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Effects of status epilepticus on the structure and function of the human brain

Submission date
21/10/2024

Recruitment status
Recruiting

Registration date
19/11/2024

Overall study status
Ongoing

Last Edited
19/11/2024

Condition category
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The IMPOSE study aims to investigate how seizures, especially a prolonged type called status epilepticus (SE), affect the brain's structure and function. SE is a neurological emergency that can cause brain damage. This study uses advanced brain imaging (MRI), EEGs (to measure brain activity), and blood/CSF samples to understand the effects of SE and potentially develop ways to protect the brain. It also looks at how seizures impact cognitive functions like thinking and memory over time.

Who can participate?
The study includes four groups of participants:
- Adults who have experienced SE
- Adults with focal epilepsy (a type of epilepsy where seizures start in one area of the brain, but without SE)
- Adults admitted to the ICU for other reasons, but who have not experienced seizures
- Healthy adults without any neurological conditions to serve as a comparison group

What does the study involve?
Participants will undergo several assessments to measure the effects of their condition on the brain and overall health. This includes:
- Neurological exams (physical and cognitive evaluations)
- MRI scans to look at brain structure
- EEGs to measure brain activity
- Blood and CSF samples to identify biomarkers of brain damage

Participants in the SE group will have three visits (baseline, at hospital discharge, and at 6 months), while other groups will have two visits (baseline and follow-up at 6 months).

What are the possible benefits and risks of participating?
There is no direct personal benefit from participating in this study. However, the results could help improve treatment and care for people with epilepsy and SE in the future. The tests involved, such as MRI, EEG, and blood sampling, are standard procedures and carry minimal risks. Participants may experience some minor discomfort, such as from blood draws.

Where is the study run from?
University Hospital Zurich (Universitätsspital Zürich) (Switzerland)

When is the study starting and how long is it expected to run for?
October 2023 to December 2027

Who is funding the study?
The study is funded by the Swiss National Science Foundation (SNF), which supports medical research in Switzerland.

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
BASEC-Nr: 2023-02258

Study information

Scientific Title
Impact of Status Epilepticus on Human Brain Structure and Function

Acronym

IMPOSE

Study objectives
Hypotheses and primary objective:
1. Status epilepticus (SE) causes detectable brain atrophy in areas highly connected with the epileptic focus and increases in blood/CSF biomarkers of brain damage
2. The degree of altered brain morphology and biomarker changes correlate with SE duration, type, and cause
3. Areas highly interconnected with the presumed epileptic focus are most vulnerable to structural damage during SE
4. Brain atrophy and blood/CSF biomarkers correlate with poor long-term outcome and worse neuropsychological performance at follow-up
5. Some treatments, e.g., ketamine and sodium valproate, are associated with reduced rates of atrophy and better neuropsychological performance after controlling for other confounders
6. The mechanisms of brain damage observed in human SE involve disturbances in neurotransmitters, i.e., the glutamatergic system, the degree of inflammation and blood-brain barrier disruption, and accumulation of neurofibrillary tangles
7. The outcome of status epilepticus can be predicted using biomarkers and clinical variables obtained at baseline

The primary aim of this study is to perform a prospective multi-center analysis of the longitudinal trajectory of brain morphology using structural MRI acquired at baseline (during or shortly after SE), at discharge from hospital, and at a 6-month follow-up.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 07/05/2024, Cantonal Ethics Committee Zurich (Stampfenbachstrasse 1 21, Zurich, 8090, Switzerland; +41 432597970; admin.kek@kek.zh.ch), ref: BASEC-Nr.: 2023-02258

Study design
Observational case control study

Primary study design
Observational

Study type(s)
Diagnostic, Other

Health condition(s) or problem(s) studied
Impact of status epilepticus on human brain structure and function

Interventions
In this observational study, four groups are examined: (1) patients with status epilepticus (SE) (n=75), (2) patients admitted to the ICU without seizures (n=30), (3) people with focal epilepsy and brief seizures (n=30), and (4) healthy volunteers (n=30). Study visits for each group occur at baseline, discharge, and follow-up as described below:

Cohort 1 (Patients with SE):
Baseline visit is conducted within 2 weeks of SE onset, either during SE or within 72 hours after

its conclusion. This includes a physical examination, clinical data collection, EEG, MRI, and blood sampling. CSF is collected if a lumbar puncture has been performed routinely.
A second visit is scheduled at hospital discharge. An MRI is performed if discharge occurs more than 2 weeks after the baseline visit.
A long-term follow-up visit is held 6 months after SE onset, which includes neuropsychological evaluation, MRI, EEG, and biomarker sampling. A 30% drop-out rate is expected for the follow-up visit.

Cohort 2 (ICU patients without seizures):
These patients follow the same protocol as SE patients. The baseline MRI is conducted during a routine ICU MRI scan, typically within the first two weeks of ICU admission.

Cohort 3 (People with focal epilepsy):
These participants undergo a baseline visit and a follow-up visit, both including physical examination, MRI, EEG, blood sampling, and neuropsychological testing.

Cohort 4 (Healthy comparison group):
A group of healthy volunteers will be included to adjust for the effects of normal aging on brain structure and function, as well as on biomarker measurements. Healthy volunteers will undergo the same baseline and follow-up procedures as the focal epilepsy group, including MRI, EEG, blood sampling, and neuropsychological testing.

Clinical Characteristics
Baseline assessments across all groups include demographics, FOUR score, Glasgow Coma Scale (GCS), cerebral performance category (CPC), Charlson Comorbidity Index (CCI), modified Rankin Scale (mRS), Simplified Acute Physiology Score (SAPS II), medication history, and comorbidities. SE-specific characteristics, such as type, location, duration, treatment, and level of consciousness, are additionally documented for SE patients. Follow-up data include seizure frequency, medication, and relevant outcome measures.

MRI Procedures
Research-based brain scans are performed at each site using the same scanner, and variability is reduced using the ComBat method. MRI sequences include:
T1-weighted imaging (MPRAGE) for structural imaging,
DWI and FLAIR for early status-related abnormalities,
Magnetization transfer imaging for myelin integrity,
DTI for structural connectivity,
GluCEST for glutamate imaging,
Arterial spin labeling for brain perfusion and blood-brain barrier integrity,
Neuronal current imaging (NCI) for visualizing electric epileptic perturbations.

Biomarkers
Blood and CSF samples are analyzed for biomarkers of brain damage and neuroinflammation, including tau (total and phosphorylated), neurofilament light chain protein (NfL), GFAP (gliosis), and interleukins 1 and 6 (IL-1, IL-6). Biobanking and biomarker analyses are conducted at the University Hospital Zurich.

EEG Procedures
EEG assessments, either routine or as in-kind contributions, provide data on SE localization and subtype. These findings are classified according to the American Neurophysiology Society's Critical Care EEG terminology.

Neuropsychological Testing
Neuropsychological testing focuses on assessing attention, memory, executive function, visuospatial skills, and emotional function. Testing is performed in Switzerland in either German or French, and in the UK using standardized test batteries to ensure comparability.

Intervention Type
Other

Primary outcome(s)
1. Brain Morphology Changes (MRI): Evaluate brain atrophy in patients with status epilepticus (SE) using structural MRI scans performed at baseline (during or shortly after SE), at hospital discharge, and at a 6-month follow-up
2. Biomarkers of Brain Damage (Blood/CSF): Measure and analyze blood and CSF biomarkers of brain damage, such as neurofilament light chain (NfL), GFAP, tau, and interleukins, to assess the extent of brain injury related to SE

Key secondary outcome(s))
1. Mechanisms of SE-Related Brain Damage: Investigate the underlying mechanisms of brain damage caused by SE, focusing on neurotransmitter disturbances (e.g., glutamatergic system), inflammation, blood-brain barrier disruption, axonal damage, and neurofibrillary tangle accumulation through advanced MRI sequences and biomarker analysis.
2. Correlation Between SE Characteristics and Brain Damage: Examine how SE characteristics (e.g., duration, type, and etiology) correlate with changes in brain morphology and biomarker levels, identifying areas of the brain most vulnerable to SE-related structural damage.
3. Long-Term Neuropsychological Outcomes: Assess the relationship between brain atrophy and biomarker changes with long-term neuropsychological outcomes, including cognitive performance at the 6-month follow-up.
4. Neuroprotective Effects of Treatments: Evaluate the impact of specific treatments (e.g., ketamine, sodium valproate) on reducing brain atrophy and improving neuropsychological outcomes by correlating treatment types and durations with changes in biomarkers of brain damage and cognitive performance.
5. Predictive Value of Biomarkers and Clinical Variables: Analyze whether biomarkers and clinical data obtained at baseline can predict long-term outcomes of SE, including brain damage and neuropsychological performance.

Completion date
31/12/2027

Eligibility

Key inclusion criteria
Patients with SE
1. Adults with SE admitted to the participating centers
2. Signed consent form (mandatory)
3. Capable of understanding the information provided both cognitively and linguistically (or legal representatives in case of permanent incapacity)
4. Older than 18 years
5. Meet the diagnosis of SE or prolonged seizures > 5 minutes

Comparison Group 1: Focal Epilepsy with Brief Seizures
1. Adults diagnosed with focal epilepsy and brief seizures

2. Older than 18 years
3. Diagnosis of focal seizures or epilepsy according to the proposed definition by the ILAE

Comparison Group 2: Patients Admitted to ICU Without Seizures
1. Adults admitted to the ICU
2. Older than 18 years

Healthy Comparison Group: Healthy Volunteers
1. Adults older than 18 years

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Patients with SE
1. Inability to undergo MRI scanning (e.g., MRI incompatible implanted devices, agitation, etc.)
2. Patients who did not give consent

Comparison Group 1: Focal Epilepsy with Brief Seizures
1. History of status epilepticus
2. Inability to undergo MRI scanning (e.g., MRI incompatible implanted devices, agitation, etc.)
3. Patients who did not give consent

Comparison Group 2: Patients Admitted to ICU Without Seizures
1. Active status epilepticus
2. Inability to undergo MRI scanning (e.g., MRI incompatible implanted devices, agitation, etc.)
3. Patients who did not give consent

Healthy Comparison Group: Healthy Volunteers
1. Active relevant neurological condition or a history of a relevant neurological condition (particularly those with seizures, a neurodegenerative condition, or brain lesions)
2. Patients who did not give consent

Date of first enrolment
01/09/2024

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

England

Austria

Switzerland

Study participating centre
HUG
Service de neurologie
Rue Gabrielle-Perret-Gentil 4
Geneva
Switzerland
1205

Study participating centre
CHUV
Service de neurologie
Rue du Bugnon 46
Lausanne
Switzerland
1011

Study participating centre
UCL Queen Square Institute of Neurology
Queen Square
London
United Kingdom
WC1N 3BG

Study participating centre
Universitätsklinik für Neurologie, neurologische Intensivmedizin und Neurorehabilitation
Christian-Doppler-Klinik
Ignaz-Harrer-Straße 79
Salzburg
Austria
5020

Study participating centre
Istituto di Neuroscienze Cliniche della Svizzera Italiana
Ospedale Regionale di Lugano, Civico
Via Tesserete 46
Lugano
Switzerland
6900

Study participating centre
Klinik für Neurologie
Kantonsspital St. Gallen
Rorschacher Str. 95/Haus 04
St. Gallen
Switzerland
9007

Study participating centre
Klinik für Neurologie
Universitätsspital Zürich
Frauenklinikstrasse 26
Zurich
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8091

Sponsor information

Organisation
University Hospital of Zurich

ROR
https://ror.org/01462r250

Funder(s)

Funder type
Research organisation

Funder Name
Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung

Alternative Name(s)
Schweizerischer Nationalfonds, Swiss National Science Foundation, Fonds National Suisse de la Recherche Scientifique, Fondo Nazionale Svizzero per la Ricerca Scientifica, Fonds National Suisse, Fondo Nazionale Svizzero, Schweizerische Nationalfonds, The Swiss National Science Foundation (SNSF), SNF, SNSF, FNS

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
Data collected during the study will be carefully controlled for quality and confidentiality. MRI data will undergo preprocessing and quality control following established protocols. Data entered into the electronic Case Report Form (eCRF) through the Redcap system will include regular quality checks and backups. Paper CRFs will also be used at bedside, with data transferred to the eCRF within 72 hours.

All data, including MRI and EEG scans, will be anonymized and securely transferred, stored, and kept in protected research folders. Only authorized personnel will have access to the data, which is identified by unique participant numbers rather than names. Biological material, such as blood and CSF samples, will be stored in the clinical biobank at the University Hospital Zurich.

Data will be kept for 10 years after the study's completion and may be shared with external partners under strict privacy guidelines.

IPD sharing plan summary
Available on request