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

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Ethical review	Not approved
Status	Will not start
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON38703

Source
ToetsingOnline

Brief title
neuroimaging of MRDS

Condition

- Schizophrenia and other psychotic disorders

Synonym
MRDS, psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: ZonMw VIDI

Intervention

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

Outcome measures

Primary outcome

-M1 receptor binding: ROI*s will be the hippocampus, striatum and dorsolateral prefrontal cortex.

-BOLD signal activation during cognitive tasks PAL (40) and ER -40 (62) under cholinergic challenge and in placebo. (ROI*s DLPFC, hippocampus, and striatum).

-Neuropsychological tests: CANTAB battery for schizophrenia.

Secondary outcome

-DTI

-RSfMRI

-MRS placebo & biperideen

-(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 help identify 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 schizophrenia. Since cognitive dysfunction is the most disabling and untreatable characteristic of schizophrenia there is an urgency to look for new potential therapeutic targets. The M1 receptor is receiving increased interest as a potential target for the development of cognitive enhancers (36-38). However, studies testing this hypothesis in-vivo are lacking. Therefore, we wish to investigate the muscarinic cholinergic system, specifically the M1 receptor, in-vivo and clinically and neurobiologically characterize a subgroup of schizophrenia patients using cholinergic markers and specific cognitive tasks. In order to determine changes in M1 receptors and the modulatory role of acetylcholine in first episode psychosis patients in cognitive functioning.

Study design

The study is a cross-sectional study with a cross-over placebo-controlled arm. All participants will receive muscarinic SPECT imaging using 123IDEX to assess M1 binding affinity. 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 fMRI, DTI, and MRS recording 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. Minimal reversible unwanted effects have been found at 4 mg of biperiden administration (eg. dry mouth, obstipation, concentration difficulties).

The radiation exposure of the SPECT scan is classified as category IIb (intermediate), and frequently conducted at the department of nuclear medicine AMC both in patients as also in healthy human volunteers. Moreover, 123I-IDEX is a registered radioactive ligand, which is produced routinely according to GMP-criteria.
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, involving 1 venous puncture for the administration of a radioligand and cholinergic challenge. The risks involved are negligible as all the agents and techniques employed are registered for their use and/or routinely performed at AZM and the AMC. There are indirect benefits for patients in the study. Outcomes of this study are highly relevant to the development of new treatments that can treat cognitive impairments in schizophrenia, thereby substantially improving quality of life of these patients.

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)
Elderly (65 years and older)

Inclusion criteria

-Patients with first-episode psychosis as defined by the standardised criteria of the CASH
-Antipsychotic naïve
-Duration of untreated psychosis no more than 1 year.
-16 years and older

Exclusion criteria

-Use of antipsychotics or 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

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	90
Type:	Anticipated

Medical products/devices used

Generic name:	Biperden
Registration:	Yes - CE intended use

Ethics review

Not approved Date:	25-04-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	NL43804.000.13