Cerebrospinal Fluid and Psychiatric Disorders (CSFPsych)

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Primary objectives- To investigate CSF autoantibodies (NMDAR, AMPAR, VGKC, and GABA receptors) in patients with a psychotic disorder and healthy controls. - To compare levels of immune parameters between patients with a psychotic disorder and...

Ethical review	Approved WMO
Status	Pending
Health condition type	Schizophrenia and other psychotic disorders
Study type	Observational invasive

Summary

ID

NL-OMON47432

Source
ToetsingOnline

Brief title
Cerebrospinal Fluid and Psychiatric Disorders

Condition

- Schizophrenia and other psychotic disorders

Synonym
or psychotic disorders, schizophrenia spectrum disorders

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cerebrospinal fluid, psychiatrische aandoeningen

Outcome measures

Primary outcome

Primary parameters:

CSF constituents:

- Autoantibodies to CNS receptors.

- A panel of cytokine, chemokine and growth factor levels.

- MiRNA levels.

- Neurotransmitter concentrations (including GABA, glutamate and all major amino acids).

Secondary outcome

Secondary parameters:

- Plasma: Plasma levels of the CSF constituents mentioned under primary parameters.

- Genetic assessments: To unravel the contribution of genetic variation to the quantitative phenotypes under investigation here, and thereby potentially aid in the identification of genetic variation underlying psychosis, a hypothesis-driven genetic approach will be adopted.

-To link biochemical and genetic data to the behavioral level, we will have participants fill out questionnaires assessing a range of behavioral traits, as mentioned below.

Study description

Background summary

The relevance of cerebrospinal fluid to neurobehavioral traits
Being part of the central nervous system (CNS), cerebrospinal fluid (CSF) is the body fluid in closest proximity to the brain. In clinical practice, CSF is typically targeted in neurology to determine CNS inflammation (e.g. infections and autoimmune diseases), exclude subarachnoid bleeding and aid in the diagnosis of Creutzeldt-Jacob disease. Moreover, CSF constituents have proven highly valuable diagnostic biomarkers for Alzheimer*s disease. CSF may also provide a snapshot of other molecular processes with relevance to the functioning of the CNS, including processes related to immunology, neurotransmission and microRNA (miRNA).
With regard to the field of psychiatry, recent CSF studies have proven informative for a range of biological and behavioral measures, including seasonal variation in monoamine metabolites; genetic determinants of GABA, monoamine metabolite concentrations and NMDAR coagonists; smoking behavior; schizophrenia; and depressive symptoms. These studies demonstrate that CSF is a valuable and promising body fluid that is in direct contact with the brain. It may therefore provide insight into the neurobiological background of neuropsychiatric (intermediate) traits. So far, studies have been carried out in healthy subjects or in heterogeneous study populations of psychiatric patients that have measured a range of constituents with diverging analytical methods. On the other hand, we and others have demonstrated that by using modern techniques many CSF constituents and their genetic underpinnings may be reliably determined illustrating the feasibility and validity of CSF studies.

The neurobiology of psychotic disorders
From the previous paragraph, it is apparent that CSF may be informative for neurobiological and immunological processes underlying psychiatric disorders. One important group of incapacitating mental illnesses is psychotic disorders, including schizophrenia, bipolar disorder and depression with psychotic features. These disorders have far-reaching detrimental effects on mental wellbeing and psychosocial functioning. Current treatments allow reduction of psychotic symptoms but treatment options are limited due to i) incomplete treatment response; ii) low treatment adherence (on average 26% at 18 months; and iii) a high burden of adverse effects. Moreover, the underlying neurobiology for these disorders remains largely unknown. Measuring CSF constituents may elucidate CNS processes underlying psychotic disorders. Therefore, this study aims to measure the following relevant constituents in psychotic disorders and healthy controls, as mentioned below.

CSF constituents and the underlying neurobiology of psychotic disorders
A range of CSF constituents has been associated with psychosis.
First, it has recently become evident that autoimmune encephalitis caused by

autoantibodies may present with primarily psychotic symptoms, mimicking psychiatric disorders such as schizophrenia and bipolar disorder. Autoantibodies to a range of synaptic proteins, in particular to the N-methyl-D-aspartate receptor (NMDAR), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), the GABAB receptor, and components of the voltage-gated potassium channel complexes (VGKCs) can trigger either isolated psychotic symptoms or neurological symptoms (e.g. seizures and reduced consciousness), with or without delusions and/or hallucinations. These subtypes of autoimmune encephalitis can cause psychosis, which is often clinically indistinguishable from other psychotic disorders and may respond well to immunotherapy. Since the outcome is dependent on the time lag between appearance of first symptoms and treatment initiation, improved diagnosis of this subgroup of patients with a treatable cause of psychosis is essential. Importantly, it has been shown in patients with both neurologic and psychiatric symptoms that autoantibodies may go undetectable in blood, while they are present in CSF. However, it has not been investigated to which extent auto-antibodies are present in the CSF of patients suffering from psychotic disorders.

Second, several lines of evidence implicate immune pathways in the pathogenesis of psychotic disorders. This hypothesis is supported by the observation that genes with a role in the immune system (including the MHC region) are shared between schizophrenia and bipolar disorder. On the other hand, CSF immune system parameters have not been comprehensively investigated in psychotic disorders.

Third, CSF miRNA levels may be informative for specific biological processes underlying psychotic disorders. MiRNAs are small non-coding RNA molecules (~20 nucleotides) which regulate RNA silencing and gene expression. Evidence linking miRNA to psychotic disorders stems from genome-wide association studies (GWAS), including CSF-specific miRNAs 11. Other lines of research also support the role of miRNAs in the pathophysiology of schizophrenia: postmortem studies, blood plasma investigations and mouse models. Moreover, miRNAs influence dopamine receptor 2 (DDR2) expression in humans and cognitive functioning in schizophrenia. It was recently shown that the relatively small amounts of RNA in human CSF yield sufficient RNA for both targeted expression profiling and RNA sequencing. Taken together, although evidence pleads for a role of miRNA in psychotic disorders, CSF miRNA levels have not been examined in psychotic disorders.

Fourth, several major neurotransmitter systems that may be measured in CSF have been linked to psychotic disorders, including the dopamine, GABA and glutamate systems. Converging evidence points to a role for glutamate in schizophrenia, and low CSF levels of glutamate have been found in schizophrenia patients relative to healthy controls. Nevertheless, most later studies have been negative, but those studies were underpowered and could not pick up small and medium effect sizes. In bipolar disorder, no study has specifically investigated glutamate or glutamine concentrations in CSF, but a small CSF study in a heterogeneous group of patients with affective disorders and a magnetic resonance spectroscopy (MRS) study detected aberrations in

glutamate/glutamine concentrations in bipolar disorder patients. Other lines of evidence implicating glutamate in schizophrenia and bipolar disorder include pharmacological studies demonstrating schizophrenia-mimicking symptoms for the NMDA receptor antagonist ketamine; postmortem investigations showing NMDAR NR-subunit RNA expression aberrations in brain tissue of both schizophrenia and bipolar patients; and solid and consistent genetic findings. Evidence implicating GABA dysfunction in psychotic disorders comes from preclinical, electrophysiological and postmortem studies. GABAergic involvement in bipolar disorder is illustrated by pharmacological studies demonstrating efficacy of GABA-ergic anticonvulsants and by MRS. In the current study, we will therefore measure glutamate, the metabolite glutamine and GABA in psychotic disorders and compare these levels to those in controls.
Finally, several amino acids, e.g. D-serine and glycine, act as coagonists for the NMDAR, and many of them have been implicated in schizophrenia bipolar disorder and depression with psychotic features. Small and heterogeneous study populations and outdated measurement methods with limited sensitivity have resulted in inconsistent and underpowered studies into neurotransmitter concentrations in psychotic disorders. In the present study we therefore compare concentrations of D and L-isoforms of amino acids in psychotic patients to controls.
Here, we hypothesize that at least 5% of individuals with psychosis and none of the healthy controls have positive titers of one of the abovementioned autoantibodies; that immune system parameters, miRNA levels, as well as GABA, glutamate and amino acid concentrations differ between the two groups; and finally that subjects with positive titers of autoantibodies carry genetic mutations in pathways involved with NMDAR, AMPAR, VGKC, and GABA signaling.

Relationships between plasma and central (CSF) levels
Biomarkers for psychotic disorders are currently unavailable, rendering reliable diagnostics cumbersome given the clinical heterogeneity of these conditions. A probable explanation behind such lack of reliable biomarkers for the two maladies constitutes the scarcity of investigations into biomarkers carried out to date. The focus of previous biomarker studies on peripheral body fluids - mostly serum and plasma - further compounds this shortfall. Shortage of data on the association between body fluid constituents and psychotic disorders particularly applies to CSF. Most studies performed in this context have targeted monoamine metabolites in patients suffering from a range of psychiatric disorders. To our knowledge, no study to date has investigated a comprehensive set of CSF constituents in psychotic disorders to detect possible case-control differences in concentrations or ratios between constituents. For some constituents (e.g. auto-antibodies), it is already known that measurements in peripheral tissues may yield different results compared to CSF analyses. Importantly, recent evidence shows that auto-antibodies in anti-NMDAR encephalitis may be negative in serum while they are positive in 100% of the anti-NMDAR cases. Moreover, changes in CSF titers correlate more strongly with clinical outcome than serum titers. For psychotic disorders, it is therefore also important to establish to which extent CSF concentrations are similar to

plasma levels of neurotransmitters and miRNA given the availability of plasma and therefore the potential of developing blood biomarkers for psychosis. Therefore, this study aims to compare CSF levels of the abovementioned constituents to those in plasma levels.

Genetic background may determine CSF constituent levels
Although schizophrenia candidate genes have been replicated, the role of these genes in the context of CSF intermediate phenotypes has not been investigated. We previously demonstrated how genetic studies targeting CSF may further our insight into both genetic determinants of CSF constituent concentration variability and neurobehavioral traits. In analogy to these previous hypothesis-driven and hypothesis-generating studies, here we aim to unravel such genetic determinants in both patients and controls.

Summary
In summary, the rationale to investigate CSF in psychosis is supported by four lines of reasoning:
First, it is currently unknown which percentage of psychotic patients may suffer from an underlying autoimmune disorder, e.g. autoantibody encephalitis. An LP is rarely performed in Dutch departments of psychiatry and autoantibodies are not routinely investigated.
Second, CSF is the body fluid in closest proximity to the brain and constitutes a valuable and promising target to gain insight into the neurobiological background of psychotic disorders, including potential biomarkers, such as GABA, glutamate, immune parameters and microRNAs.
Third, the genetic underpinnings of CSF variability are currently unknown and may shed light on the genetic susceptibility for psychotic disorders and the existing clinical heterogeneity.
Fourth, biomarker research in psychiatry has been hampered by clinical and methodological heterogeneity, lack of power and absence of replication. As a consequence, only one biomarker currently meets established biomarker criteria for psychosis 58. CSF aliquots derived from psychotic patients would allow researchers who have detected candidate biomarkers and autoantibodies to enable replication of preliminary findings and cross-validate findings in other body fluids (e.g. plasma) to CSF.

Potential yields of the study
The potential yields of the current project are:
1. Assessment of the percentage of subjects with positive autoantibodies against the NMDAR, the AMPAR, the GABABR and components of the VGKCs so that in the future such patients may be more readily recognized in clinical practice and treated with immune modulatory agents according to established, efficacious guidelines.
2. Detection of CSF constituents that are altered in psychotic disorders compared to healthy controls and possible associations with clinical symptoms (e.g. specificity to schizophrenia, bipolar disorder, or psychotic depression); in the long run, this may yield biomarkers that differentiate patient from

control status and be informative for prognosis.
3. Homogeneously collected CSF aliquots for future research involving both patients with psychotic disorders and healthy controls.

Study objective

Primary objectives
- To investigate CSF autoantibodies (NMDAR, AMPAR, VGKC, and GABA receptors) in patients with a psychotic disorder and healthy controls.
- To compare levels of immune parameters between patients with a psychotic disorder and healthy controls.
- To compare neurotransmitter levels in CSF between patients with a psychotic disorder and healthy controls.
- To compare microRNA (miRNA) levels in CSF between these patients and healthy controls.

Secondary objectives
- To correlate CSF levels of the constituents mentioned under the first primary objective with peripheral plasma levels.
- To unravel the contribution of genetic variation to the variation in the primary outcomes.
- To relate temporal changes in CSF constituents to clinical outcome, i.e. improvement in symptoms.
- To assess how specific the detected differences in these constituents are for psychotic disorders.

Study design

This a case-control study. Inclusion is estimated to be completed in approximately 7 years with an inclusion rate of 3-4 patients with a psychotic disorder per month and 5-6 healthy controls per month. There are two visits for patients, during which LPs and venipunctures are performed. CSF sampling at two time points will allow for association testing with clinical improvement and other prognostic factors. Healthy controls will also be asked to allow for an additional LP, thus providing the necessary data to compare CSF concentrations at repetitive time points between patients and controls.

Study burden and risks

This study does not include incapacitated subjects. Patients with psychotic or affective disorders will be given a compensation fee of ¤20 for their cooperation and time. In addition, possible travel costs will be reimbursed. Risks for participants are minimal. The most common adverse reaction to a lumbar puncture (LP) is post-puncture headache, transient nerve root irritation, lower back pain and a local hematoma (none of which jeopardizes patients* health). In the patient group we aim to minimize this risk by using

an a-traumatic needle and applying standardized operating procedures (SOPs), including abiding by the UMCU LP protocol (see *C1_Addendum_bij_Onderzoeksprotocol_Werkdocument Lumbaal punctie_herzien april 2015.pdf*), performance of LPs by experienced personnel and having the patient rest for at least 10 minutes prior to standing after the LP. Rare adverse reactions of LPs include hematoma (spinal, epidural, subdural or intracranial), infections (meningitis and discitis) and transient brain nerve damage. The prevalence of minor and transient neurological symptoms may be up to 15%, while the most serious adverse reaction (paraparesis) is not associated with LPs in patients who are not on anticoagulants during or shortly after the LP 1.
Patients will be educated in detail about these possible adverse reactions and as mentioned above we minimize these risks by abiding to evidence-based standards 2.
Healthy subjects will not be financially compensated. Our experience with these procedures in previous studies has shown that none of the >550 subjects included in these studies has suffered from adverse reactions to the lumbar punctures performed for these studies 3-7. These subjects undergo spinal anesthesia and a venipuncture for their minor surgical procedure, i.e. independent of the current study design. They thus do not undergo invasive procedures for the purpose of this study. Although suctioning of CSF in these individuals entails a longer LP duration (on average 30 seconds) compared to when they do not participate in the current project, no other types of burden are expected for these individuals.
There are no direct benefits for participants. In the future, patients may benefit from the current study in that treatment consisting of immunotherapy may be investigated for those patients with both psychosis and positive auto-antibody titers in their CSF. Moreover, possible aberrant neurotransmitter or miRNA profiles in their CSF may spur further research into treatment targets in psychosis.

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

A DSM-IV or 5 classification of schizophrenia, schizophreniform disorder, schizoaffective disorder (both depressive and bipolar types), psychosis not otherwise specified (or other unspecified psychotic disorders), major depressive disorder (with and without psychotic features), bipolar disorder (with and without current psychotic features or a history of psychotic features) and psychosis during the peripartum period (8 weeks after giving birth).

Exclusion criteria

Patients with a psychotic or affective disorder:
Subjects meeting any of the following criteria will be excluded from participation in this study:
-Lumbar-puncture specific (relative) contra-indications, again abiding by the UMCU protocol for LPs (see *C1_Addendum_bij_Onderzoeksprotocol_Werkdocument Lumbaal punctie_herzien april 2015.pdf*): a history of a severe adverse reaction to a previous lumbar puncture (reported by the subject and/or evident from the medical record, including post-puncture headache), the use of anticoagulant agents, thrombocytopenia, local infection of the skin, clinical signs of raised intracranial pressure or a suspected spinal epidural abscess.
- Although clotting abnormalities and suspected bacteraemia do not constitute contraindications for LPs, patients suffering from these will be excluded to avoid risks of excessive bleeding and infections.
- Patients who are not mentally competent and who don't have decisional capacity to decide about participation in this study will not be included. Doctors assess mental competence and decisional capacity of patients to ascertain whether they are able to express a choice, understand and appreciate the information provided and reason about their possible participation. If there is any doubt about their mental competency or decisional capacity, the patient will not be included.
- Patients who were admitted to a psychiatric unit involuntarily after being given an

inbewaringstelling (IBS) will not be included. Patients with *rechterlijke machtigingen* (RM) may be included, but only if they are mentally competent (see section on mental competence and decisional capacity above). The reasons for including the latter category of patients is that the inclusion of these patients will contribute to assembling a study population representative of all Dutch psychotic disorder patients.
- Some patients may participate in other studies as well. In those instances, the researchers of both studies discuss the option of simultaneous enrollment and decide about inclusion of the patient. Any decision about participation of patients in two studies will be based on balancing the advantages of dual study participation with the burden of such participation for participants. ;Healthy controls
Subjects meeting any of the following criteria will be excluded from participation in this study:
- A current or past history of self-reported major psychiatric or neurological illness.
- Lumbar-puncture specific (relative) contra-indications: the anesthesiologist assesses these during routine pre-operative screening.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2017
Enrollment:	500
Type:	Anticipated

Ethics review

Approved WMO

Date:	29-08-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC NedMec

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	NL56840.041.16
Other	Nog niet gekregen (NTR)