New Onset Refractory Status Epilepticus (NORSE)

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Disclosures

• Seed grant (AES-NORSE Institute/Daniel Raymond Wong Neurology Research Fund) to develop a nanoparticle-bound anakinra for the treatment of NORSE

• Junior Investigator Research Award (AES) to study the role of inflammation in autoimmune seizures
Learning Objectives

• Discuss the definition, most common etiologies, and existing pathophysiological hypotheses of NORSE
• Review the most common clinical and electrographic features of autoimmune encephalitis syndromes relevant to NORSE
• Identify the ictal, interictal, and other EEG patterns in NORSE/FIRES
• Summarize the current treatment approaches in NORSE/FIRES
Status epilepticus (SE)

Refractory SE (RSE): failure of treatment with ≥ two anticonvulsants

Super refractory SE (SRSE): failure of treatment with anesthetics ≥ 24 h

Prolonged refractory SE (PRSE): failure of treatment without anesthetics ≥ 7 days

Prolonged super refractory SE (PSRSE): failure of treatment with anesthetics ≥ 7 days

Hirsch et al., Epilepsia 2018
Definition of NORSE

- Clinical presentation of an acute RSE without clear active structural, toxic or metabolic causes
- Includes patients with resolved epilepsy secondary to the structural brain lesion
- Includes autoimmune and infectious etiologies
- Febrile infection-related epilepsy syndrome (FIRES) requires an antecedent fever within 1-14 days in any age group
- Infantile hemiconvulsion-hemiplegia and epilepsy syndrome (IHHE) requires a unilateral motor RSE and persistent high-grade fever in patients <2 years old

Hirsch et al., Epilepsia 2018
The evolution of our knowledge

Epidemiology

• Over 400 cases in adults and children
• Incidence
  o ~ 7% of SE cases (or 1/100,000 per year)
  o ~ 20% of RSE cases
  o ~ 50-70% of SRSE cases
• Sex distribution
  o adults: F > M
  o children: M > F
• Mortality
  o adults: 16-27%
  o children: 12%

Gaspard et al., *Epilepsia* 2018; Sculier and Gaspard *Seizure* 2019; Speccio and Pietrafusa *Dev Med Child Neurol*. 2020
Proposed mechanisms of seizures in NORSE

Polymorphism in the SCN2A and IL-1R antagonist genes

- Dysfunction of inflammasome NLRP3
- Deficient activity of the endogenous antagonist of the IL-1R

The role of neurogenic inflammation in NORSE

Evidence for intrathecal and systemic inflammation

- Increased CSF levels of IL-6, CXCL 9-11 in FIRES but not in other SE syndromes (Kothur et al., Epilepsia 2019)
- Upregulated CSF IL-6 and serum IL-6, IL-1β and endogenous IL-1 receptor antagonist in FIRES (June et al., Ann Neurol 2018; Clarkson et al., Ann Neurol 2019)

Dysfunction of inflammasome NLRP3

- Normal function: mediates recruitment of and activation of caspase and release of IL-1β and IL-18
- Dysfunction: excessive production of inflammatory cytokines
**Known etiologies of NORSE/FIRES**

**Cryptogenic cases:**
- adults ~ 52%
- pediatric ~ 58%

**Pediatric cohorts (n = 77, 40)**
- autoimmune: 8-35% (anti-VGKC, anti-GAD)
- viral: 20%
- other: 15%

Clinically recognizable syndromes associated with NORSE

- Anti-NMDA receptor encephalitis

- Limbic encephalitis (LE) with anti-leucine-rich glioma-inactivated 1 (LGI1) antibodies

- Autoimmune encephalitis (AE) with anti-GABA$_A$ or GABA$_B$ receptor antibodies

Husari and Dubey Neurotherapeutics 2019
Anti-NMDA receptor encephalitis

- Multifocal CNS syndrome
- Number of reported cases ~ 2,000
- Constitutes ~ 12-15% of NORSE etiologies
- New-onset seizures are present in 78-86%
- Seizures as a first symptom are more common in males and children
  - adults: generalized > focal
  - children: focal >> generalized
- SE develops in 7-8% of adults and children

Extreme delta brush

• Found in 30% of adult and 53% of pediatric patients with anti-NMDAR encephalitis

• In adults is associated with prolonged recovery and EEG monitoring

• May be related to altered modulation of NMDAR-mediated currents

Schmitt et al., Neurology 2012; Haberlandt et al., Eur J Paediatr Neurol 2017
Extreme delta brush

Schmitt et al., Neurology 2012; Haberlandt et al., Eur J Paediatr Neurol 2017
Evolution of generalized EEG patterns in anti-NMDAR encephalitis

Schmitt et al., Neurology 2012; Vogrig et al., Epilepsia 2019; Irani et al., Brain 2010
In children unilateral discharges may carry more favorable prognosis than diffuse patterns

Gitiaux et al., Clin Neurophysiol 2013
AE associated with anti-leucine glioma inactivated 1 (LGI1) protein

- Limbic encephalitis
- Number of reported cases ~250
- Contributes to ~6% of NORSE cases
- Seizures in 50-90% of patients
- Semiology: myoclonic, dystonic, sensory, GTCs
  - facial brachial dystonic seizures (FBDS)
  - unilateral piloerection
- SE in 22% of cases

Facial brachial dystonic seizures (FBDS)

- Present in 15-50% of patients with anti-LGI1 antibodies
- Unilateral, brief, frequent (median 50/day)
- Associated symptoms: loss of awareness (64%), vocalizations (24%)

van Sonderen et al., Neurology 2016; Irani et al, Ann Neurol 2011
Representative EEG during FBDS: focal rhythmic activity

Ictal EEG changes occur in ~ 5% of FBDSs

Irani et al., *Ann Neurol* 2011; Navarro et al., *Brain* 2016; Aurangzeb et al., *Seizure* 2017
Representative EEG during FBDS: diffuse attenuation

Ictal EEG changes occur in ~ 5% of FBDSs

Wang et al., *Front Neurol* 2020
Ictal piloerection in anti-LGI1 encephalitis
Anti-GABAB receptor encephalitis

• Limbic encephalitis with ataxia (9%)
• Number of reported cases ~90
• Seizures in 84-88% (refractory, temporal lobe predominant)
• SE
  o on presentation: 9.6%
  o during acute phase: 16-62%
• Chronic epilepsy: 29%
• Paraneoplastic etiology in the majority of patients
• No survivals among patients who did not receive immunotherapy, chemotherapy or their combination

Lancaster et al, Lancet Neurol, 2010; Höftberger et al., Neurology 2013; Boronat et al., Neurology 2011; McKay et al., Neurol Neurochir Pol 2019; Frangaj and Fan, Neuropharmacology 2018; Wang et al., Front Neurol 2020
Anti-GABAA receptor encephalitis

- Antibodies against α1, β3 and γ2 subunits cause reduced surface receptor density \textit{in vitro}
- Early refractory seizures (88%) with crescendo pattern
- SE of any type: 33-45%
- Characteristic non-enhancing multifocal cortical-subcortical lesions
- Mortality: 20%
- Full recovery: 20%

Petit-Pedrol et al., \textit{Lancet Neurol} 2014; Pettingill et al. \textit{Neurology} 2015; Spatola et al., \textit{Neurology} 2017; O’Connor et al., \textit{Neurol Neuroimmunol Neuroinflamm} 2019; Husari and Dubey \textit{Neurotherapeutics} 2019
Summary of ictal findings in AE

• Extreme delta brush in anti-NMDA receptor encephalitis
• No other pathognomonic EEG features
• FBDS is associated with anti-LGI1 antibodies
• Refractory seizures manifest early in anti-GABAA and GABAB-receptor encephalitis
Cryptogenic NORSE (C-NORSE)
Epidemiology and outcomes of C-NORSE

- Constitutes ~ 52-58% of all NORSE cases
- Mortality: 12-30%
- Rapid development of brain atrophy
- Survivals: > 60% with refractory epilepsy and 30% with severe cognitive deficits
- Guidelines for the management of C-NORSE are not defined
Semiology of seizures in C-NORSE/FIRES

Specchio and Pietrafusa, Dev Med Child Neurol. 2020; Serino et al., Neuropsychiatr Dis Treat 2019
Ictal EEG findings in C-NORSE/FIRES

Specchio and Pietrafusa, *Dev Med Child Neurol* 2020
Can C-NORSE be predicted early?

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Proportion of patients, %</th>
<th>Cryptogenic (n = 11)</th>
<th>Anti-NMDAR IgG-positive (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodromal fever</td>
<td></td>
<td>91</td>
<td>38</td>
</tr>
<tr>
<td>Encephalopathy prior to SE</td>
<td></td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td>Abnormal movements</td>
<td></td>
<td>27</td>
<td>94</td>
</tr>
<tr>
<td>Generalized or NC refractory SE</td>
<td></td>
<td>100</td>
<td>19</td>
</tr>
<tr>
<td>Good outcome (mRS 0-2)</td>
<td></td>
<td>27%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Clinically-based score to predict C-NORSE *

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset RSE</td>
<td>1</td>
</tr>
<tr>
<td>Previously healthy individual</td>
<td>1</td>
</tr>
<tr>
<td>Presence of prodromal high fever of unknown origin before the onset of SE</td>
<td>1</td>
</tr>
<tr>
<td>Absence of prodromal psychobehavioral or memory alterations</td>
<td>1</td>
</tr>
<tr>
<td>Absence of orofacial-limb dyskinesia</td>
<td>1</td>
</tr>
<tr>
<td>Symmetric DWI or T2/FLAIR hyperintensities</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

Sensitivity: 94%
Specificity: 100%

* does not apply to NCSE

Iizuka et al., *Neurol Neuroimmunol Neuroinflamm* 2017; Yanagida et al *Neurol Neuroimmunol Neuroinflamm* 2020: Iizuka and Yanagida *Clin & Experimental Neuroimmunol* 2020
Ictal and interictal findings in NORSE/FIRES
Ictal EEG findings in NORSE

Pediatric cohort (n=40)
- all seizures on EEG: 68%
- generalized: 15%
- focal: 85%

Gaspard et al., Neurology 2015; Husari et al., Pediatr Crit Care Med 2020
Other EEG patterns in NORSE

- Periodic discharges: 72%
  - lateralized: 39%
  - bilateral independent: 24%
  - generalized: 22%
  - multifocal: 2%
- Epileptiform discharges
  - focal: 36%
  - frontotemporal: 66%
  - bilateral: 18%
  - multifocal: 37%
- No difference between the electrographic characteristics in patients with and without established etiology

Gradual evolution of seizures to SE in pediatric FIRES

- Orobuccal automatisms
- Head deviation with autonomic changes
- Oral clonus with hypersalivation

Farias-Moeller et al., Epilepsia 2017; Specchio and Pietrafusa, Dev Med Child Neurol 2020; Serino et al., Neuropsychiatr Dis Treat 2019
Ictal shifting in pediatric FIRES

Howell et al., *Epilepsia* 2012; Farias-Moeller et al., *Epilepsia* 2017; Mohammad et al., *Clin Neurophysiol* 2016
Focal fast activity at seizure onset in children with FIRES

Farias-Moeller et al., *Epilepsia* 2017; Specchio and Pietrafusa, *Dev Med Child Neurol* 2020
Summary of electro-clinical findings in NORSE/FIRES

• Clinical semiology and EEG are similar in NORSE with established etiology and C-NORSE
• Focal myoclonic seizures are prevalent in FIRES
• Interesting findings in FIRES:
  o gradual seizure evolution to RSE
  o ictal shifting
  o focal fast activity at ictal onset
## Treatment of cryptogenic NORSE

<table>
<thead>
<tr>
<th>Therapeutic line</th>
<th>Specific treatments</th>
<th>Patients with improvement, % total (number of cases)</th>
<th>NORSE</th>
<th>FIRES</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>Steroids</td>
<td>38% (40)</td>
<td>17% (63)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVIG</td>
<td>30% (17)</td>
<td>5% (94)</td>
<td></td>
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<tr>
<td></td>
<td>Plasma exchange</td>
<td>40% (15)</td>
<td>11% (18)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Second line</td>
<td>Rituximab</td>
<td>0% (5+5)</td>
<td>33% (3)</td>
<td></td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>0% (5)</td>
<td>0% (1)</td>
<td></td>
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<td></td>
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<tr>
<td>Interleukin receptor</td>
<td>Anakinra</td>
<td>None</td>
<td>48% (26)</td>
<td></td>
</tr>
<tr>
<td>antagonists</td>
<td>Canakinumab</td>
<td></td>
<td>100% (1)</td>
<td></td>
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<tr>
<td></td>
<td>Tocilizumab</td>
<td>86% (7)</td>
<td>None</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Cannabidiol</td>
<td>100% (5)</td>
<td>90% (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bortezomib</td>
<td>44% (13+34)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketamine</td>
<td>67% (12)</td>
<td>100% (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketogenic diet</td>
<td>40% (2)</td>
<td>59% (35+9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td></td>
<td>100% (2)</td>
<td></td>
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</table>

Treatment of FIRES

• Favorable outcomes in FIRES were associated with
  o using ketogenic diet in acute or chronic phase
  o using steroids in acute or chronic phase
  o living in Japan or China

• No association was found for the use of IVIG or plasma exchange and better outcomes

Kessi et al., Seizure 2020
Updates on the NORSE initiatives

• Prospective Observational Study (NORSE Institute/Yale University)
  o ongoing since June 2020
  o enrolled 40 patients and stored their biological specimens and clinical data

• NORSE Family Registry: international online registry that collects demographic, geographic, and outcome data for persons affected by NORSE/FIRES
  http://www.norseinstitute.org/norse-registry-2

• Development of a consensus protocol for investigation, treatment, and research sampling in NORSE/FIRES using the Delphi approach
  o international facilitator group has developed a survey
  o first survey was sent to 48 experts worldwide (January 2021)
Ultimate goals *in improving care* for NORSE

- Refine the clinical criteria
- Establish the pathogenies of seizures in NORSE
- Improve the early diagnosis
- Develop international collaboration
- Establish interventional trials