatic carriers of dominant ataxia genes

Published: 25-01-2011
Last updated: 03-05-2024

This project has three separate but complementary research objectives. First, to find out whether there is indeed evidence of subclinical cerebellar dysfunction in these subjects, by specifically focusing on cerebellar motor learning. Second, to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational non invasive

Summary

ID

NL-OMON34216

Source
ToetsingOnline

Brief title
Cerebellar changes in presymptomatic SCA-carriers

Condition

- Movement disorders (incl parkinsonism)

Synonym
Cerebellar ataxia, coordination diffulties

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Subsidieaanvraag loopt bij PBF;alternatief is ZonNW/Klinische Fellowship

Intervention

Keyword: Cerebellar ataxia, Compensation, Motor system, Presymptomatic carriers

Outcome measures

Primary outcome

The various studies that are part of this project focus on demonstrating

differences in the:

-percentage of conditioned eye blink responses

-adaptation to splitbelt gait paradigm

-motor cortex excitability

-cerebellar modulation of motor cortex excitability

-structural connection in cerebellum-motor cortex pathway

-brain areas involved in the control of gait

Secondary outcome

Not applicable

Study description

Background summary

The dominant spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of degenerative cerebellar diseases. There are family members of SCA patients who have been tested positive for a gene mutation but who do not yet have any symptoms, which they are however prone to develop at some point as the mutations are fully penetrant. These so-called presymptomatic carriers offer a unique opportunity to study the early, subclinical stages of cerebellar dysfunction, as well as the consequences and the compensation thereof within the motor system.

Study objective

This project has three separate but complementary research objectives. First,

to find out whether there is indeed evidence of subclinical cerebellar dysfunction in these subjects, by specifically focusing on cerebellar motor learning. Second, to investigate whether the presumed latently defective cerebellum has already led to altered functional and structural coupling between the cerebellum and the motor cortex in these subjects. Third, to explore the compensatory mechanisms in these individuals that allow them to circumvent their latent cerebellar motor disturbance.

Study design

Cross-sectional, observational study with a strong neurophysiological and neuroimaging emphasis.

For objective 1:
Two implicit motor learning tasks will be used: 1) the classic and well-established eye blink conditioning, and 2) the adaptation to a rather novel, highly demanding gait task on a splitbelt treadmill, which forces the cerebellum to adapt to a different speed for left and right leg.

For objective 2:
The functional coupling will be studied by using transcranial magnetic stimulation to search for changes in motor cortex excitability and the cerebellar modulation thereof. The structural integrity of the cerebello-thalamo-cortical pathway will be quantified by means of diffusion tensor imaging (DTI) MRI.

For objective 3:
This issue will be tackled by using a functional MRI paradigm that involves motor imagery of gait, which is able to show which cerebral networks are differentially engaged in gait control.

Study burden and risks

The participants will undergo several experiments, with a combined duration of approximately 12 hours, spread out over three days. None of the experiments are painful or invasive.

There is a small risk of a seizure during the transcranial magnetic stimulation session, but this has been proven to be almost negligibly low over the recent years. The more relevant issue to mention here is the scenario that the SCA mutation carrier thinks that he/she is still unaffected, but that the clinical examination reveals subtle signs, indicating that the disease has started. The potential participants will repeatedly be reminded of this before consent is obtained and also before the actual clinical examination. If someone unexpectedly turns out to be symtomatic, he/she is offered to be follow-up in our Ataxia outpatient clinic.

Still, investigating these subjects is of great importance. The results of this project will give us new and unique fundamental insight into the characteristics of a very early-stage cerebellar defect and the consequences this has for a central pathway within the motor system. Also, understanding the mechanisms that compensate for a dysfunctional cerebellum is essential when starting to think about potential targets for neuromodulatory interventions.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Reinier Postlaan 4
6525 GC Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Reinier Postlaan 4
6525 GC Nijmegen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Proven mutation in one of the SCA genes
Age > 18 years
Free of ataxia

Exclusion criteria

Contraindications for MRI scanning (e.g. pacemaker)
Epilepsy
Other neurological disorders
Gait disorder for any reason

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-04-2012
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	25-01-2011
Application type:	First submission
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	NL34874.091.10