Autoimmune epilepsy Modulated by IVIg - effects on Cortical Excitability, the AMICE study

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1. Assessing the efficacy of IVIg in autoimmune epilepsy, both clinically and serologically.2. Identifying an objective marker of therapy response in epilepsy, measuring cortical excitability by TMS-EEG/EMG, in vivo.3. Providing evidence that...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON56107

Source
ToetsingOnline

Brief title
AMICE study

Condition

- Autoimmune disorders
- Seizures (incl subtypes)

Synonym
Autoimmune epilepsy / epilepsy caused by brain inflammation by auto-antibodies

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Nederlands Epilepsie Fonds;Interlaken

Leadership Award

Intervention

Keyword: autoimmune encephalitis, cortical excitablity, epilepsy, intravenous immunoglobulins

Outcome measures

Primary outcome

The proportion of patients with a seizure frequency reduction >50% and the proportion of patients that achieve full freedom of seizures in week 6, 7 and 8 (compared to the baseline frequency), for all patients with autoimmune epilepsy and compared by subgroup.

Secondary outcome

- Antibody levels pre- and post-treatment correlated to the seizure frequency, for all patients with autoimmune epilepsy and compared by subgroup. In addition, the amount of patients with antibody titer reduction >50% and the amount of patients that become antibody free, for all patients with autoimmune epilepsy and compared by subgroup.

- Clinical improvement:

- Changes in the PNS neurological scale and FAB at 3, 6, 12 and 18 weeks, for all patients with autoimmune epilepsy and compared by subgroup.

- Changes in the MOCA at 6, 12 and 18 weeks, for all patients with autoimmune epilepsy and compared by subgroup.

- Changes in the QOLIE-31-P at 3, 6, 12 and 18 weeks, for all patients with autoimmune epilepsy and compared by subgroup.

- Proportion of patients with a relapse within 18 weeks, for all patients

with autoimmune epilepsy and compared by subgroup at 18 weeks.

- Exploratory analysis of TMS-EEG/EMG markers (inter-individual), linked to the

seizure frequency in week 6, 7 and 8 and the relapse chance at 18 weeks.

Study description

Background summary

Autoimmune epilepsy is a severe syndrome. Using a conservative estimation, 1% of the 70 million epilepsy patients worldwide will have an autoimmune origin. It is most frequently refractory to anti-epileptic drugs, but often responds to immunotherapy. Intravenous immunoglobulins (IVIg) are used off-label to treat patients with autoimmune epilepsy, but there have been no structured prospective studies with immunotherapy. A structured prospective study with a complete set of matched serum and CSF samples before and after IVIg treatment is needed, to provide proof of a therapeutic effect of IVIg in autoimmune epilepsy (both clinically and serologically). Thereby there is need for a biomarker for prognosis and treatment decisions. Transcranial Magnetic Stimulation (TMS) can assess cortical excitability safely and non-invasively. Also in vitro experiments are necessary to provide a direct link between antibodies and cortical excitability.

Study objective

1. Assessing the efficacy of IVIg in autoimmune epilepsy, both clinically and serologically.
2. Identifying an objective marker of therapy response in epilepsy, measuring cortical excitability by TMS-EEG/EMG, in vivo.
3. Providing evidence that patients' antibodies affect cortical hyperexcitability, in vitro.

Study design

Prospective single group open label clinical intervention trial with IVIg.

Intervention

All patients receive 2 courses of IVIg; 0.4 grams/kg/day for 5 days, starting on day 1 and day 22.

Study burden and risks

There is a small risk from participation of this trial, because patients receive 2 courses of IVIg with an interval of 3 weeks, whereas in the standard care this interval is 4 weeks. Direct side effects of IVIg are mild and manageable. Potential serious side effects are rare (0.01-0.1%) to very rare (<0.01%) and include haemolytic anaemia, aseptic meningitis, thromboembolism, acute renal failure and transfusion-related acute lung injury. In case of <50% epilepsy reduction after the first course, deterioration or relapse, choice for additional immuno- or antiseizure therapy is in accordance with standard of care. In practice, we will add ivMP to IVIg for the second course. Generally, we will not alter anti-seizure medication during the first 6 weeks. Of course, if clinical care necessitates AED, we will do this.
A substantial part of the burden is regular care, such as the admission and a great part of the investigations. The burden consists of 2 admissions of 5 days for daily IVIg infusions (10 IVIg infusions in total, if possible second course of IVIg in daycare); followed by 3 outpatient visits and 2 telephone consultations. In total, 7 venepunctures, 2 lumbar punctures, 2 brain MRIs and 3 TMS-EEG/EMGs are performed, combined with the outpatient visits. During all visits, general physical and neurological examinations will be performed and 3 questionnaires will be conducted repeatedly at 6 time points. A diary will be kept during the research. TMS-EEG/EMG is generally well-tolerated. Transient mild pain in head and neck are frequently described. The risk of seizures is very low (almost zero). TMS-EEG/EMG has no individual interest, but does have a group interest, since it has major implications for patients with autoimmune epilepsy in the future. TMS-EEG/EMG can possibly be used as a biomarker for prognosis and treatment decisions in autoimmune epilepsy.
Since autoimmune epilepsy is a severe disease often accompanied by severe neurologic deficits, it should be treated aggressively. IVIg are generally well tolerated and have a better side effect profile than corticosteroids. IVIg are more convenient and cost-effective compared with plasmapheresis. With a cumulative dosing scheme of IVIg, we expect patients to improve in days to weeks. Thereby, IVIg does not have an epileptogenic effect itself and does not influence the TMS-EEG/EMG.
This study will fill important gaps in the knowledge of treatment of epilepsy in autoimmune encephalitis. The serological and EEG data will learn us much about the effect of IVIg on antibodies and brain networks and might provide new options to predict treatment response.

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

- Age of 18 years and older. - Epilepsy, with at least one seizure per week at baseline. - Antibodies proven in serum and/or CSF in cell-based assay and/or ELISA and on immunohistochemistry. In case of anti-GAD antibodies, antibody titer with ELISA has to be >10,000 IU in serum or >100 IU in CSF.

Exclusion criteria

- Another identified cause of epilepsy (i.e. viral/bacterial encephalitis, stroke, tumor). - Severe encephalitis in which escalation of therapy (second-line immunotherapy, i.e. Rituximab or Cyclophosphamide) is expected within the study period (mainly anti-NMDAR encephalitis with mRS 5, at the ICU). - Use of immunotherapy < 3 months ago. - Use of monoclonal antibodies < 1 year ago. - Premorbid mRS >=3. - Known hypersensitivity to Privigen or contraindication for Privigen, i.e. IgA deficiency. - Patient and/or legal representative is withholding informed consent. - Patient objects after initial informed consent.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-08-2020
Enrollment:	55
Type:	Actual

Medical products/devices used

Generic name:	TMS-device: MagPro X100
Registration:	No
Product type:	Medicine
Brand name:	Privigen
Generic name:	Normal immunoglobulin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-03-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-06-2020
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2021
Application type:	Amendment
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
EudraCT	EUCTR2019-002078-30-NL
CCMO	NL70122.078.20
Other	NTR: NL8880