Clinical and neurobiological characterisation of "muscarinic receptor-deficit schizophrenia" (MRDS)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON41528

Source
ToetsingOnline

Brief title
SMURF (Schizophrenia and MUscarinic Receptor Functioning)

Condition

- Schizophrenia and other psychotic disorders

Synonym
MRDS, psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw VIDI toegekend aan Prof. Dr. van Amelsvoort (nr. 91712394)

Intervention

Keyword: cognitive impairment, MRDS, muscarine receptor M1, neuroimaging

Outcome measures

Primary outcome

-M1 receptor binding: ROI*s will be the hippocampus and the dorsolateral

prefrontal cortex.

Secondary outcome

-BOLD signal activation during cognitive tasks PAL (40) and ER -40 (62) under

cholinergic challenge and in placebo. (ROI*s DLPFC and the hippocampus).

-Neuropsychological tests: CANTAB battery for schizophrenia.

Additional study parameters:

-DTI, RSfMRI, MRS

-(Epi)genetics

Study description

Background summary

Schizophrenia is a serious chronic disorder, usually starting in adolescence. Currently available treatments show no therapeutic effects on cognitive dysfunction, one of the most disabling characteristics of the disease. Cognitive impairment is a predictor of functional outcome and thus pertinent to successful treatment paradigms. Post mortem studies have found evidence of changes in acetylcholine neurotransmission at the muscarinic (M1) receptor, both in the frontal cortex and hippocampal regions of the brain, associated with cognitive functioning in both healthy control subjects and schizophrenia. Results from a hallmark post-mortem study identified a subgroup of patients among schizophrenia with *muscarinic receptor-deficit schizophrenia (MRDS)* with up to 75% loss of muscarinic receptors. It is not known whether MRDS patients present schizophrenia-associated cognitive deficits. This study will

test the hypothesis that MRDS can be identified in-vivo and that clincal and neurobiological characteresation of this group of patients will help identifying the neurobiological basis of cognitive impairments in schizophrenia.

Study objective

The main objective of the study is to investigate the muscarinic cholinergic system as a biological substrate for cognitive dysfunction in first episode psychosis patients, i.e. at onset of illness. We seek to assess whether deficits in M1 cholinergic neurotransmission exist at onset psychosis and if there is dissociation between MRDS patients, with significantly lower M1 binding, and non*MRDS patients. Furthermore, M1 bindingpotential in these regions will be related to cognitive functioning. The modulatory role of acetylcholine at M1 and differentiation in functional activation patterns will be assessed in comparison to healthy control subjects in verbal learning and memory and social cognition.

Study design

The study is a single-blind, cross-sectional placebo-controlled study. Only the first episode psychosis patients will receive SPECT imaging using 123I-IDEX on one occasion to assess brain M1 receptor binding. All Participants will then undergo two MRI scanning sessions with cognitive tasks- once under a cholinergic challenge with biperiden, and once after receiving a placebo.

Intervention

On two occasions non- invasive 3.0 Tesla MRI recordings will be conducted following a single dose of 4 mg biperiden or placebo, administered orally. For the SPECT study a registered, well- validated radioligand 123I-IDEX will be administered intravenously.

Study burden and risks

No serious side effects are foreseen. MRI is a non-invasive measuring apparatus. Mild reversible unwanted effects have been found at 4 mg of biperiden administration (eg. dry mouth, obstipation, concentration difficulties) but these are transient if occur.
The radiation exposure of the SPECT scan is classified as category IIb (intermediate), and frequently conducted at the department of nuclear medicine AMC. Moreover, 123I-IDEX will be produced according to GMP-z criteria quality benchmark.

The nature of the burden is classified as moderate considering that subjects will have to come to the AMC on 2 different occasions, undergo 2 different

types of scans. For the SPECT scan the nature of the burden is 1 venous puncture and for the MRI scan participants will be given biperiden orally as cholinergic challenge. For the healthy control subjects, the burden is considered low given that they only undergo 1 type of scan (MRI). The risks involved are negligible as all the agents and techniques employed are registered for their use and/or routinely performed at the AMC. Potential unwanted effects are mild and transient. The study will be conducted at all times under direct supervision of physicians. There are indirect benefits for patients in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with first-episode psychosis as defined by the standardised criteria of the CASH

-Medication free
-Duration of untreated psychosis no more than 1 year.
-18 years and older

Exclusion criteria

-Use of antipsychotics and anticholinergics
-Contraindications for MRI
-Severe neurological, endocrine or psychiatric disorders
-Pregnancy
-Current use of recreational drugs; participants must be abstinent of recreational drugs such as cannabis at least 4 weaks prior to participation.
-Tardive dyskinesia

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-02-2015
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO

Date:	26-01-2015

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28658
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL44908.018.13
OMON	NL-OMON28658