May 2020 AES-NORSE Institute Seed grant decision will be announced mid-July. September 2020 AES-NORSE Institute Seed grant opportunity here.

New and Ongoing Investigations of NORSE and FIRES During Covid-19

Recipient, 2019 NORD-NORSE Institute grant

Beyond negative exome – Understanding the genetics of FIRES
Principal Investigator and Contact: Ingo Helbig, MD (Children’s Hospital of Philadelphia) Helbigi@email.chop.edu
Co-Investigators: Rima Nabbout, MD, Ph.D (Hôpital Necker-Enfants Malades, Paris) rimanabbout@yahoo.com and Andreas van Baalen, MD (University Medical Center Schleswig-Holstein, Germany) Andreas.vanBaalen@uksh.de
IRB 15-012226

Over the last decade, our team has recruited a cohort of 50 individuals with a definitive diagnosis of FIRES from France, Germany, and the US and performed in-depth genetic analysis, including whole-exome sequencing. None of the individuals with FIRES carried a disease-causing variant in a known epilepsy gene and in none of the individuals could other plausible causes for the disease be identified. Accordingly, in contrast to most other severe epilepsies where at least a subset of individuals with genetic causes can be identified, the cause of FIRES remains completely unsolved and the disease-mechanism remains mysterious.

We plan to expand the genetic analysis of FIRES to perform gene network analysis in 50 patients with FIRES who underwent exome sequencing and to expand genetic analysis to whole-genome sequencing in 10 patient-parent trios with FIRES. It is our working hypothesis that FIRES is caused either by genetic variation in specific novel molecular pathways or is caused by pathogenic variants outside the coding region. We reason that if such variants can be identified in FIRES, they will highlight disease mechanisms that can subsequently be targeted for the development of novel treatments. By the end of this 24-month project, we will have achieved two critical steps in transforming FIRES from an exome-negative disease to a condition with further genomic research potential, namely to perform an in-depth pathway analysis of existing genomic data and providing preliminary whole-genome data to identify novel genomic causes outside the classical coding region.

Relevant publications

Recipient, 2019 NORD-NORSE Institute grant

Gut microbiome as a mechanism of immune dysregulation in NORSE

Principal Investigators: Claude Steriade, MD (NYU) PI and Contact, claud.steriade@nyulangone.org and Deepak Saxena, Ph.D (NYU) ds100@nyu.edu

Research coordinator: Nader Daoud nader.daoud@nyulangone.org

IRB number: s20-00525

Cytokine abnormalities and response to immunomodulation among people suffering from NORSE imply pathogenic immune dysregulation. Response to anakinra, an IL-1 receptor antagonist, and IL1RN polymorphisms in subjects with NORSE suggest a central role for IL-1b, which promotes neuronal excitability in animal models of epilepsy. Beyond a genetic predisposition, the cause of immune dysregulation often remains unknown, and etiology-targeted interventions are still lacking. Gut dysbiosis occurs in systemic and central nervous system inflammatory disorders and drug-resistant epilepsy. In experimental models of epilepsy, gut dysbiosis mediates the effects of the ketogenic diet, an effective epilepsy therapy, through modulation of hippocampal GABA and glutamate ratios. Gut dysbiosis also modulates cytokine responses in healthy subjects and those with brain injury. The investigation of gut dysbiosis offers a unique opportunity for the discovery of mechanisms of immune dysregulation in NORSE.

Our goal is to explore the potential role of gut dysbiosis as a central mechanism of immune dysregulation in NORSE and a potential treatment target. This pilot study seeks to characterize gut microbiota alterations in a pilot group of NORSE and disease controls (refractory status epilepticus of known cause).

We hypothesize that in subjects with status epilepticus, gut dysbiosis leads to IL-1b upregulation, which enhances neuronal hyperexcitability and contributes to refractory status epilepticus.

Eligibility: We will recruit 2 cohorts:

- NORSE and FIRES subjects. All ages (adult and pediatric) will be included. NORSE and FIRES will be defined as per the recently published consensus definition. Target sample size: 20 subjects
- Refractory status epilepticus of known cause subjects (disease controls). We will identify subjects with refractory status epilepticus of known cause (previous diagnosis of epilepsy, acute brain injury such as traumatic brain injury, ischemic or hemorrhagic stroke, and brain tumor). Target sample size: 20 subjects

Phase of disease: Acute and subacute
*Call for samples:* We welcome stool and serum samples, collected in the acute phase of disease of NORSE or FIRES subjects, from external sites with an existing IRB allowing for collection of samples for research purposes. Samples which would benefit enriching our NORSE cohort would include 5 cc serum and stool collected through the Omnigene kit.

**Relevant publications**

**Recipient, 2018 NORD – NORSE Institute grant**

**NLRP3 inflammasome dysfunction as a cause for FIRES and NORSE**
Principal Investigators: Eric Payne, MD, MPH, (Alberta Children’s Hospital, Canada)
Eric.Payne@albertahealthservices.ca PI and Contact
Charles Howe, PhD (Mayo Clinic) howe@mayo.edu
Study Coordinator: Jessica Sagen sagen.jessica@mayo.edu
Research Manager: Reghann LaFrance-Corey lafrance.reghann@mayo.edu

**Covid-19 update: Project is continuing and accepting bio samples**

*Call for samples:* We welcome bio samples, collected in the acute and chronic phases of the disease in children and adults with FIRES and NORSE. Dr Howe has an IRB to allow for receipt of bio samples; IRB is not required from investigator donating bio sample. Contact Jessica Sagen for sample collection SOP.

**Background**
- The NLRP3 inflammasome activates the highly pro-inflammatory cytokines IL-1beta and IL-18.
- Evidence suggests that for some patients with FIRES, aberrant NLRP3 inflammasome activity may be driving the disease process.
- Specifically, some children with FIRES appear to have dysfunctional IL-1 receptor antagonist protein. This likely explains why some patients respond well to treatment with anakinra, which activates the IL-1 receptor antagonist protein, thereby decreasing IL-
1beta activity and its downstream effectors.

**Hypotheses**

1) Some patients with FIRES and NORSE have increased activation of the NLRP3 inflammasome which is secondary to either dysfunctional IL-1RA activity or other defective mediators of the NLRP3 inflammasome.

2) Early elevations in the NLRP3 inflammasome potentiate and may predict subsequent increased EEG-confirmed seizure burden; in turn, measuring this may help to identify patients early in the disease course that are amenable to targeted suppression of the NLRP3 inflammasome.

**Design**

Population: 60 children and/or adults with FIRES or NORSE.

Intervention: Quantify serum and CSF pro-inflammatory (e.g. IL-1beta, IL-18) and anti-inflammatory (e.g. IL-1RA, IL-10) cytokines and chemokines involved in NLRP3 inflammasome activity. Depending on sample availability, we will obtain a measurement within the first 48 hours of admission to hospital for refractory status epilepticus and repeat the serum measurement at a minimum two weeks later. Some of these patients will receive anakinra, so preferably we will obtain pre- and post-anakinra cytokine/chemokine measurements. Maximum daily-EEG confirmed seizure burden will be quantified during the first week of the ICU admission and will be associated with initial levels of NLRP3 inflammasome-related factors. We will also perform ex vivo stimulation of freshly collected peripheral blood monocytes to assess IL1RA and NLRP3 function and the ability of the cells to secrete cytokines. Patients exhibiting dysfunctional IL1-RA will be further processed for IL1RN gene sequencing. Similarly, when other dysfunctional NLRP3 inflammasome mediators are identified, we will pursue appropriate genetic evaluation. Finally, all samples will be assessed for a broad panel of chemokines and cytokines [TNFa, IL1b, IL6, IL8, IL10, IL12p70, IL18, CCL2, CCL5, CXCL1/2, CXCL9, CXCL10, IFNg, GM-CSF, G-CSF, CCL3, CCL4, IL1a], so that even if the current hypothesis is incorrect or inconclusively supported, we will gather a profound understanding of the inflammatory status of these patients.

**Relevant publications**


Developing a network to investigate and treat NORSE and FIRES
Principal investigator, Project Coordinator and Contact: Ronny Wickström, MD, Ph.D
ronny.wickstrom@ki.se

**Covid-19 update: Timeline extended due to Covid. Delphi process to resume shortly.**

This project aims to develop standardized investigation, treatment and research protocols for New Onset Refractory Status Epilepticus (NORSE) and Febrile Infection–Related Epilepsy Syndrome (FIRES) of all ages. Such protocols are needed to allow clinical studies of outcome and molecular studies of activated pathophysiological mechanisms that should be targeted in treatment.

To achieve this goal, a Delphi approach will be applied in a selected group of experts in the field. This process will initially take place online after which finalized consensus guidelines will be created at a face-to-face meeting. The multi-round Delphi survey approach ensures both maximal accuracy of the protocols and increases compliance by treating physicians.

**Specific Aims**
- To develop a consensus protocol for investigation, treatment and research sampling in NORSE and FIRES,
- To create a platform for a research consortium that will use the consensus protocols to conduct clinical studies in NORSE and FIRES, and
- To ensure that results from these clinical studies are rapidly disseminated and incorporated in clinical guidelines worldwide.

**Workplan**
Development of consensus protocols is ongoing since January 2020 with a timetable as follows:

<table>
<thead>
<tr>
<th>Month</th>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2020</td>
<td>Establishment of facilitator group (n=8)</td>
<td>Completed</td>
</tr>
<tr>
<td>Feb 2020</td>
<td>Establishment of Delphi panel (n=48)</td>
<td>Completed</td>
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<tr>
<td>Mar 2020</td>
<td>Pre-questionnaire concerning the Delphi process answered by all participants</td>
<td>Completed</td>
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<tr>
<td>Mar-May 2020</td>
<td>Development of questionnaire 1 by facilitator group</td>
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<tr>
<td>June 2020</td>
<td>First round</td>
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<tr>
<td>July 2020</td>
<td>Data collation and development of questionnaire 2</td>
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<tr>
<td>Aug 2020</td>
<td>Second round</td>
<td></td>
</tr>
<tr>
<td>Sep-nov 2020</td>
<td>Data collation and development of basis for consensus statement</td>
<td></td>
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<tr>
<td>Dec 2020</td>
<td>Face-to-face meeting to finalize protocol and prepare publication (AES Seattle)</td>
<td></td>
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</tbody>
</table>

**Investigators**

**Facilitator group:** Robertino Dilena (Italy), Nicolas Gaspard (Belgium), Lawrence Hirsch (USA), Sooky Koh (USA), Eric Payne (Canada), Nicola Specchio (Italy), Olga Taraschenko (USA) and Ronny Wickström (Sweden)

**Delphi panel:** 48 experts in the field from different specialties and countries
Prospective, observational study of NORSE patients (including sub-type FIRES)
Principal Investigators: Nicolas Gaspard, MD, PhD (Erasme Hospital, Brussels)
nicolas.gaspard@erasme.ulb.ac.be PI and Contact
Lawrence J. Hirsch, MD (Yale) lawrence.hirsch@yale.edu PI and Contact
Study Coordinator: Yashwanth Pulluru yashwanth.pulluru@yale.edu

**Covid-19 update:** The study is continuing, including enrollment. But specimens should be held at collecting institutions and not sent to Yale until further notice.

IRB update: Submitting revised IRB to lower age inclusion criteria to 2 years, and to include stool and saliva collection.

The study is being conducted by participating member centers of the Critical Care EEG Monitoring Research Consortium (CCEMRC) as well as a few additional sites, with 24 active sites as of April 2020. Clinical data and biological samples (serum, whole blood, CSF, brain tissue) are being collected. The purpose of this study is to identify possible cause(s) of NORSE and to determine the best treatments and the range of outcomes. The primary objective is to create a biorepository and database to support future research on NORSE and its sub-type FIRES.

Patient commitment and support includes bio-specimen collection (mostly "leftover" samples taken during clinical care), two years total enrollment, and three follow up visits (3-6 months, 12 months, and 24 months after hospital discharge; can be via phone or video visit).

Total current enrollment is 29 patients, led by Yale (7 patients) and the Mayo clinic (5 patients). More sites are being activated. Enrollment goal is 100 patients, with at least 25 pediatric cases and 25 adult cases. Inclusion Criteria -Patient must be 6 years old or older (soon lowering to 2 years) -SE Refractory to first and second line of therapy -No definite etiology found in the first 24 hours. Exclusion Criteria -Major ongoing acute or subacute medical issues (e.g. organ failure, active cancer, etc.) in the opinion of the investigator.

Clinical presentation of new-onset refractory status epilepticus (NORSE) in children (the pSERG cohort)
Principal Investigators:
Claudine Sculier, MD (Erasme Hospital, Brussels) Claudine.Sculier@erasme.ulb.ac.be
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Project coordinator: Justice Clark, MPH Justice.Clark@childrens.harvard.edu
IRB-P00001207
This is a retrospective study of prospectively collected data obtained from 11 centers within the pSERG cohort. The study aims to describe the characteristics of the cohort, including the clinical presentation and outcomes, according to the updated proposed operational definitions of NORSE and FIRES. We analyzed three subgroups of patients by the occurrence and the time of onset of fever relative to the status epilepticus (SE): previous fever (FIRES cases), fever at SE onset (febrile status epilepticus), and no fever. A fourth group was described, with NORSE with identified etiology.

**Eligibility**

**Inclusion criteria:**
1) age from 1 month to 18 years; 2) admission to a pSERG institution between June 1, 2011, and October 1, 2016; and 3) focal or generalized convulsive seizures at onset that continued after administration of at least two anti-seizure medications (ASM), including at least one non-benzodiazepine medication, or the use of a continuous infusion to treat SE.

**Exclusion criteria:**
1) non-convulsive SE (NCSE) detected on electroencephalogram (EEG) lacking convulsive seizure at onset; 2) NCSE with motor manifestations limited to infrequent myoclonic jerks; 3) previous history of epilepsy; and 4) readily identifiable cause of SE easily detected by routine diagnostic tests (e.g., stroke, brain lesion, acute brain injury, acute medical condition, bacterial meningitis).

If more than one episode of RSE occurred during the study period, only the first episode was included.

**Sample size** We included 46 children who met the NORSE criteria.

**Project hypothesis** This paper is a descriptive study of a prospective cohort of NORSE children using the updated proposed operational definitions. We addressed therefore their advantages and brought possible suggestions for improvement.

The significance of the preceding febrile episode and the relationship between fever onset and SE onset has not been investigated yet. In most previous studies, only FIRES cases were reported, and fever was most of the time an inclusion criterion. We hypothesize that children presenting as NORSE with preceding fever (corresponding to FIRES) had a distinct course from other NORSE of unknown etiology cases.

**Relevant publications**
Long-term neuropsychology outcomes in children with FIRES treated with Anakinra
Principal Investigator and Contact: Krista Eschbach, MD (Children's Hospital of Colorado) 
krista.eschbach@childrenscolorado.org
COMIRB Protocol 19-0045

This is a retrospective review of a small series of children with FIRES who received treatment with Anakinra. The aim of the review is to describe the long-term neuropsychology outcomes in this population, with a comparison to historical controls. We are requesting neuropsychology testing at approximately 12 and 24 months after the initial presentation (longer follow-up is also available for a few patients). We have identified approximately 7 patients. We have the potential to add other sites if additional patients are identified.

Call for data: Currently, the IRB includes children up to 18 years old, although we could potentially increase the age limit if additional patients are identified. We welcome patient data from other sites. Data collection expected to be completed by end of summer.

Impact of Febrile Infection Related Epilepsy syndrome on patient and family and Effect of social media on coping and patient care
Principal Investigator and Contact: Raquel Farias-Moeller, MD, (Medical College of Wisconsin) rfarias@mcw.edu
IRB: PRO00036742

The objective of this study is to assess the impact of Febrile Infection Related Epilepsy syndrome on the patient and the family as well as to understand coping via the utilization of social media. We use a questionnaire completed by parents to assess demographics, trajectories and outcomes of children with FIRES.

We aim to estimate FIRES-related social media participation, trust in the institutions managing FIRES complications, and the emotional impact of FIRES impact on caregivers as means for coping.

• Characterize type (e.g., Facebook, Twitter, online news), amount (e.g., total hours), and nature (e.g., types of data) of FIRES social media participation associated with risk perceptions, and emotional responses.

• Investigate parental desire to interface with the medical community via social media, including advertising FIRES research.

Content media analysis and predictive modeling that examines moderators of social support acquisition will be performed.
**Inclusion criteria:** Family members with children who have FIRES will be included. Members of the Facebook group F.I.R.E.S. (only one family member can fill out the survey) will be approached and will meet inclusion criteria if they care for a child with the diagnosis of FIRES. If other FIRES related social media outlets are discovered, their members will be approached.

**NORSE Family Registry**

**Registry is undergoing revision. Encourage participation beginning Fall 2020.**

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Funding: Funded by the Robert N. Kohn NORSE Family Registry Memorial Fund

HSREB: 112269 (Health Sciences Research Ethics Board)

The goal of the NORSE Family Registry is to build a broader understanding of the patient profile, trajectories and outcomes of NORSE. Survivors, substitute/surrogate decision makers or physicians (with patient/SDM permission) can enter data directly into this international, online registry using REDCap. Access to the Registry is through the NORSE Institute website.

We collect information including demographics, past medical history, types of investigations and treatments during the acute phase, and clinical and quality of life outcomes in the acute and chronic phases.

Respondents may upload de-identified medical files at their discretion. No samples required. No maximum participant number in Registry.

We invite you to share annotated references to your work to be included in future Bulletins and our website. For questions/contributions or to unsubscribe to this Bulletin, contact Nora Wong, Executive Director, NORSE Institute (nora.norse@gmail.com).