Psychiatric co-morbidity in dystonia-(plus) syndromes: is serotonin the common pathway?

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

Summary

ID

NL-OMON40547

Source
ToetsingOnline

Brief title
Dystonia en Psychiatry

Condition

- Other condition
- Movement disorders (incl parkinsonism)
- Anxiety disorders and symptoms

Synonym
dystonia (there are no synonyms)

Health condition

depressieve stemmingsstoornissen en afwijkingen

Research involving

Human

Sponsors and support

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

Intervention

Keyword: dystonia, PET, psychiatry, serotonin

Outcome measures

Primary outcome

The main study parameter is the proportion of dystonia patients having psychiatric co-morbidity, compared to the proportion having psychiatric symptoms in a healthy control population (part A), and the percentage difference in serotonin metabolism (serotonin transporter (SERT) on a [11C]DASB PET scan between subjects with dystonia and healthy controls, and between subjects with and without psychiatric disorders (part B).

Serotonin metabolism will be assessed as [11C]-DASB binding potential (BP) as outcome measure for SERT availability in different brain regions of interest (ROIs): brainstem, striatum and frontal cortex. Additionally, a whole brain voxelwise comparison will be performed using Statistical Parametric Mapping (SPM).

Secondary outcome

Motor assessment:

Severity of dystonia, severity of myoclonic symptoms, clinical severity

Psychiatric assessment

Adults: the presence of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-VI) diagnosis, Life-time prevalence of any psychiatric diagnosis, severity of anxiety symptoms, severity of panic symptoms, severity of social anxiety symptoms and avoidance, severity of OCD symptoms, severity of depressive symptoms

Children: the presence of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-VI) diagnosis

Concentrations of serotonin in platelets

Genetics: the presence of polymorphisms of 5-HTTLPR (serotonin-transporter-linked polymorphic region), DNA methylation rate of the serotonin transporter gene

Study description

Background summary

Dystonia is a disabling movement disorder characterized by involuntary, sustained muscle contractions that result in twisting and repetitive movements of abnormal postures. Growing evidence indicates an important non-motor component including psychiatric symptoms to primary dystonia. In DRD (dopa-responsive dystonia), M-D (myoclonus dystonia) and CD (cervical dystonia), psychiatric symptoms are part of the phenotype, with a significantly higher incidence of major depression, obsessive-compulsivity, and anxiety compared to the general population. Psychopathology in dystonia can not solely be attributed to a reaction to chronic disability, but a neurotransmitter dysfunction underlying the movement disorder is hypothesized to also influence the psyche. This assumption is supported by the findings that the psychiatric symptoms often precede the motor symptoms in patients with dystonia There are several important clues for the involvement of serotonin, but surprisingly this has thus far not been investigated in patients. This in

spite of the accumulating evidence that the psychiatric symptoms in particular put the greatest strain on the quality of life. Serotonin is involved in the pathophysiology of a variety of mood and anxiety disorders and many psychotropic drugs act by modulating serotonin metabolism. We hypothesize that a hyposerotonergic metabolism is the common pathway in different forms of dystonia: DRD, M-D and CD and psychiatric comorbidity. Since not all patients with CD, M-D or DRD exhibit psychiatric symptoms, genetic susceptibility and environmental influences are thought to play an additional or modifying role in the eventual phenotype.

Study objective

Primary Objective is to determine whether (A) patients with dystonia(plus) syndromes exhibit more psychiatric symptoms compared to a healthy control group and (B) whether dystonia patients show an altered serotonin metabolism (serotonin transporter status on PET-scanning of the brain).

Secondary objectives are to evaluate:
- whether an altered serotonin metabolism (serotonin transporter status) is associated with
a) psychiatric comorbidity
b) the severity of dystonia
c) a lowered concentration of serotonin in platelets
d) the presence of SERT polymorphisms
e) the methylation rate of the serotonin transporter gene

- whether a lowered concentration of serotonin in platelets/ the presence of polymorphisms/ the methylation rate of the serotonin transporter gene correlates with
a) psychiatric comorbidity
b) the severity of dystonia

Study design

Observational case-control study

Study burden and risks

The serotonin transporter (SERT) status in the brain of adult participants will be assessed with PET scan. A single intravenous catheter for the administering van radioligand will be placed in the antecubital vein of subjects. In total the scan will result in a radiation dose of 2,8 mSv, equivalent to less than 2 times the normal yearly background radiation. All participants will undergo a standardised interview including medical history, family history, psychiatric evaluation, a standardised neurologic examination and standardised video recording. The psychiatric evaluation will consist of the Mini International

Neuropsychiatric Interview (MINI-PLUS; DSM IV) and several questionnaires. Blood will be drawn in all participants to determine concentrations of serotonin in platelets and for the genetic analysis.
With this study we will be able to provide new insights in the pathophysiology of psychiatric and dystonic symptoms in patients with cervical dystonia and dystonia-plus syndromes. There are no good (pharmaco)therapeutic options for dystonia at this moment. If our hypothesis of a hyposerotonergic metabolism proves to be correct, we will proceed to modulate the serotonin level in future studies with serotonin medication and investigate the effect on both clinical aspects (including quality of life) as on PET scans. This may directly lead to the implementation of new therapeutic strategies. In this case the dystonia patients will benefit from participating in this study.

Participation of the minors in the DRD subgroup: DRD typically presents in the first decade of life. In more rare case when it presents in adult patients the presenting symptoms differ from whose in the childhood. As far as the neurotransmitter metabolism in children differs from those in adults it is necessary to include pediatric patients with DRD in this study in order to obtain the biochemical explanation of the disease symptoms in the childhood.

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

Patients with clinically confirmed diagnosis of idiopathic cervical dystonia (CD) or
Carrier of mutation in DYT11 gene for myoclonus-dystonia (MD) or
Carrier of mutation in GTP-cyclohydrolase 1 gene for dopa-responsive dystonia (DRD)
Only adults (>= 18 years old) will be eligible for PET-scans

Exclusion criteria

General exclusion criteria: other neurological conditions past of present, treatment with deep brain stimulation ;Additional exclusion criteria from the PET-scanning:
- SSRI use in the past 6 months to or during the study
- use of medication with a known effect on serotonin receptors or transporters
- pregnancy or nursing
- exhibition to a radiation dose for other reasons, exceeding the maximum annual dose

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-08-2014

Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	15-07-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	11-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-03-2021
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	NL45260.042.14