FDG-PET imaging in idiopathic REM-Sleep-Behaviour Disorder (RBD)

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

Summary

ID

NL-OMON38554

Source
ToetsingOnline

Brief title
Brain network activity in RBD

Condition

- Movement disorders (incl parkinsonism)

Synonym
REM Sleep Behaviour Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: International Parkinson Foundation

Intervention

Keyword: FDG, metabolic brain pattern, RBD, SSM/PCA

Outcome measures

Primary outcome

SSM/PCA (plus decision tree method) determination of the specific

interrelationship between brain regions in patients with isolated REM sleep

behaviour Disorder.

Secondary outcome

None

Study description

Background summary

Movement disorders or neurodegenerative brain diseases in general are difficult to diagnose at early disease stages. One reason for this is the slow development (years) of such conditions with only few complaints or unclear signs at the beginning. Well-known examples of these diseases are Parkinson*s disease (PD) and Alzheimer*s disease (AD). But there are many more less frequent conditions as well. An accurate diagnosis as early as possible is however necessary to avoid superfluous further procedures or unjustified treatments and, most importantly, to begin with potential protective therapeutic strategies as they may emerge in the course of time. A correct diagnosis is equally important to reliably inform the patient about his condition and to anticipate prognostic actions.
Sophisticated neuroimaging methods of the brain provide an inroad into this problem in that they can detect pathological changes in the brain pertinent to the group of diseases investigated here. Structural scan methods like X-ray CT and MRI scans are not helpful in early disease stages since at that stage no clear anatomical changes can be noticed apart from slight to moderate global atrophy. At later stages some diseases may show structural abnormalities in some of these conditions. But by that time the clinical picture is usually already clear.
Radiotracer PET scans on the other hand can reflect regional brain biochemical activity depending on the type of tracer applied. The PET tracer [18F]-fluorodeoxyglucose (FDG) allows the measurement of regional cerebral metabolic rate of glucose. FDG is a glucose analogue with physiological aspects almost identical to glucose. It is transported from the blood to the brain by a carrier-mediated diffusion mechanism. Glucose is then phosphorylated to glucose-6-PO4 , and FDG to FDG-6-PO4 , catalyzed by hexokinase. While glucose

phosphate is metabolized further to carbon dioxide and water, FDG phosphate is not a substrate for any enzyme known to be present in brain tissue, and is trapped for some longer time and therefore a useful imaging marker of the first step of the glycolysis.
In neurodegenerative brain diseases, specific brain regions degenerate with the characteristic consequence of specific patterns of altered metabolic brain activity. This happens before clear structural changes can be detected with imaging techniques. Measurement of glucose consumption with FDG PET imaging thus allows us to identify disease-specific cerebral metabolic brain patterns in several neurodegenerative brain diseases at an early disease stage.
Several methods have been used to identify these metabolic brain patterns. First, univariate methods like voxel-based statistical parametric mapping (SPM) were used to identify group differences between patients with neurodegenerative brain diseases and controls (1,2). However, Scaled Subprofile modelling/principal component analysis (SSM/PCA), a multivariate method, not only identifies group differences, but is also able to identify relationships between relatively increased and decreased metabolic activity within different brain regions in combined samples of patients and control scans (see Chapter 7 of this protocol *Statistical analysis*) (3,4). By using the SSM/PCA method, metabolic disease-specific patterns have been developed for several neurodegenerative diseases (5-7). In close collaboration with the New York group of Eidelberg we have installed and operationalized the SSM/PCA method at our department. This has resulted in the build-up of the GLIMPS project in collaboration with various RUG and UMCG departments (Target, NeuroImaging Center (NIC), Department of Nuclear Medicine and Molecular Biology, Department of Neurology, and Neuroscience). In clinical practice we can now check each subject for the metabolic patterns of multiple system atrophy (MSA), progressive supranuclear palsy (PSP), PD and AD.
REM-sleep-behaviour disorder (RBD) is a parasomnia characterized by apparent dream-enacting behaviours and loss of normal REM sleep muscle atonia (8). For establishing the diagnosis, polysomnography (PSG) is required and represents the clinical gold standard. RBD can be idiopathic, but is commonly associated with neurodegenerative disorders characterized by α-synuclein deposition, including PD, MSA and Lewy body dementia (DLB) (9,10). In a significant proportion of cases, RBD occurs prior to the development of clinically evident parkinsonism, and therefore idiopathic RBD may represent an early warning of PD, MSA or DLB.
With idiopathic RBD being possibly an early feature of parkinsonism, and the importance of an early diagnosis in parkinsonism, it is now possible to investigate whether metabolic patterns are present in patients with idiopathic RBD and if they could contribute to an earlier diagnosis.

Study objective

The main aim of this study is to create a specific disease related pattern in the patients with idiopathic RBD.

Study design

In this study 20 patients with idiopathic RBD and 20 gender- and age matched healthy volunteers will be included.

After metabolic brain imaging, Statistical Parametric mapping (SPM8, functional Imaging lab, London) and MATLAB (Mathworks, Sherborn, USA) is used for image processing and statistical analysis. These image data will be used to explore if it is possible to create a disease related pattern for RBD.

Both patients with RBD (or expected to have RBD) and healthy volunteers will be recruited by means of advertisements in local newspapers and posters. Besides these advertisements, patients with RBD will be recruited from referrals to the University Medical Center Groningen. Voluntary written informed consent will be obtained from each volunteer before performing any study-related procedures. Each subject will be given both verbal and written information describing the nature and duration of the study. The subjects will have two weeks to decide about participation in the study. There will be an independent physician who is available for further questions (Drs. J.J. de Vries). The subjects will not incur direct costs by participating in the study.
After obtaining written informed consent all subjects will get an RBD-Screening Questionnaire (RBDSQ) (see Appendix 1) (20). When it concludes a suspicion for RBD (five or more questions answered with *yes*) they will get a polysomnography, to validate the diagnosis of RBD. When they already have a validated diagnosis of RBD (by polysomnography) the RBDSQ and polysomnography will not be done again. When the RBDSQ concludes no suspicion for RBD, subjects can participate as healthy volunteer.
When patients are diagnosed with RBD after the polysomnography, they will undergo a neurological (by UPDRS I-III) and cognitive examination (MoCA). Also healthy volunteers will undergo this neurological and cognitive examination. Furthermore a smell test (Sniffin* Sticks Test or UPSIT - University of Pennsylvania Smell Identification Test) and a colour test (Farnsworth-Munsell 100 hue Test) will be done with all subjects.
When subjects can be included they will undergo a FDG PET scan according to protocol.

Study burden and risks

Risks in connection with FDG-scans or polysomnography are not known.
The time spent for the investigations is limited. The 15 hours polysomnography is mostly performed sleeping.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Diagnosis of RBD according to the criteria of International Classification of Sleep Disorders (ASDA Criteria 2005):
- Age between 40 and 70 years
- Women only if they are postmenopausal (> 1 year no menses)
- Written informed consent
- Capacity to understand the risks and complications of the study

Exclusion criteria

No RBD

Study design

Design

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

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-03-2013
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	11-04-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-07-2015
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	NL42857.042.12