A biomarker for deep brain stimulation efficacy in cervical dystonia

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(I) Investigating the role of the cholinergic system and CBGTC-loop in the pathophysiology of CD, related to both motor and NMS; (II) Finding a biomarker for DBS efficacy in CD, including motor and NMS.

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

Summary

ID

NL-OMON49897

Source
ToetsingOnline

Brief title
A biomarker for deep brain stimulation efficacy in cervical dystonia

Condition

- Movement disorders (incl parkinsonism)

Synonym
disorder of muscle tension, Dystonia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Wetenschapsfonds Dystonie

Intervention

Keyword: Coherence, DBS, Dystonia, FEOBV

Outcome measures

Primary outcome

The main study parameters are:

- The difference in [18F]FEOBV PET binding between CD patients and controls,

and its relation to motor- and NMS.

- The difference in intermuscular coherence between CD patients and controls,

and its relation to motor- and NMS.

Secondary outcome

The secondary endpoint of this study is the intermuscular coherence (pre- and

post-DBS) and cholinergic binding (only pre-DBS), and whether pre-operative

measurements are predictive for the effect of DBS on motor- and NMS.

Study description

Background summary

Cervical dystonia (CD) is a complex hyperkinetic movement disorder characterized by abnormal movements and postures of the head and neck, as well as a wide range of non-motor symptoms (NMS). The exact pathophysiology is still unknown. Based on electrophysiological and functional imaging studies, it is hypothesized to be caused by dysfunctional neuronal networks including the basal ganglia, thalamus, cerebellum and cortices (CBGTC-loop). The activity of this network can be investigated by intermuscular coherence, quantified through electromyography (EMG). In this network, an abnormal function of acetylcholine is hypothesized. The anticholinergic drug trihexyfenidyl is one of the only effective drugs for dystonia, and in combination with the cognitive deficits in dystonia patients, this points towards cholinergic dysfunction as a possible factor in the pathofysiology of the disease.
Deep brain stimulation (DBS) of the globus pallidus interna (GPi) can be considered in CD patients who are refractory to medical treatment, especially

botulinum toxin injections. However, there are still challenges for DBS. For instance, DBS is not effective in all patients and the time required to observe the stimulation effect can take months. To optimize therapy and select suitable candidates for DBS treatment, a biomarker to indicate the expected response in individual patients is yet to be defined.
In the present project we aim to increase knowledge on the pathophysiology of CD, by investigating the CBGTC-loop and the activity of the cholinergic system in CD patients. Next, we want to use this to develop a biomarker for DBS efficacy in CD including motor- and NMS.

Study objective

(I) Investigating the role of the cholinergic system and CBGTC-loop in the pathophysiology of CD, related to both motor and NMS;
(II) Finding a biomarker for DBS efficacy in CD, including motor and NMS.

Study design

This study is a single center prospective case-control study.

Study burden and risks

Burden: Patients will undergo DBS surgery as part of regular care. As part of this regular care and before surgery (t=0), motor symptoms and NMS will be assessed, as well as a general interview about medication use and medical history. Also, an anatomical MRI and neuropsychological investigation will be performed, as well as a videotaped motor examination.
In addition to this, we will send the patients four short questionnaires about psychiatric symptoms, fatigue and quality of life which can be filled in at home. During an additional visit, we will perform EMG-recordings to record intermuscular coherence and perform a cholinergic PET-scan.
After twelve months (t=1), we will perform the motor- and non-motor examinations once more. For the study we will additionally repeat EMG-recordings and the questionnaires.

The controls will be tested at the same time points and this will consist of the non-motor questionnaires, a shortened neuropsychological investigation, EMG-recordings, an anatomical MRI scan with gadolinium contrast and one cholinergic PET-scan.

Risks: The risks involved in the measurements of clinical characteristics and intermuscular coherence are considered to be minimal. The PET scan will result in a radiation dose of 6,1mSv per scan. According to the recommendations from the International Commission of Radiological Protection (ICRP) a dose of 1-10mSv in one year for volunteers for biomedical research falls in a moderate risk category (ICRP publication 103.2007). With one scan per year, participants

receive 6,1 mSv and therefore we are our study falls into this moderate risk category. The MRI scan does not provide radiation risk, the only burden and associated risk is the injection of contrast fluid (gadolinium).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to participate in this study, CD patients must meet the following criteria:
• Patients with a clinically confirmed diagnosis of idiopathic CD and age >= 18 years;
• A life expectancy of at least one year after surgery;
• For the patients in the EMG-part: DBS indication approved by the DBS team of the patients hospital.

The inclusion criteria for the controls are:
• Age- and gender match to the participating patients;
• Life expectancy of at least one year after inclusion in the study;
• Age >= 18 years.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study.

CD patients and controls:
• Relevant neurological conditions other than CD;
• Previous brain surgery;
• Impossibility to stop anticholinergic medication;
• Pregnancy or breast feeding;
• Exhibition to a radiation dose for medical research, exceeding the maximum annual dose;
• Contra-indication for MRI scanning (MR incompatible implants, risk of metal particles in the eyes, tattoos containing red pigments, sensitivity to contrast fluid);
• Claustrophobia.

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:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-03-2022
Enrollment:	30

Type:	Actual

Medical products/devices used

Generic name:	FEOBV PET scan
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	10-02-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL78606.042.21