# Autoimmune inflammation as cause of RelapsIng Symptoms in patients with viral Encephalitis

Published: 13-12-2019
Last updated: 08-02-2025

Primairy objective:- Identify causes of secondary deterioration or failure to improve after viral encephalitis by studying activation of the immune system and production of autoantibodies.Secondary Objectives are to:- Determine if the delayed...

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| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Autoimmune disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON55224

**Source**
ToetsingOnline

**Brief title**
ARISE

### Condition

- Autoimmune disorders
- Viral infectious disorders
- Central nervous system infections and inflammations

**Synonym**
autoimmune encephalitis, Inflammation of the brain", Viral encephalitis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum

**Source(s) of monetary or material Support:** Stichting de Merel

## Intervention

**Keyword:** Autoimmune, Inflammation, Viral encephalitis

## Outcome measures

### Primary outcome

- Identify causes of secondary deterioration or failure to improve after viral encephalitis by studying activation of the immune system and production of autoantibodies.

### Secondary outcome

- Proportion of patients with viral encephalitis that fail to improve or have secondary deterioration

- Determine if the delayed inflammatory response of the brain can be predicted by clinical characteristics upon presentation, blood or cerebrospinal fluid tests and cranial imaging.

# Study description

### Background summary

Encephalitis is a rapidly progressive neurological disorder caused by inflammation of the brain. The most common etiology is infection but also autoimmune encephalitis have been frequently identified (5). Acute encephalitis is characterized by headache, altered mental status, fever and seizures (1). Approximately 800 patients per year in the Netherlands develop encephalitis of which two thirds have an infectious cause and one third is caused by autoimmune or paraneoplastic disease (6). Encephalitis is a severe disease with a mortality rate of 10-20% and half of the survivors have cognitive deficits or behavioural problems (7-9). Patients with encephalitis frequently fail to improve after the initial phase of the disease has passed, and some even deteriorate weeks after the infection started (2, 3). It has been suggested that activation of the immune system leads to a secondary inflammation of the

brain, which clinically presents with an increase in memory deficits and behavioural changes, but also movement disorders or epileptic seizures can occur (2-4). The theory is that due to neuronal damage and disruption of the blood-brain barrier during encephalitis neuron specific proteins enter the blood stream. Some of these proteins are thought to invoke an immune response in the blood stream that subsequently targets the recovering brain tissue resulting in new symptoms or failure to recover. Several case reports supports this theory and have described a viral induced autoimmune encephalitis, such as anti-N-methyl-D-aspartate (NMDA) receptor antibodies in patients with herpes simplex encephalitis (HSE) and Japanese encephalitis virus (2-4). Anti-NMDAR encephalitis is characterized by a multi stage progression and manifests within weeks or, rarely months and is recognisable on these clinical grounds (4, 5). However, existing criteria for autoimmune encephalitis are still too reliant on antibody testing and response to immunotherapy, which might delay the diagnosis (5). Moreover, there are no systematic studies evaluating this immune response after the acute phase of viral encephalitis and investigating whether this is correlated to neuropsychological deficits or increased brain inflammation on cranial MRI.

**Study objective**

Primairy objective:
- Identify causes of secondary deterioration or failure to improve after viral encephalitis by studying activation of the immune system and production of autoantibodies.

Secondary Objectives are to:
- Determine if the delayed inflammatory response of the brain can be predicted by clinical characteristics upon presentation, blood or cerebrospinal fluid tests, neuropsychological tests and cranial imaging.
- Determine the proportion of patients with viral encephalitis fail to improve or have secondary deterioration

**Study design**

All adult patients with viral encephalitis proven by PCR or serology in the Amsterdam UMC (location AMC) and patients included in the I-PACE biobank, that have given informed consent to participate in future research projects, are eligible for this study.

We will collect detailed clinical data and leftover cerebrospinal fluid. To evaluate the autoimmune mechanism we will perform laboratory tests, neuropsychological investigation and brain imaging with MRI scan. Blood or cerebrospinal fluid tests on brain degradation products S100β, glial fibrillary acidic protein (GFAP), Tau and neuron-specific enolase (NSE), and the presence of anti-neuronal antibodies (LGI-1, anti-CASPR2, anti-NMDA, AMPAR, anti-GABA,

anti-Gly, DPPX, anti-GAD) and cytokine levels indicative of ongoing inflammation.

Patient that are admitted in the Amsterdam UMC will have a first blood withdrawal after 1 week and when the clinical condition will allow a neuropsychological investigation will be performed.

All patients will be aksed to visit the outpatient clinic of the Amsterdam UMC, blood samples will be withdrawn from the former patient in week 4 and 12. After this blood withdrawal, the patient will fill in the questionnaires and performs the neuropsychological assessment (Cognitive Basic Assessment Test set (COGBAT) of the Vienna Test System (VTS), Cognitive and emotional consequences of stroke (CLCE-24), Profiles of mood states (POMS), Research and development (RAND-36). In week 12 an cranial MRI will be performed. After one year, patients will be contacted by telephone to answer the final questionnaires

**Study burden and risks**

Three times a blood withdrawal will be performed in each participant. Risks of a blood withdrawal are negligible.
The cognitive functioning and memory tests will be assessed by the researcher and will take 1- 1,5 hour.
All participants will get an MRI scan of the brain. Risks of an MRI scan are negligible.

# 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

All patients, aged >16 yearsor older. with viral encephalitis proven by PCR or serology

### Exclusion criteria

- Patients with encephalitis but no viral pathogen
- Neurosurgical operation or neurotrauma, in the 3 months previous to the encephalitis episode
- Presence of neurosurgical devices in the central nervous system
- Insufficient mastery of the Dutch language
- Severe cognitive impairment prior to the encephalitis episode

## Study design

### Design

**Study type:** Observational invasive

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 15-05-2020 |

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|---|---|
| Enrollment: | 25 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 13-12-2019 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 29-04-2020 |
| 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

No registrations found.

### In other registers

| Register | ID |
|---|---|
| CCMO | NL69567.018.19 |

## Study results

Date completed: 01-12-2024

**Summary results**
Trial ended prematurely