2nd Nordic Status Epilepticus Meeting

Bergen, Norway, 1-2 June 2023

Hotel Norge by Scandic

Bergen

Norway

The meeting is financially supported by Desitin.

Overarching theme: From bad to worse: Therapeutic and ethical challenges in super-refractory status epilepticus.

Bergen, 1-2.06.2023

Faculty:
Erik Taubøll (Head of committee, Norway), Johan Zelano (Sweden), Christoph P Beier (Denmark), Reetta Kälviäinen (Finland). From Norway: Kjell Heuser, Line Bédos Ulvin, Bernt Engelsen, Gyri Veiby, Kjersti Nesheim Power, Christian Samsonsen, Ketil Berg Olsen, Ellen Molteberg, Morten Horn

Day 1

Basic mechanisms of status epilepticus (SE) - from single seizures to refractory SE

Chair: Erik Taubøll, Oslo

10.00-10.05 Opening and welcome. *Erik Taubøll*

10.05-10.15 Epileptogenesis – definitions and basic principles. *Erik Taubøll*

10.15-10.55 Epileptogenesis and the role of inflammation. *Annamaria Vezzani*

10.55-11.20 Astrocyte-driven epileptogenesis and its role in development of refractory SE. *Kjell Heuser*

11.20-11.40 DNA methylation as a preventive treatment target of epileptogenesis. *Toni C Berger*

11.40-12.00 Discussion

12.00-13.00 Lunch

SE after anoxic brain damage

Chair: Christian Samsonsen, Trondheim

13.00-13.20 Postanoxic convulsions – a clinical challenge. SE or not SE, that's the question. *Kjersti Nesheim Power*

13.20-13.50 How useful is EEG in the early phase? *Erik Westhall*

13.50-14.10 What is the place for radiology in postanoxic SE? *Mona Kristiansen Beyer*

14.10-14.40 Postanoxic convulsions. To treat or not to treat – and with what? *Johan Zelano*

14.40-15.00 Discussion

15.00-15.30 Break

Prognostication

Chair: Bernt Engelsen, Bergen

15.30-16.00 Prognostication of long-term mortality after SE. *Christoph P Beier*

16.00-16.30 Differences in prognosis after anoxic SE – the insight from two cases. *Christian Samsonsen*

16.30-16.55 Discussion. How should this information be handled in everyday practice? *Bernt Engelsen (panel leader), Christoph P Beier, Christian Samsonsen* Discussion with the audience.

16.55-17.00 Closing remarks, *Day 1, Erik Taubøll*

20.00 Dinner

Day 2

Challenges in SE treatment in complex epilepsy syndromes – case-based presentations

Chair: Ellen Molteberg, Oslo

08.30-09.30 POLG disease and status epilepticus. *Omar Hikmat and Gyri Veiby*

09.30-10.15 SE in mental retardation – what is different? *Morten Horn*

10.15-10.45 Break/ coffee

10.45-11.30 SE in progressive myoclonic epilepsy syndromes. *Reetta Kälviäinen*

11.30-12.30 Lunch

Chair: Morten Horn, Oslo

12.30-13.15 Case presentations.
12.30–12.45 FIRES syndrome in a child. Possible effect of anakinra. *Inger Sandvig*
12.45-13.00 SE in a child with a new glutamate receptor mutation. *Marianne Ullestad Huun*
13.00–13.15 SE in an adult successfully treated with hemispherectomy. *Kjell Heuser*

13.15-14.15 Ethical roundtable discussion.
SE treatment – how long, how many alternatives, to what price?
Morten Horn (panel leader). Panel from organising committee and representatives from the Norwegian Epilepsy Foundation - the norwegian branch of IBE

14.15-14.30 Closing remarks. *Erik Taubøll*

Faculty and speakers

Erik Taubøll
Professor of Neurology and Senior Consultant, Department of Neurology, Oslo University Hospital - Rikshospitalet, Oslo, Norway. Head of ERGO, Epilepsy Research Group of Oslo, in Department of Neurology. The group is active in both clinical, translational and basic epilepsy research, see: https://www.ous-research.no/ergo/

Johan Zelano
Section Head and assistant professor, Department of Neurological Care, Sahlgrenska university hospital, Gothenburg, Sweden. He has a special interest in epilepsy with emphasis on poststroke epilepsy, and biomarkers in neurology.

Christoph Patrick Beier
Professor of neurology and consultant for general neurology with specialist interest in epilepsy. Head of the epilepsy research group and affiliated to the Center for Innovative Medical Technology at the Odense University Hospital, Denmark. His research interest are prognostication and optimization of treatment of status epilepticus, pathophysiology of drug resistant idiopathic generalized epilepsies, and new approaches for optimized ambulatory patient care.

Erik Westhall
is senior consultant in clinical neurophysiology at Skane University Hospital and associate professor at Lund University, Sweden. His research area is electrophysiological measurements in critically ill patients suffering from acute brain injury, mainly focusing on neuroprognostication and assessment of electrographic seizures in comatose patients resuscitated after cardiac arrest.

Gyri Veiby
MD, PhD, is a senior consultant neurologist at Haukeland University Hospital in Bergen, working at the section for acute neurological diseases. Veiby has a special clinical interest in the treatment of refractory status epilepticus, and specifically in relation to POLG disease. Main scientific research is focused on different female aspects of epilepsy, and in particular the investigation of teratogenic effects of antiepileptic drugs based on large register-based studies.

Reetta Kälviäinen
is Full Professor and Chair of Neurology in the University of Eastern Finland and Director of the Kuopio Epilepsy Center in Kuopio University Hospital. Her special research interest is clinical epileptology including identifying biomarkers of seizure activity and drug-resistancy in cohorts of newly diagnosed and drug-resistant chronic patients. These aspects of scientific projects are combined with therapeutic neuropharmacological interventions. She serves in the executive committee of the European Reference Network for rare and complex epilepsies EpiCARE (of which Kuopio Epilepsy Center is a member) and in the management group of the Epilepsy Scientific Panel of the European Academy of Neurology. She is the chair of the board of the Neurocenter Finland and the Finnish Neurological Society.

Annamaria Vezzani
PhD in Neuropharmacology, Head of the Laboratory of Experimental Neurology, Department of Neuroscience at the Mario Negri Institute in Milano. Main research focus is on mechanisms of seizures and epileptogenesis for developing new treatments and biomarkers. Author of over 200 original papers, several book chapters and reviews in peer-reviewed high impact scientific journals. Past Chair of the Commission on Neurobiology of ILAE (2005-2009). Member of the Innovative Medicine Initiative (IMI) Scientific Committee (2018-2019). Member of the ILAE Commission on European Affairs (2013-2017). Serving in several editorial boards of scientific journals and American Epilepsy Society (AES) and ILAE committees. Recipient of the Research Recognition Award for translational research in 2009 by the AES.

Kjell Heuser
MD, PhD, is a Senior Consultant and Clinical epileptologist in Department of Neurology, Oslo University Hospital. He is Head of Translational Epilepsy Research Group which is part of ERGO (Epilepsy Research Group of Oslo), with a special interest in translational and clinical epilepsy research.

Bernt Engelsen
Professor of Neurology since 1989. Research background; neurotransmission research on glutamate in the 1980ies-90ies, and since 1994 head of the clinical epilepsy unit at Haukeland University Hospital. Research interests; clinical epileptology, POLG related epilepsy and Status epilepticus.

Faculty and speakers

Kjersti Nesheim Power
is a neurologist with a PhD in cognitive consequences of status epilepticus. She is a member of Bergen Epilepsy Research Group and works at Department of Neurology at Haukeland University Hospital.

Christian Samsonsen
Head of department/neurologist at Department of Neurology and Clinical Neurophysiology, St Olav's hospital; Associate professor, INB, NTNU.
Special fields of interest: Clinical epileptology, seizureprecipitants.

Morten Horn
MD, PhD, is a consultant in neurology at Oslo University Hospital. He is a lecturer in medical ethics at the University of Oslo, and a member of the Medical Ethics Council for the Norwegian Medical Association.

Inger Sandvig
is a medical doctor currently working at Oslo University Hospital as Senior Consultant, Department of Child Neurology. Her area of special interest is epilepsy and autoimmune neurological diseases.
She graduated from Copenhagen University in Denmark in 1980. Before taking on this position at Oslo University Hospital in 1997, she worked at various hospitals as a paediatrician. Sandvig has co-authored several publications, with topics ranging from the causes of febrile seizures to multiple sclerosis in children and adolescents.

Ellen Molteberg
MD, Neurologist and Head of the Adult Department at the National Center for Epilepsy in Norway. Special interest in non-medical treatment, i.e modified Atkins diet for adult patients.

Marianne Ullestad Huun
Consultant Pediatrician, PhD, Department of Child Neurology, Oslo University Hospital, Rikshospitalet, Norway.

Ketil Berg Olsen
Senior Consultant in Neurology and Clinical Neurophysiology, Østfold Hospital Trust and Oslo University Hospital, Rikshospitalet. Member of ERGO, Epilepsy Research Group of Oslo. Many years experience in epileptology/neurology/clinical neurophysiology, about 7 years experience in SEEG and IOM.

Line Bédos Ulvin
is a neurologist and clinical neurophysiologist working at Oslo University Hospital. Her field of interest is epilepsy and EEG, and she is involved in several research projects on status epilepticus.

Mona Kristiansen Beyer
Professor of Neuroradiology, Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway. Research leader at the University of Oslo for Radiology and nuclear medicine. Main areas of research are within translational research in Parkinson's disesease, Post stroke dementia, Multiple sclerosis and Lyme Neuroborreliosis.

Omar Hikmat
MD, PhD, is a senior consultant in paediatric neurology, working at the Paediatric Neurology section- Paediatric Department, Haukeland University Hospital, Bergen, and researcher at the Mitochondrial Medicine and Neurogenetic research group, Clinical Institute 1, University of Bergen, Norway.
Hikmat has a special interest in paediatric neuro-metabolic, mitochondrial disorders and complex epilepsies with focus on POLG disease. He is responsible for the National Norwegian POLG registry and the multinational POLG database.

Toni Berger
MD, PhD student, Department of Neurology, Oslo University Hospital - Rikshospitalet, Oslo, Norway. After working one year in the Department of Neurology, Østfold hospital trust, he joined ERGO (Epilepsy Research Group of Oslo in Department of Neurology, OUS-RH) in 2017. His PhD is financed by a Marie-Curie scholarship as part of the "EU Glia PhD" project - a European network for brain research.

Organising Committee:

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(Head og organising committee)
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Reetta Kälviäinen
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She serves in the executive committee of the European Reference Network for rare and complex epilepsies EpiCARE (of which Kuopio Epilepsy Center is a member) and in the management group of the Epilepsy Scientific Panel of the European Academy of Neurology. She is the chair of the board of the Neurocenter Finland and the Finnish Neurological Society.

Kjell Heuser
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Morten Horn
MD, PhD, is a consultant in neurology at Oslo University Hospital. He is a lecturer in medical ethics at the University of Oslo, and a member of the Medical Ethics Council for the Norwegian Medical Association.

Line Bédos Ulvin
is a neurologist and clinical neurophysiologist working at Oslo University Hospital. Her field of interest is epilepsy and EEG, and she is involved in several research projects on status epilepticus.

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Born 1951. Professor of Neurology since 1989. Research background; neurotransmission research on glutamate in the 1980ies-90ies, and since 1994 head of the clinical epilepsy unit at Haukeland University Hospital. Research interest; clinical epileptology, POLG related epilepsy and Status epilepticus.

Gyri Veiby
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Abstracts

for the 2nd Nordic Status Epilepticus meeting 2023

Epileptogenesis – definitions and basic principles

Erik Taubøll
ERGO – Epilepsy Research Group of Oslo, Department of Neurology, Oslo University Hospital – Rikshospitalet, Oslo, Norway

Epileptogenesis has traditionally been defined as the process during which changes occur in the brain after a precipitating injury or insult that results in the development of spontaneous recurrent seizures or epilepsy. Epilepsy is now considered a network disease, and epileptogenesis can therefore also be considered a process by which a brain network that was previously normal is functionally altered toward increased seizure susceptibility and an increased probability to generate spontaneous seizures. The time period between the insult and the first clinical seizure has been denoted the latent period. The latent period is still a bit of a "black box" with limited knowledge about the basic mechanisms leading to development of epilepsy.

Many both experimental and and clinical studies have, however shown that seizure frequency and severity can increase also after the first unprovoked seizure. For instance, especially temporal lobe epilepsy has been suggested to be a progressive disease. This suggests that epileptogenesis do not stop at the first seizure but is a continuous and prolonged process. For this reason, a Working Group on "Issues related to development of anti-epileptogenic therapies" of ILAE and AES updated the terminologies related to epileptogenesis. Epileptogenesis no longer refers only to the time period between the epileptogenic insult and diagnosis of epilepsy, but includes the mechanisms of progression that can continue to occur even after the diagnosis (see figure 1). The formal definition of epileptogenesis is now: "*Epileptogenesis is the development and extension of tissue capable of generating spontaneous seizures, resulting in a) development of an epileptic condition and/or b) progression of the epilepsy after it is established*". The new definition does not specify the trigger. By this, the trigger can be either genetic or acquired, not only acquired as considered before.

The mechanisms behind epileptogenesis are only partly known and involves both cellular and network mechanisms, and molecular mechanisms. A cascade of processes is started after an insult involving 1) ion channel activation, 2) activation of immediate early genes, 3) transcriptional factors, epigenetic changes, changes in methylation, 4) inflammation including microglia activation, 5) neuron death, 6) neurogenesis, 7) sprouting and network reorganization. This will end up with damage to inhibitory neurons and their circuitry and increased excitation. At the same time, coordinated changes in gene expression will take place. But still, the cellular and molecular mechanisms of epileptogenesis are partly unknown.

Elucidating the mechanisms of epileptogenesis is crucial as this will open for development of true antiepileptogenic treatment that would not only stop seizures but also be preventive and could possibly cure epilepsy in the future.

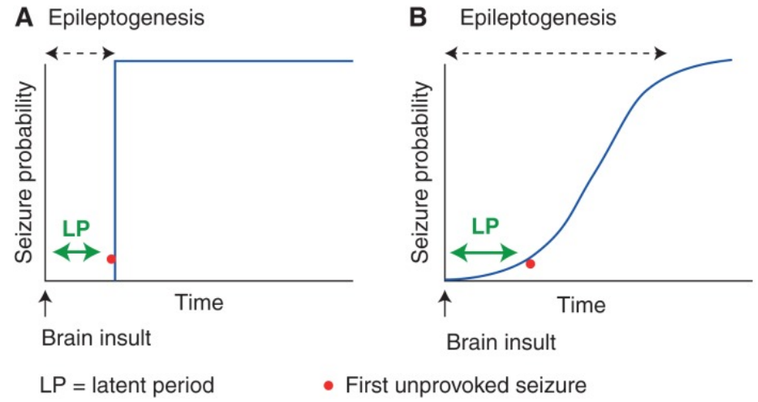

Fig 1. A) Epileptogenesis, earlier definition. Epileptogenesis defined as the processes taking place in the period from insult until first unprovoked seizure. B) New definition of epileptogenesis considering epileptogenesis to include processe beyond the first seizure. The latent period is still defined as the periode until first seizure.

Figure from: Pitkänen A, Lukasiuk K, Dudek E, Staley KJ. Epileptogenesis. Cold Spring Harb Perspect Med. 2015 Oct; 5(10): a022822. doi: 10.1101/cshperspect.a022822

Epileptogenesis and the role of inflammation

Annamaria Vezzani
Department of Acute Brain Injury, Lab. of Epilepsy and Therapeutic Strategies; Mario Negri Institute for Pharmacological Research, Milano, Italy

Epilepsy is a chronic neurological disease characterized by an enduring propensity to generate epileptic seizures. The pathogenic processes leading to the generation and recurrence of seizures are the subject of intensive investigations in both human epilepsy and animal models of the disease. Their identification would allow to design novel treatments apt to prevent the generation of epileptic seizures or for reducing seizure burden. These new treatments are urgently needed to fill the gaps in the development of preventative or disease-modifying interventions, and for controlling pharmacoresistant seizures which affect about 30% of patients.
Neuroinflammation is a maladaptive homeostatic response commonly ignited in human epileptogenic brain regions from structural epilepsies, as well as in animal models of the disease. Most recently, neuroinflammation has been described also in genetic epilepsy models. This brain response includes the biosynthesis and release of inflammatory mediators from brain parenchymal cells, chiefly reactive glial cells and neurons. Inflammatory molecules are endowed of neuromodulatory properties by affecting neuronal ion channels activity and by promoting glial dysfunctions (Vezzani and Viviani, 2005; Vezzani et al, 2022). Neuroinflammation has been the focus of much attention for its clear involvement in the pathogenesis of seizures, neuronal cell loss and neurological comorbidities developing in animal models of epileptogenesis.
The elucidation of the complexity and dynamics of neuroinflammation in epilepsy has generated potential cellular and molecular targets for developing new drugs, or for repurposing available anti-inflammatory drugs, acting on key pathogenic mechanisms. This mechanistic approach to therapy should overcome the mere symptomatic control of seizures which is attained with the current medications.
Proof-of-concept clinical studies have indeed shown that specific anti-inflammatory interventions endowed of therapeutic effects in animal models of acquired epilepsies, reduce seizures in epilepsy patients who are resistant to current antiseizure medications (*Vezzani et al, 2019; Lai et al, 2020*).
Neuroinflammation also offers the possibility of discovering and validating potential biomarkers of epileptogenesis, as recently described in animal models and in proof-of-concept clinical studies (*Vezzani et al, 2019; Vezzani et al, 2022*).

Lai, Y.-C., et al. (2020). Anakinra usage in febrile infection related epilepsy syndrome: an international cohort. Ann. Clin. Transl. Neurol. 7(12), 2467-2474. doi:10.1002/acn3.51229

Vezzani, A. & Viviani, B. (2015). Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. Neuropharmacol. 70-82. doi:10.1016/j.neuropharm.2014.10.027

Vezzani, A., Balosso, S. & Ravizza, T. (2019). Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat. Rev. Neurol. 15(8), 459-472. doi:10.1038/s41582-019-0217-x

Vezzani, A., Ravizza, T., Bedner, P., Aronica, E., Steinhäuser, C. & Boison, D. (2022). Astrocytes in the initiation and progression of epilepsy. Nat. Rev. Neurol. 18(12), 707-722. doi:10.1038/s41582-022-00727-5

Astrocyte-driven epileptogenesis and its role in development of refractory SE

Kjell Heuser

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Astrocytes are key homeostatic regulators in the central nervous system and play important roles in brain physiology. After brain damage caused by e.g. traumatic brain injury, stroke or brain inflammation, astrocytes may adopt a reactive phenotype. This process of reactive astrogliosis seems to be a critical mechanism to restore brain homeostasis. However, reactive astrogliosis can be detrimental for the brain and may contribute to the development of epilepsy. While astrocyte dysfunction has been extensively studied in the later stages of epileptogenesis and chronic epilepsy, little focus has been put on the role of astrocytes in ictogenesis and in status epilepticus. Current knowledge and hypotheses of astrocyte-related processes in both ictogenesis and status epilepticus will be presented and discussed.

DNA methylation as a preventive treatment target of epileptogenesis

Toni C Berger
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Epileptogenesis (Greek: genesis – “to create”), describes the metamorphosis of a physiological brain into an epileptic one. It involves an initial trauma (e.g. severe febrile seizures, head trauma,…), a seizure-free latent phase, and a chronic phase that is defined by the occurrence of spontaneous, and often progressive, epileptic seizures. Pro-epileptogenic processes leading to the first seizure are set in motion during the latent phase and continue through the chronic phase. For anti-epileptogenic intervention (in line with neurodegenerative conditions like AD/PD,…), there is a need to:

A) Detect subjects at risk at an early (during latent phase)
B) Intervene in an anti-epileptogenic manner.

Epileptogenesis is orchestrated by a tight interplay of neurons and glia and major hallmarks consist of e.g., neuronal death, reactive (astro-) gliosis, and inflammation; these, in turn, are also interconnected. Upstream of morphological alterations, gene expression (GE) serves as an estimate of biological function. GE in turn, has been shown to be modifiable by epigenetic mechanisms. Epigenetic mechanisms contribute to which genes are used or not (transcriptome) and are modifiable. As such, they are potential upstream mechanisms for diverse molecular pathways, including, for example epileptogenesis. DNA methylation (DNAm), the most extensively studied epigenetic mechanism, is defined as the methylation (adding of a -CH3 group) of the DNA-base cytosine in a CpG (Cytosine – phosphate – Guanine) dinucleotide. DNAm has been shown to influence gene expression (GE) in a tissue-, context-, and cell-dependent manner, usually in a close interaction with transcription factors. To date, the most-established correlation of DNAm and GE is long-term gene silencing via promoter/CpG island hypermethylation. The role of DNAm in epilepsy and potential therapeutical implications can be grouped into the following aspects:

Altered DNA-methylation patterns in peripheral blood as biomarker for epilepsy and epileptogenesis (A)

Disease-specific blood-DNAm pattern alterations have been reported in several diseases and proposed as possible biomarkers. In epilepsy, the blood of patients with mTLE-HS has shown specific DNAm patterns and a concordant-twin study detected patterns that enabled distinction between focal and generalized epilepsy. These results suggest that blood-based DNAm could be a potential biomarker for epilepsy and comorbidities, potentially paving the way to a more personalized management of PWE. Blood-based DNAm could serve as an early biomarker of epileptogenesis, detecting subjects at risc (A).

Anti-epileptogenic intervention by means of DNA methylation (B)

Wide-spread general alterations of DNAm have been shown in epileptogenesis, especially chronic epilepsy (DNA hypermethylation). Further, an association of DNAm and GE in epileptogenesis has been documented in several neuronal and glial genes. Lastly it may be possible to alter the

expression of epileptogenesis relevant genes and pathways by means of epigenetic editing. In order to achieve this goal, an epigenetic tool, such as a modified CRISPR system with either a DNMT (in order to facilitate hypermethylation and potentially gene silencing) or a TET oxidase (in order to gain hypomethylation and gene activation), applicable both to the anatomical region and cell type of choice, would be necessary.

Neurons and glia orchestrate epileptogenesis, with glia playing a crucial part in neuronal death, reactive gliosis, and inflammation in early epileptogenesis. Several, mostly inflammation-related and glia-derived genes may serve as targets for anti-epileptogenic intervention (B) in subjects at early time points of epileptogenesis (A) or later.

Postanoxic convulsions - a clinical challenge. SE or not SE, that's the question

Kjersti Nesheim Power
BERG - Bergen Epilepsy Research Group, Department of Neurology, Haukeland University Hospital, Bergen, Norway

Various involuntary movements like shivering, tremor, dystonia, myoclonus and tonic clonic seizures are common after anoxic events. The most common form of postanoxic convulsions is myoclonus, typically after cardiac arrest, while generalized tonic clonic seizures and focal motor seizures are rare. Myoclonus may be of both cortical and subcortical origin and may be epileptic or non-epileptic. Clinically, it can be impossible to distinguish these from each other. Furthermore, the interpretation of EEG recordings is far from straightforward, and there can be disagreements whether or not a pattern represents an epileptic seizure, let alone repeated with a frequency and duration qualifying for a status epilepticus. Early, acute post-anoxic myoclonus is often termed myoclonic status epilepticus (MSE), even at times when there is nothing suggesting an epileptic process. About 2/3 of the patients with acute myoclonus exhibit a concomitant epileptiform EEG. It is debated whether these patients have status epilepticus, and some regard them as boundary entities.

MSE is considered a very poor prognostic factor after CA. However, there are several case reports of more favorable outcome in individual patients after MSE, also when awakening after weeks of prolonged treatment with antiseizure medications and narcosis. Aggressive treatment in patients with other beneficial prognostic signs (for instance in EEG, MRI and SEP) is therefore recommended. Yet, it is still debated whether post-anoxic SE is mainly a marker of more severe injury, or by itself produces further injury. The lacking consensus regarding the very definition of MSE makes this field difficult to study. Factors such as sedatives necessary for ventilation treatment further confuse both the clinical and the electrographic picture, and different authors may be referring to different entities when discussing outcome after MSE.

Lance-Adams syndrome (LAS) denotes a more chronic form of post anoxic, or post hypoxic myoclonus. It is related to respiratory arrest of various causes, including cardiac arrest. Myoclonus in LAS is usually multi-focal or generalized; it is intention- and stimulus-induced and normally occurs when the patient awakes. The myoclonus does not have a consistent correlate in EEG. LAS typically occurs much later, but can also occur hours after cardia arrest. In those cases, it is important to differentiate from MSE since the associated outcome is far better.

Freund B, Kaplan PW. Post-hypoxic myoclonus: Differentiating benign and malignant etiologies in diagnosis and prognosis. Clin Neurophysiol Pract. 2017 May 5; 2:98-102.

Rossetti AO, Alvarez V. Update on the management of status epilepticus Curr Opin Neurol. 2021 Apr 1;34(2):172-181. DOI: 10.1097/WCO.0000000000000899

How useful is EEG in the early phase after cardiac arrest? – prognostic value and status epilepticus

Erik Westhall
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Electroencephalogram (EEG) is recommended in guidelines to detect seizure activity and for prognostication after cardiac arrest (CA). EEG is the most widely used tool to assess prognosis in comatose post-CA-patients.

EEG definitions varies in studies and interpretation is prone to interrater variability. Therefore, using a standardized terminology is very important. In 2021, the American Society of Clinical Neurophysiology released its updated standardized EEG terminology.

The EEG activity changes considerably during the first days after CA. The prognostic value of EEG depends on the time-point after cardiac arrest. An early (within 12-24 hours) return of a continuous normal voltage (above 20 µV) background strongly indicates a good prognosis. Failure of EEG-recovery and appearance of highly malignant patterns predicts poor outcome. Periodic discharges or seizure activity are associated with a poor prognosis, but a subgroup of patients have good outcome.

Suppression is a very low-amplitude EEG background (below 10 µV). When suppression periods constitute more than half of the recording and are alternating with bursts of cortical activity, the pattern is called burst-suppression. According to the recent European guidelines updated in 2021, suppression or burst-suppression (with or without superimposed discharges) predict poor outcome if these patterns remain beyond 24 hours after CA. The guidelines suggest waiting until after rewarming and clearing of sedation before using EEG to predict poor outcome, typically corresponding to around 48 hours after CA or beyond. However, if consecutive bursts appear identical according to strict criteria the pattern is called burst-suppression with identical bursts and there is growing evidence that this pattern reliably predicts poor outcome also very early after CA.

The detection and treatment of postanoxic status epilepticus (SE) is the other main indication for recording EEG after cardiac arrest. Epileptiform discharges and rhythmic or periodic discharges, sometimes fulfilling criteria for possible or definitive seizure activity occur in around 30% of patients who are comatose after CA. Most of these are periodic discharges, while definitive seizures are less common. In the majority of patients clinical convulsions do not appear or are transient. Myoclonus is the most common clinical manifestation but tonic-clonic seizures may also occur.

Postanoxic SE is strongly associated with poor prognosis. However, a subgroup of patients may have a good outcome. How do we identify this subgroup? "Favourable" EEG signs are late (beyond the first day) start of possible or definitive SE from a continuous normal-voltage background, preserved EEG-reactivity, lack of highly malignant EEG patterns and discharges with a limited field close to the midline. Importantly the subgroup with a chance for good outcome also lack other signs of extensive brain injury on clinical examination, neuroimaging, or blood biomarkers.

Observational studies report that around one third of the patients in this subgroup of SE may recover, typically after receiving antiseizure medications and prolonged intensive care, often 1-2 weeks or more. There is no definite evidence that antiseizure drugs improve the outcome in postanoxic SE. A recent trial (TELSTAR) randomized patients to antiseizure treatment or standard care and could not detect a difference in outcome. The study also showed that all patients with SE superimposed on a discontinuous or suppressed EEG background had a poor outcome. However, the trial was not powered to evaluate the subgroup of SE patients who lacks highly malignant EEG and other signs of extensive brain injury. Further trials are needed to clarify if status epilepticus is simply a marker of brain injury or if antiseizure treatment is beneficial.

What is the place for radiology in postanoxic SE?

Mona Kristiansen Beyer
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Imaging after cardiac arrest and hypoxic/anoxic injury is sometimes very challenging in both children and adults.

We can use the term hypoxic-ischemic injury (HII), which includes global hypoxic-ischemic injury, global anoxic injury, and cerebral hypo perfusion injury. Such injury can be secondary to suffering from cardiac arrest, cerebrovascular disease, drowning, and asphyxiation. One challenge is that the injury pattern in the brain is highly variable depending on the brain maturity, severity and length of the insult. Sometimes we have this information from clinical information, while other times this is unknown.

We often differ between two imaging patterns

- Mild to moderate event: Watershed zone infarcts.
- Severe event: Gray matter structures (basal ganglia, thalami, cortex, cerebellum, hippocampi)
- Global hypoxic-ischemic damage is a term used when there is both changes in central brain structures, brain stem and diffuse white matter or cortical injury.

MRI is the method of choice in patients with hypoxic/anoxic injury. Within hours after the event, an MRI can be taken to assess the overall extent of the injury. The first MRI sequence to detect changes related to hypoxia/anoxia is the diffusion weighted imaging. DWI is expected to show such changes within a few hours after the event. MR spectroscopy can also show changes within the first 24 hours after hypoxia/anoxia where increased peaks of lactate and glutamine-glutamate can be seen. Later-occurring changes, includes increased T2/FLAIR signal in the cerebellum, basal ganglia and cortex. It is important to be aware of how the different imaging sequences are expected to change in the hours-days after the hypoxic/anoxic event to avoid misinterpretation of findings.

Imaging with brain CT may show

- Diffuse cerebral edema with effacement of cerebrospinal fluid containing spaces
- Decreased cortical gray matter attenuation with loss of normal gray-white differentiation
- Decreased bilateral basal ganglia attenuation
- Reversal or white cerebellum sign indicates severe injury with poor prognosis
- We must always consider differential diagnoses with similar looking brain imaging changes.

Examples of both MRI and CT will be presented.

Postanoxic convulsions. To treat or not to treat – and with what?

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Different convulsions frequently occur after cardiac arrest. Status epilepticus or myoclonia occur in about a third of patients post cardiac arrest and are common reasons for a neurological consult in the ICU. This lecture discusses occurrence of seizures after cardiac arrest, the prognostic impact of different kinds of status epilepticus after cardiac arrest and occurrence of myoclonia, like in Lance-Adam syndrome.

There are several mechanisms of injury after brain anoxia, including apoptosis, excitotoxicity, and laminar necrosis. The understanding of different epileptiform signaling patterns in post anoxic coma has advanced over time, and is more nuanced than such activity being simply an end stage of irreversible coma.[1] In fact, the most severe forms of brain injury seem to render the brain incapable of electrographic seizures. Because of status epilepticus being interpreted as negative predictors, much of the literature on their prognostic impact was uninformative, describing self-fulfilling detrimental outcome. Since about 15 years, case reports, case series, and subsequently prospective observational studies have clarified that a small proportion (5-10%) of patients with post anoxic clinical or electrographic seizures including myoclonia can have a good prognosis.[2-4] Survivors are characterized by preserved brainstem functions, less biochemical evidence of brain injury, and intact N20-responses, underlining the importance of a multimodal assessment and avoidance of reliance on seizures as a red flag. Findings in the last decade indicate that the pattern of EEG from which seizure activity emerges is of importance. Regarding treatment of postanoxic SE, there is little evidence on optimal therapy. Use of antiseizure medication with little potential for cardiac side effects seem intuitive. Regarding the benefits of treatment, the talk will also review the TELSTAR trial,[5] the recently published randomized study on the topic.

A similar literature is emerging regarding post anoxic myoclonia, which can be the clinical outflow of different electrographic patterns and have different prognosis. Some forms respond to treatment, but others do not. In the long term, cardiac arrest is associated with a slightly increased risk of epilepsy, which most likely represent co-morbidities.

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Prognostication of long-term mortality after SE

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Prognostication of patients with status epilepticus remains challenging. Seizure-induced impairment of consciousness, symptoms of the brain disease triggering and maintaining status epilepticus, and the patient's age and co-morbidities influence each and result in a large inter-individual variability and high complexity. The long post-ictal phase with very high morbidity and mortality further adds to the complexity. The high in-hospital mortality and the even higher mortality in the long-term stresses the importance of ways to estimate prognosis and improve treatment.

The talk will focus on three different aspects with importance for prognostication of long-term survival after SE. (I) The impact of age, level consciousness at admission and duration of SE on long-term outcome, and how the strong associations may help the clinician to make treatment decisions. (II) Prognostication of super-refractory SE, and how and why this patient population differs from "normal" SE patients. (III) Contributors to the post-ictal state, which is characterized by new neurological deficits, symptoms of encephalopathy, and delirium.

POLG disease and status epilepticus

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Variants in *POLG*, the gene encoding the catalytic subunit of DNA-polymerase gamma (polγ), the enzyme that replicates and repairs the mitochondrial genome, are among the most common causes of inherited mitochondrial disease.

POLG disease is associated with a variety of clinical phenotypes ranging from infantile refractory epilepsy and liver failure to juvenile and adult onset epilepsy, myopathy and ataxia, and to late onset myopathies with progressive external ophthalmoplegia.

Epilepsy, including status epilepticus (SE), is a common and major feature of POLG disease, particularly in early and juvenile onset disease, and is associated with high morbidity and mortality. Early recognition and immediate, aggressive seizure treatment are crucial to improve patient survival. Treatment with a single anti-seizure medication (ASM) is usually not effective and high dose, multiple ASM treatment is often required.

Management of SE in POLG disease is challenging; benzodiazepines, phenytoin, levetiracetam, phenobarbital and lacosamide can be used as first and second line treatment, however, failure to control the seizures is common. Sodium valproate is absolutely contraindicated. In the case of refractory SE, presenting as generalized or new-onset focal seizures, anaesthetic agents such as propofol or barbiturate should be instituted promptly. Continuous EEG monitoring is essential. We propose that EEG burst suppression should be obtained for 48 hours, and prolonged to 78 hours if epileptic discharges are still present or recur after the cessation of anaesthetics. In our experience barbiturate (pentothal) is the preferred first-choice agent to obtain rapid and adequately deep suppression. Often, use of additional anaesthetics such as midazolam and/or propofol is still necessary to control seizure activity. Propofol should be used with caution due to the risk of propofol infusion syndrome particularly in the paediatric population. Rational polytherapy using ASM with different mechanisms of action must be optimized during general anaesthesia. If seizures are not controlled after the first round of anaesthesia the treatment cycle should be repeated at least once. Other agents, as isoflurane, ketamine, magnesium infusion, and corticosteroids have been reported to be effective in terminating SE in single case reports. Ketogenic diet and hypothermia can be considered but have not been proven effective in terminating SE in POLG disease. Established epilepsia partialis continua is often resistant to pharmacotherapy and generally predicts a poor prognosis. Non-invasive neuromodulation such as dTCS and rTMS can be applied, but scientific reports on efficacy in epilepsia partialis continua are scarce or conflicting. Survival time after the development of refractory of super-refractory SE is usually limited to months. During this phase palliative measures are essential, including adequate pain relief and if necessary, sedation treatment with i.e., benzodiazepines or propofol.

ASM – Anti-seizure medication

dTCS – direct Transcranial current stimulation

rTMS – repetitive Transcranial magnetic stimulation

SE in mental retardation – what is different?

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Treatment of status epilepticus can be challenging, yet still rather straightforward, in cases where the patient is previously healthy or at least with intact cognition, and with either no or well-controlled epilepsy prior to status epilepticus. However, in patients with chronic, drug-refractory epilepsy syndromes, typically as part of congenital or early acquired brain disorders with mental retardation or progressive encephalopathy, other challenges may arise.

In these patients, the diagnosis of status epilepticus may be difficult, as the normal state for the patient may be frequent or near-continuous seizures that are refractory to treatment, even using several anti-seizure drugs or other therapeutics. At which point is seizure activity so intense that the transition to genuine status epilepticus has occurred? The EEG in these patients may habitually be gravely pathological, and even continuous EEG may not necessarily help discriminate between the habitual state and status epilepticus.

In status epilepticus, the main treatment goal is to achieve seizure control which allows removing anaesthetics and treating with anti-seizure medication alone. However, in these patients, what should be reckoned as acceptable seizure control, if the habitual state is a very poorly controlled epilepsy? Again, cEEG may actually complicate handling of these cases, because the EEG may never become really acceptable in terms of seizure activity. This means that these patients may be at risk for prolonged ICU stays and intensive treatment efforts, with treatment goals that are really unattainable for them.

In “ordinary” status epilepticus patients, a grave concern is long-term outcomes following status epilepticus, with cognitive deficits and impact on daily living. How is this to be measured, or even defined, in patients who even prior to status epilepticus had severely reduced cognitive functions, and frequently no language?

More fundamentally, how should status epilepticus be viewed in this patient group? Is it a temporary episode that occurs, is treated, and thus the patients may go on with their lives? Or is it rather part of a progressive, continuing decline which will eventually cause the patient to succumb to the underlying brain disorder? How should we balance the patients’ need for and right to disease-specific treatment, and their need for and rights to adequate palliative care and reasonable end-of-life decisions?

Finally, status epilepticus in this patient group raises ethical questions, both with regards to the principles of beneficence and non-maleficence, as alluded to above. But also with regards to the principles of justice, and the allocation of costly health care services that are short in supply. On the one hand, patients with pre-existing disabilities should have the same access to the health care they need as have patients with no prior disabilities. On the other hand, all patients admitted to the ICU are subject to difficult prioritizations with regards to how likely they are to benefit from advanced ICU treatment. Whether ICU treatment, including intubation, respirator treatment and treatment of usual ICU complications, will actually benefit them. There is no medical imperative to

treat every patient to the utmost extent, rather the ideal is to provide the right treatment to the right patients. Furthermore, while it's imperative to respect patient autonomy, this may be challenging if the patient, due to brain disease, has never had the ability to make autonomous decisions.

These aspects make status epilepticus in patients with chronic epilepsy syndromes and mental retardation different from the more traditional status epilepticus patients.

Status epilepticus in progressive myoclonic epilepsies

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Progressive myoclonus epilepsies (PMEs) are neurodegenerative diseases and among the most disabling and often fatal forms of epilepsy. They are clinically and genetically heterogeneous, characterized by core features of action myoclonus, tonic-clonic seizures and progressive neurological decline. More than 40 genes are reportedly associated with PMEs.

Symptomatic pharmacologic and rehabilitative management are the mainstay of the patient care. As antiseizure (ASM) and antimyoclonic medication valproate is the first drug of choice. It diminishes myoclonus and the frequency of generalized seizures. Clonazepam, the only drug approved by the FDA for the treatment of myoclonic seizures, is used as add-on therapy. Levetiracetam/brivaracetam and perampanel seems to be effective for both myoclonus and generalized seizures. Topiramate and zonisamide may be also used as add-on treatment. Generalized seizures are often controlled with ASMs whereas myoclonic seizures are drug-resistant and patients often have also subcortical myoclonus.

In mitochondrial diseases, however, valproate as well as other ASMs, which may interfere with the mitochondrial function (zonisamide and topiramate), should be avoided, valproate especially due to increased risk of liver damage. In all PME patients, phenytoin should be avoided, since it has been found to have aggravating side effects on the neurological symptoms and on the cerebellar degeneration. This is true also regarding fosphenytoin in acute setting. Sodium channel blockers (carbamazepine, lamotrigine, oxcarbazepine, phenytoin) and GABAergic drugs (tiagabine, vigabatrin) as well as gabapentin and pregabalin should in general be avoided as they may aggravate myoclonus and myoclonic seizures.

In situations where myoclonic jerks are exacerbated into series or into myoclonic status, all loud noises and bright lights should be avoided, and the patient should be treated in a quiet room as peacefully as possibly. Buccal or nasal midazolam or other rapid acting benzodiazepines can be used out-of-hospital setting to stop increase of myoclonus. Emergency treatment includes the intravenous use of benzodiazepines (diazepam, lorazepam, clonazepam, midazolam). If second-line treatment is needed, valproate and or levetiracetam/brivaracetam iv additive doses can be given depending on the baseline medication. If patients are not able to swallow their oral ASMs, they need alternative administration routes to prevent subtherapeutic ASMs serum levels. Also, in acute situations sodium channel blockers need to be avoided. General anesthesia is rarely needed. Treatment of SE is an essential topic of advance care planning for patients with PME and should be discussed with the patient and the family. Aggressive unlimited ICU treatment of refractory SE in PMEs is mostly futile because of the high mortality and morbidity of the condition. Palliative sedation may be considered if no other forms of treatment can be used to make the patient's condition tolerable.

FIRES syndrome in a child. Possible effect of anakinra

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A 9 year old girl with FIRES (febrile infection related epilepsy) is presented.
She have parents from Bangladesh and was born in Norway with no health issues before the actual disease. After 4 days with symptoms of gastroenteritis and fever, she was attended to hospital with increasing encephalopathy and seizures. Treatment with levetirazepam, acyclovir and cefotaxim was initiated.
In the CSF was found 6/33 cells, protein normal/ slightly elevated 0,6 g/l and no oligoclonal bands. Negative findings for virus and bacteria. Cerebral autoantibodies in serum and CSF were negative. Nasopharynx testing was positive for rhinovirus.
The first cerebral MRI showed leptomeningeal contrast enhancement - meningitis? MR control after one week was normal. In the chronic phase was found moderate global cerebral atrophy.
EEG was encephalopatic with focal ictal activity in the frontal/frontocentral areas of the right hemisphere sometimes spreading to the left hemisphere. She had both subclinical and clinical seizures with eye blinking, stearing and reduced consciousness. After some time she also had seizures starting in her left hemisphere. From day 7 EEG showed non-convulsive status.
Our tentative diagnosis was autoimmune autoantibody negative encephalitis, and she got immunomodulating treatment from day 4 with intravenous methylprednisolone followed by prednisolone for several weeks and from day 6 IVIG for three days.
Her seizures were refractory to treat with levetirazepam, midazolam, valproate (after negative POLG test), phosphenytoin and lacosamide.
When she developed non-convulsive status epilepticus she was treated with thiopental from day 9 (and for 10 days). Still with high dose 6 mg/kg/hour we did not succeed to achieve complete burst-suppression and there was epileptic activity on the EEG.
We suspected the diagnosis FIRES and from day 12 anakinra 5 mg/kg/d was introduced. Together with treatment with ketamine it was possible to achieve complete burst suppression and reduce thiopental and midazolam. She was on mechanical ventilation for 21 days, and in the ICU for 24 days.
The treatment with subcutaneous anakinra/ilaris was continued for 2 months in combination with lacosamide and clobazam. After 7 weeks from debut of symptoms she became almost completely seizurefree. Her cognitive function is still reduced with attention problems, problems with short memory, regulation difficulties and “changed personality”.
With the theory that FIRES may be caused by an intrathecal overproduction of proinflammatory cytokines (such as IL-1 and IL-6) with proepileptic activity, we suspect that treatment with anakinra and ilaris did have positive effect on the prognosis of this patient.

The importance of case history and rapid genetic diagnosis in pediatric super-refractory status epilepticus

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An increasing number of epileptic syndromes are being genetically verified. It is now recognized that specific genes can be associated with a variety of disorders such as epileptic encephalopathy, hemiplegic migraine or ataxia.

We report a 6 year old girl with a history of febrile seizures and hemiplegic migraine who developed episodes with acute fluctuations of consciousness and ultimately a super refractory status epilepticus. Continuous EEG monitoring demonstrated increasing epileptic activity with increasing burst-suppression. MRI showed large areas of fluctuating vasogenic oedema in both hemispheres. Rapid genetic diagnosis revealed a mutation in the *ATP1A2*-gene. Anti-seizure medication was changed to target postsynaptic AMPA-receptors and i.v. treatment step-down. Following discharge from intensive care, guidelines for acquired brain injury were followed. The patient has shown good recovery.

Rapid genetic diagnosis leads directly to changes in treatment in this case history. Understanding the exact pathological mechanism gave important information for treatment choices as well as heritability in this case.

Status Epilepticus in an adult successfully treated with hemispherectomy

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Here we describe the case of a 23-year-old female with the diagnosis of epilepsy from age four initially presenting with generalized tonic clonic seizures during night sleep. After being effectively treated with valproate for the first five years, the attempt to taper off VPA resulted in new, more difficult-to-treat, seizures. In the following years diverse combinations of ASM were introduced, finally leading to acceptable seizure control around age eleven.

At age 13 she was diagnosed with mild mental retardation. EEG at that time showed focal epileptic activity in the left frontal/central and probably temporal region. MR was considered as normal. From age 19 to age 21 her clinical condition worsened, and she was hospitalized several times with more severe seizures, some of which with bradycardia and hypoxia, or series of focal motor seizures involving the right side of her face and arm. At that time, she used 4 different ASM in different combinations. MRI of the brain showed left hemispheric changes consistent with hemimegaloencephaly, as well extensive migration disorder as well as signal intensity changes in the white matter. In retrospect similar but mild changes could also be seen in earlier MRI series.

At age 21 the patient was hospitalized with focal motor status epilepticus, but also with tachycardia and tachypnea, unstable respiration, partly somnolence. She was intubated and sedated and treated with a multitude of ASM, and additional therapeutics including ketogenic diet. Several attempts to taper off anesthesia led to recurrence of her seizures, and she also developed critical illness neuro/myopathy. EEG consistently showed left sided pathology, and after almost 2 months of treatment in the ICU, a team consisting of neurologists, neurosurgeons, anesthesiologists, and clinical neurophysiologists decided, in accordance with the patient´s relatives, to perform an acute functional hemispherectomy. At that time this seemed to be the only option, besides of discontinuing treatment and letting the patient die. Performing acute surgery in SE patients is rarely performed but should be considered.

For registration see NES website:

www.epilepsiselskapet.no