Patient Reported Outcomes while Manipulating the Immune System in autoimmune Encephalitis

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1. To measure clinical outcome of patients with an autoimmune encephalitis longitudinally.2. To evaluate existing PROMS, developed for other (neurological) disease, for patients with an autoimmune encephalitis.3. To develop and validate disease-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system infections and inflammations
Study type	Observational non invasive

Summary

ID

NL-OMON50854

Source
ToetsingOnline

Brief title
The PROMISE study

Condition

- Central nervous system infections and inflammations

Synonym
autoimmune encephalitis, autoimmune inflammation of the brain

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Dioraphte

Intervention

Keyword: Autoimmune encephalitis, Cognition, Outcome, Patient-reported outcome measures

Outcome measures

Primary outcome

The outcome of patients with an autoimmune encephalitis over time, also per

subtype of autoimmune encephalitis.

Secondary outcome

Disease-specific valid patient-reported outcome measure(s), with discriminatory

value in the acute as well as the chronic phase of the disease.

Study description

Background summary

The first notion of a type of autoimmune encephalitis was in the previous century, when *paraneoplastic neurological syndromes* were discovered. These disorders are believed to be the result of a cytotoxic T-cell mediated inflammatory response to intracellular antigens released through the apoptosis of tumour cells. The activated immune cells effectuate neuronal death, resulting in gliosis and eventually (mesiotemporal) sclerosis. These disorders respond only limited to (immune) therapy. The long-term effects are often substantial and lasting.

In the first decade of this century, a second group of neurological autoimmune syndromes was discovered. These syndromes are B-cell mediated. In contrast to the classical paraneoplastic or *onconeural* antibodies, this set of antibodies is not always related to malignancies. The B-cells may also be activated by a virus, i.e. after a Herpes Simplex encephalitis, or it may be idiopathic. The activated B-cells produce antibodies directed to neuronal surface antigens. These may be components of presynaptic ion channels involved in the release of neurotransmitters, or postsynaptic receptors to neurotransmitters. The antibodies in this group of neurological disorders are believed to be directly pathogenic. They can act as an antagonist to the neurotransmitter, cause blockage and internalisation of receptors, or act as a signalling protein to natural killer cells, resulting in neuronal death.

Frequent clinical symptoms include cognitive and behavioural disturbances, seizures, movement disorders, ataxia and autonomic dysregulation. The incidence of this novel category of neurological disorders increases rapidly with the developing knowledge and recognition of the disorders. The disorders are potentially better treatable with immunotherapy, aimed at suppressing the inflammatory reaction and depletion of antibodies. Nonetheless many patients suffer from persisting neurocognitive deficits, psychiatric symptoms and epilepsy. This is has not been studied extensively untill now.

In the literature on the prognosis of autoimmune encephalitis, outcome is generally expressed in terms of a score on the modified Ranking Scale (MRS). The mRS is developed for acute neurovascular events and does not incorporate the common neurological deficits encountered by the autoimmune encephalitis population.

Study objective

1. To measure clinical outcome of patients with an autoimmune encephalitis longitudinally.
2. To evaluate existing PROMS, developed for other (neurological) disease, for patients with an autoimmune encephalitis.
3. To develop and validate disease-specific patient-reported outcome measures with discriminatory value in both the acute and chronic phase of autoimmune encephalitis.

Study design

The Centre for Neuro-inflammatory disorders at Erasmus MC is a NFU endorsed centre of expertise. The research line on autoimmune encephalitis, mostly conducts translational research. The PROMISE study is a partially cross-sectional, partially prospective explorative observational cohort study, executed in a nationwide clinical cohort of patients with an autoimmune or paraneoplastic encephalitis.

We will start with a literature review to previously applied outcome measures in the encephalitis literature. We will focus on autoimmune encephalitis as well as infectious encephalitis. The previously applied outcome measures will be divided into categories, i.e. (1) objective somatic outcomes, (2) objective cognitive outcomes, (3) subjective (e.g. patient- and carer-reported) outcome measures, (4) diagnostic measurements (e.g. lab, imaging and electrophysiological measures) and (5) descriptive clinical data (e.g. number of days in the hospital, number of days on an Intensive Care Unit, discharge destination).

Data on somatic outcomes, diagnostic measurements and descriptive clinical data will mostly be or have been collected as part of the standard clinical care for

this population. Additionally, we will administer cognitive tests and patient-(and carer-)reported outcome measures, selected from the above-mentioned literature review.

For all the previously applied cognitive tests and PROM*s, we will evaluate what construct it aims to measure (e.g. *executive functioning*, *functionality* or *quality of life*), the time and effort to complete it and the content validity for the intended population. Taking these evaluations into consideration, we will make a selection of potentially relevant measuring instruments and individual items from these instruments, and generate an *item pool*.

We will institute a focus group of patients representative of our intended population to provide input on additional potentially relevant topics. We will transcribe and code these qualitative data to be incorporated in the item pool.

After selecting and developing disease-specific test items, we will collect data on the item pool in the cross-sectional cohort. With these data, we will perform a quantitative analysis of the validity, reliability, redundancy and difficulty of the items, through the application of Classical Test Theory (CTT) as well as Item Response Theory (IRT). These statistical methods will identify the optimal combination of items and scoring formats, to span all levels of disease severity, and place them on a linear, interval scale to assign value to the outcome (per construct) of individuals. This will create a psychometrically robust disease-specific (set of) outcome measure(s).

We will inquire a subgroup of 10 to 20 patients of the cross-sectional cohort to complete the developed instruments two times, with an interval of two weeks, to establish test-retest reliability.

We will analyse the convergent (construct) validity of the developed measure(s) by comparing the generated outcome values to scores on existing outcome measures targeting the same constructs. As the item pool will comprise mainly of items from existing outcome measures, scores can be calculated to be compared to new PROM values without additional time burden. The new generated PROM values will also be compared to a patient-reported VAS score for each construct (scale of 0 to 100). To evaluate the discriminative ability of the developed measure(s), we will compare the generated outcomes (1) between subgroups of respondents with different levels of severity in (persisting) neurological deficits, based on the cognitive tests and mRS scores, and (2) to available normative reference data from literature.

The following step is to implement a structured follow-up of the prospective cohort, provisionally terminating at two years after the diagnosis. With the longitudinal data, we will evaluate the longitudinal responsiveness of the measuring instrument.

Study burden and risks

Most of the contact moments, will be in line with the standard clinical care for patients with an autoimmune encephalitis. The Patient-Reported Outcome questionnaires and part of the cognitive tests are additional. If the patient is not primarily treated in the Erasmus MC, we aim to travel to the treatment clinic This way, we attempt to minimalize the effort for the patients.

There is no risks associated with participation; questions and tests may be experienced as time-consuming or confrontational. Filling in the Patient-Reported Outcome questionnaire will demand maximally seven times 40-80 minutes, depending on where in the disease course the patient is at inclusion.

The principal benefits of this study for the population will be (1) the development of a means to express (expected) outcome that is more informative for the patient and (2) an outcome more sensitive to subtle change, increasing the power of future studies.

A potential benefit for the individual patients in the study, is that they are closely monitored. Changes may be noticed and acted on more rapidly. However, the tests do not replace a full neuropsychological exam administered for diagnostic or therapeutic purposes.

As some of the syndromes (status epilepticus and seizures as part of an overt encephalitis) consist of cognitive deficits and lower level of consciousness, the objectives cannot be achieved without including and studying incapacitated subjects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

1. Adults or adolescents from the age of 16 years;
2. Sufficiently fluent in Dutch;
3. Have a clinical high suspicion of an autoimmune encephalitis or a paraneoplastic neurological syndrome
4. Antibodies are detected in serum and/or CSF with cell-based assay and affirmed with immunohistochemistry

Exclusion criteria

1. Impossible to assess outcome related to autoimmune encephalitis due to pre-existing comorbidities, objectified as a premorbid mRS over two.
2. The patient and/or legal representative is withholding informed consent;
3. The patient withdraws, after initial consent.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-09-2021
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO

Date:	31-08-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL77821.078.21