Improve diagnosis of psychotic disorder of autoimmune origin

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Psychiatric disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON53058

Source
ToetsingOnline

Brief title
PSYANTIB (psychosis antibodies)

Condition

- Psychiatric disorders NEC

Synonym
autoimmunity, psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: ZonMw toegekend aan Dr. Martinez (nr.40_41200-98-9257),Hersenstichting Onderzoek (co-financer)

Intervention

Keyword: autoimmunity, neuronal surface proteins, Psychosis

Outcome measures

Primary outcome

The primary outcome measure of this study is the prevalence of autoantibodies to specific neuronal surface ion channel/receptor proteins: NMDA-r, AMPA-r, GABAB-r, LGI1 and Caspr-2, in patients with an early onset stable psychotic disorder with or without autoimmune encephalitis.

Secondary outcome

a) Prediction of the presence of autoantibodies on the basis of clinical symptoms (by comparing clinical cognitive and neurological characteristics of patients with a psychotic disorder with or without an underlying autoimmune antibody).

b) Identification of the effector functions of the autoantibodies (in vitro studies). Associate autoantibody effector functions with clinical characteristics.

c) Study of the BBB integrity in a descriptive way and correlate these data with the clinical characteristics and the presence of autoantibodies.

Study description

Background summary

Psychotic disorders, such as schizophrenia and bipolar disorder, are severe mental disorders that usually have profound implications for the health and daily lives of patients and their families. Approximately 1% of the population has a severe psychotic disorder and this often starts between the age of 15 and

35 years. The possibilities for treatment are still very limited and focused on the control of symptoms with antipsychotics but fail to effectively suppress the disease process. A lack of treatment rationale follows from the fact that we still do not understand how psychotic disorders arise. We also suspect that these disorders are actually a manifestation of different disease processes. However, we now believe that we are on track to find out on one of these disease processes and think that this can have very beneficial effects on the treatment of the patients. It has recently been shown that antibodies against brain proteins may cause an autoimmune disease and that patients with this disease can have severe psychiatric and neurological symptoms. We and others have seen that occasionally neurological symptoms may be absent. We suspect that a portion of the patients with a psychotic disorder actually has an autoimmune disease and that this subgroup should be treatable as is the case with other auto-immune diseases.

Study objective

The main objective of this project is to study the prevalence of autoantibodies against the NMDA-r, AMPA-r, GABAB-r and VGKC-complex (LGI-1 and Caspr-2) in patients with an early onset psychotic disorder. Patients suffering from stable but also acute psychoses will be included in the study because it is thought that during such periods the level of autoantibodies is increased, perhaps in some cases above the level of detection.
For this, blood (and CSF samples in stable patients) will be collected and analyzed. Differences in the spectrum of neuropsychiatric symptoms between patients with different autoantibodies will be correlated.
Furthermore, the pathogenic mechanisms of how these neuronal autoantibodies affect neuronal function will be studied by testing the effect of cloned monoclonal antibodies on neurotransmitter receptors/ion channels in vitro.
The BBB dysfunction will be characterized to describe the state and the role of this barrier in this pathology.

Study design

This study concerns a cross-sectional, observational and descriptive study investigating autoantibody prevalence as correlated with cognitive, psychopathological and neurologic profiles in psychosis (see point 8.1.2).
Early onset psychotic patients will participate in the study. They will donate blood and CSF and will undergo neuropsychological tests. The study consists of one or two visits, which will take place at the azM as a single center study (see section 8.3) during 4 years. Patients will receive individual codes that will be used to store the clinical data of the neuropsychological and neurological tests. The individual codes will also be used as a label for the serum and CSF obtained from these patients for antibody testing. The correlation studies (antibodies v psychiatric & neurologic profiles) will be performed blinded by a researcher.

We seek to identify differences in the spectrum of neuropsychiatric symptoms between patients without and with autoantibodies targeting NMDA-r, AMPA-r, GABAB-r, LGI1 and Caspr-2 (see section 8, Methods).

We will isolate B-cells in the blood of selected patients (with autoantibodies, see above) and we will clone the autoantibody genes and produce relative large quantities of monoclonal antibodies (see section 8, Methods). These autoantibodies will be used in in vitro experiments in which receptors are expressed in cell cultures to study the effector functions of the autoantibodies and correlate them with the clinical characteristics.

The BBB integrity of the patients will be also studied quantifying the levels of well-known proteins like albumin and immunoglobulins in blood and in CSF (See section 8.1.2 Secondary study parameters/endpoints.

Study burden and risks

No serious side effects are foreseen. The neuropsychological tests and questionnaires are non-invasive. Blood collection and a single CSF sample extraction are mild and low risk procedures. The collection of blood has a small risk of hematoma and the lumbar puncture involves only a minor risk to the patient. With the current use of atraumatic needles, the occurrence of a drop in pressure (which may cause a serious headache) is a rare event. In addition, the possibility of a drop in blood pressure following the lumbar puncture is very small. After the dorsal puncture the patient may go home unaccompanied (also if self-driving by private car) after having taken a rest period of 15 min. The whole study can be completed in one or two visits, consuming 4-5 h in total. Overall, the nature of the burden is moderately low. All the techniques employed are registered for their use and/or routinely performed at the azM. Outcomes of this study are highly relevant to the diagnosis and treatment of patients.
Groepsgebondenheid. This study must be performed exclusively with the group of patients who suffer from a psychotic disorder where an autoimmune antibody might be the cause (*groepsgebondenheid*, article 6 CCMO*). This is especially true for the subgroup of mentally incompetent (*wilsonbekwame*) patients during a period with psychosis since the level of antibodies may then be considerably higher than during stable periods when antibodies can go back to undetectably low levels. Clearly such cases would be missed if the group of mentally incompetent patients will not be included. Several cases of autoimmune encephalitis with antibodies against NMDA receptor and VGKC complex already point in that direction.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Psychotic disorder, defined as one or more of the following symptoms: hallucinations, delusions, thought disorders or catatonia (standardized criteria of the CASH)
- Psychotic disorder, defined as one or more of the following symptoms: hallucinations, delusions, thought disorders or catatonia (standardized criteria of the CASH)
- Duration of disease shorter than 5 years
- At least 16 years of age
- Capacity to understand the purpose and details of the study in order to provide written informed consent. Alternatively, in the case of patients during a period of mental instability, the informed consent will be asked from family or a legal representative.

Exclusion criteria

- Other severe brain disease which can interfere in the neurocognitive tests
- Presence of other immune disorders with active treatment
- Psychosis due to drug abuse

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-01-2017
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	22-06-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	22-02-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	07-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL55325.068.15