



THE
4TH LONDON-INNSBRUCK
COLLOQUIUM
ON STATUS EPILEPTICUS
AND ACUTE SEIZURES

4-6 APRIL 2013
SALZBURG, AUSTRIA



FINAL
PROGRAMME

WWW.STATUSPILEPTICUS2013.EU

THE COLLOQUIUM IS HELD UNDER THE
 PATRONAGE OF THE COMMISSION OF
 EUROPEAN AFFAIRS OF THE ILAE.

ILAE-CEA
 COMMISSION ON EUROPEAN AFFAIRS



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 MEDIZINISCHE PRIVATUNIVERSITÄT



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Simon Shorvon, London, United Kingdom
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DEAR FRIENDS AND COLLEAGUES,

It is our sincere pleasure to welcome you all to Salzburg as the venue for the 4th London-Innsbruck Colloquium. The previous colloquia (London 2007, Innsbruck 2009, and Oxford 2011) were highly successful, and these biannual colloquia have become a popular feature of the international epilepsy calendar. This conference will focus on current basic and clinical research in status epilepticus, clinical aspects and new therapies – with the aim of stimulating thought and discussion and improving treatment and outcome of this condition.

It is our intention over the 3 days of the conference to have intensive and interactive discussion on the cutting edge of research and clinical practice in the field of Status Epilepticus. We have deliberately left space in the programme for the audience to question and challenge - for we believe, as a fundamental pillar of the Colloquia, that academic debate is at the heart of all learning and discovery. We hope you will all join in this endeavour.

In addition we have arranged a ‘Salzburg evening’ at the Stiegel Brauwelten, which should be entertaining. Salzburg is capital to the province of the same name and that it is home to 150,000 inhabitants. We hope you also have time to explore the charming town which is the birthplace of Mozart, and visit its historic city centre and the many interesting and historical sites.



Eugen Trinkla and Simon Shorvon
Co-Chairs, 4th London-Innsbruck Colloquium on Status Epilepticus and Actue Seizures

Acknowledgements:
These academic activities of this conference would not have been possible without the generous support of our sponsors listed on the back page of this booklet, and we offer our sincere thanks to them all. A lot of detailed preparation was needed and we have been most ably assisted in this by Ina Kähler and her excellent team from Congress und Messe Innsbruck GmbH. The conference is conducted under the patronage of University College London, Paracelsus Medical University Salzburg and the ILAE Commission on European Affairs. To all we offer our gratitude.

CONFERENCE VENUE

Radisson Blu Hotel & Conference Centre, Salzburg
Fanny-von-Lehnert-Straße 7
5020 Salzburg/ Austria
www.radissonblu.com

REGISTRATION DESK

The registration will be located in the lobby of the Radisson Blu Hotel.
Opening hours are as follows:

Wednesday, 3 April	16:00 – 18:00
Thursday, 4 April	08:00 – 17:00
Friday, 5 April	07:30 – 17:30
Saturday, 6 April	08:00 – 13:00

CONGRESS ORGANISERS

PCO Tyrol Congress
Congress und Messe Innsbruck GmbH
Rennweg 3
A-6020 Innsbruck, Austria
E: se2013@cmi.at
I: www.pco-tyrolcongress.at, www.cmi.at



INTERNET ACCESS

Wi-Fi access is available at the hotel and all conference rooms. The internet access is free and there are two terminals available in the lobby.

CERTIFICATE OF ATTENDANCE

All registered delegates receive an official certificate of attendance together with their registration documents.

TRADE EXHIBITION

A trade exhibition of pharmaceutical companies and manufacturers of medical equipment is held next to the plenary room.

EXHIBITION ORGANISERS

S12! studio 12 GmbH
Kaiser Josef Straße 9
6020 Innsbruck, Austria
T: +43-(0)512-890438
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COFFEE BREAKS AND REFRESHMENTS

Coffee and tea will be served during the official coffee breaks. On Thursday, Friday and Saturday lunch will also be provided. All refreshments are served in the exhibition area.

CITY TRANSPORTATION AND PARKING

Parking is available at the underground car park of the Radisson Blu Hotel. For city transportation a dense network of trolley buses and the new suburban railway guarantee fast and uncomplicated transport in the city of Salzburg. Please check www.svv-info.at for further information.

CURRENCY

The official currency in Austria is the Euro. Major credit cards are accepted in most hotels, shops and restaurants. Automatic teller machines (ATMs) are available throughout the city.

NAME BADGES

All registered participants receive a name badge together with their registration documents. Please make sure to wear your badge at all times while attending the meeting, exhibition and social events.

LIABILITY AND INSURANCE

Neither the organisers, nor the congress secretariat or other suppliers accept liability for personal injuries or loss or damage of property belonging to congress delegates, either during or as a result of the Congress or during any of the excursion tours. It is recommended that participants arrange for their own personal health, accident and travel insurance.

SOCIAL PROGRAMME

Get-together

Wednesday, April 3, 2013

17:00 – 19:00, Radisson Blu Hotel

An informal get together for all participants arriving on April 3 will take place between 17:00 and 19:00hrs at the Radisson Blu Hotel.

Salzburg Evening at the Stiegl Brauwelten

Friday, April 5, 2013

The Stiegl Brauwelten is a new attraction built for visitors to the city of Salzburg by the Stiegl brewery for visitors to discover the secrets of a traditional Salzburg brand. We will meet there and enjoy food, drinks and nice music. Tickets are at EUR 55,00 p.p.

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THURSDAY, 4 APRIL 2013

08:30 – 08:45	ILAE Address and opening of the conference E. Perucca (Italy), E. Trinka (Austria), S. Shorvon (United Kingdom)
08:45 – 09:30	Introduction
08:45 – 09:15	The status epilepticus colloquia 2007-2011, and the main advances in the topic of status epilepticus over this period S. Shorvon (United Kingdom), E. Trinka (Austria)
09:15 – 09:30	Discussion
09:30 - 12:45	Molecular studies of status epilepticus Chair: D. Kullmann (United Kingdom), A. Pitkänen (Finland)
09:30 – 09:50	Receptor trafficking hypothesis – revisited J. Kapur (USA)
09:50 – 10:10	Discussion
10:10 – 10:40	Coffee Break
10:40 – 11:00	Antagomirs and microRNA in status epilepticus D. Henshall (Ireland)
11:00 – 11:20	Discussion
11:20 – 11:40	Role of Adenosine in status epilepticus – a potential new target? D. Boison (USA)
11:40 – 12:00	Discussion
12:00 – 13:40	Poster session I: PO1-P31 Basic Science, Therapy Lunch

13:40 – 15:00	Neurophysiology of status epilepticus I Chair: G. Bauer (Austria), L. Hirsch (USA)
13:40 – 14:00	The neurophysiological types of nonconvulsive status epilepticus - EEG patterns of different phenotypes P. Kaplan (USA)
14:00 – 14:20	Panel discussion L. Hirsch (USA), G. Bauer (Austria), S. Beniczky (Denmark), R. Pressler (United Kingdom)
14:20 – 14:40	Non-synaptic transmission D. Janigro (USA)
14:40 - 15:00	Discussion
15:00 – 15:40	Coffee break
15:40 – 17:00	Neurophysiology of status epilepticus II Chair: C. Baumgartner (Austria), E. Schmutzhard (Austria)
15:40 – 16:00	Intrinsic epileptogenicity of dysplastic cortex G. Battaglia (Italy)
16:00 – 16:20	Discussion
16:20 – 16:40	Status as a system disturbance: is status due to synchronisation or desynchronisation? SS. Cash (USA)
16:40 – 17:00	Discussion

FRIDAY, 5 APRIL 2013

08:00 – 10:00	Advances in basic science of status epilepticus Chair: I. Blümcke (Germany), H. Cross (United Kingdom)
08:00 – 08:20	Neurogenesis and neuronal regeneration in status epilepticus L. Aigner (Austria)
08:20 – 08:40	Discussion
08:40 – 09:00	Gene therapy in status epilepticus M. Walker (United Kingdom)
09:00 – 09:20	Discussion
09:20 – 10:00	Coffee break supported by 
10:00 – 11:00	Satellite Symposium UCB
11:00 – 13:20	Aetiological aspects of status epilepticus Chair: N. Bharucha (India), C. Kellinghaus (Germany)
11:00 – 11:20	Autoimmunity, seizures and status epilepticus J. Dalmau (Spain)
11:20 – 11:40	Discussion
11:40 – 12:00	Status Epilepticus in sub-Saharan Africa: new findings C. Newton (Kenya)
12:00 – 12:20	Discussion
12:20 – 12:40	FIRES and IHHE – delineation of the syndromes R. Nabbout (France)
12:40 – 13:00	Discussion
13:00 - 14:00	Poster session II: P32-P62 Clinical Epileptology Lunch

14.00 – 18:00	Treatment of refractory status epilepticus Chair: I. Leppik (USA), G. Singh (India)
14.00 – 14:20	Multimodal invasive monitoring – what is the evidence it has a place? R. Helbok (Austria)
14:20 – 14:40	Discussion
14:40 – 15:00	The complications of anaesthesia and ITU E. Wijdicks (USA)
15:00 – 15:20	Discussion
15:20 - 15:40	Coffee break
15:40 – 16:00	The evolution of therapy for status epilepticus S. Shorvon (United Kingdom)
16:00 – 16:20	Discussion
16:20 – 16:40	Surgical treatment of status epilepticus P.A. Winkler (Austria)
16:40 – 17:00	Discussion
17:00 – 17:20	What can we learn from status epilepticus registries? M. Ferlisi (United Kingdom), S. Hocker (USA)
17:20 – 17:40	Discussion
17:40 – 18:00	Panel discussion led by: T. Bleck (USA) and A. Rossetti (Switzerland) Treatment of super refractory status epilepticus C. Kellinghaus (Germany), S. Shorvon (United Kingdom), E. Trinka (Austria), E. Wijdicks (USA)
19:00	Salzburg Evening at the Stiegl Brauwelten

SATURDAY, 6 APRIL 2013

08:30 – 09:30	Treatment of early status epilepticus Chair: D. Lowenstein (USA), E. Perucca (Italy)
08:30 – 08:45	Lessons from the RAMPART study – and which is the best route of administration of benzodiazepines in status epilepticus R. Silbergleit (USA)
08:45 – 09:00	Discussion
09:00 – 09:15	Initial therapy of status epilepticus – polytherapy? C. Wasterlain (USA)
09:15 – 09:30	Discussion
09:30 – 10:30	Ongoing and new trials in status epilepticus Chair: M Feucht (Austria), G. Kraemer (Switzerland)
	Established Status Epilepticus Trial J. Kapur (USA)
	Treatment of recurrent electrographic seizures (TREndS) trial A. Husain (USA)
	French trial: Clobazam vs. Lorazepam M. Baulac (France)
	Trial of SGE-102 in refractory status epilepticus A. Cole (USA)
10:30 – 10:50	Discussion
10:50 – 11:20	Coffee Break

11:20 – 12:20	Satellite Symposium ViroPharma
12:20 – 14:20	Novel therapies and innovation Chair: H. Cock (United Kingdom), T. Loddenkemper (USA)
12:20 – 12:40	Valnoctamide and SPD for acute seizures and status epilepticus M. Bialer (Israel)
12:40 – 13:00	Discussion
13:00 – 13:20	Stiripentol in status epilepticus D. Mott (USA)
13:20 – 13:40	Discussion
13:40 – 14:00	Neuroactive steroids for status epilepticus M. Rogawski (USA)
14:00 – 14:20	Discussion
14:20 – 14:30	Concluding remarks S. Shorvon (United Kingdom), E. Trinka (Austria)
14:30	Farewell Gulyas

SATELLITE SYMPOSIUM 1
FRIDAY, 5 APRIL 2013, 10:00–11:00 AM

Loading doses – considerations in epilepsy treatment
 sponsored by UCB



- 10:00 – 10:04 **Welcome and introduction**
L. Lagae & C. Kellinghaus
- 10:04 – 10:29 **Management of acute seizure settings from infancy to adolescence**
L. Lagae (Belgium)
- 10:29 – 10:54 **Management of acute seizure settings from adulthood to the elderly**
C. Kellinghaus (Germany)
- 10:54 – 11:00 **Questions and answers/Closing remarks**
L. Lagae & C. Kellinghaus

SATELLITE SYMPOSIUM 2
SATURDAY, 6 APRIL 2013, 11:20 – 12:20

Managing Epilepsy in the Community: Insights and Clinical Perspectives – Challenges and approaches to managing prolonged, acute, convulsive seizures in children and adolescents

sponsored by ViroPharma



Chair: E. Trinka (Austria), S. Shorvon (UK)

- 11:20 – 11:25 **Introduction and welcome**
E. Trinka (Austria) and S. Shorvon (UK)
- 11:25 – 11:45 **Introducing the PERFECT™ Initiative: Aims, results highlights and key insights**
A. Arzimanoglou (France)
- 11:45 – 12:10 **Managing prolonged, acute, convulsive seizures in children in the community setting: perspectives from the PERFECT™ Initiative**
B. Wilken (Germany)
- 12:10 – 12:20 **Questions and close**
E. Trinka (Austria) and S. Shorvon (UK)



Providing therapies that empower people suffering from CNS diseases

Advancing pharmacotherapy. Improving life.SM

POSTER SESSION 1

BASIC SCIENCE

P01

New onset refractory status epilepticus - NORSE (SE) and electrophysiological -treatment insights
Sabino Guillermo Echebarria Mendieta (Areeta, Spain)

P02

Hyponatremia augments kainic-acid induced status epilepticus in the mouse: a model for dysmetabolic status epilepticus
Johan Zelano, Imad Halawa, Fredrik Clausen, Eva Kumlien (Uppsala, Sweden)

P03

GABAA receptor trafficking in hippocampal neurons during status epilepticus
Ramona Eckel, Josef Kittler, Matthew Walker (London, United Kingdom)

P04

Effects of long-term treatment with losartan on behavioural disturbances in kainate model of temporal lobe epilepsy
Natasha Ivanova, Jana Tchkalarova, Daniela Pechlivanova, Alexander Stoynev (Sofia, Bulgaria)

P05

Effects of long-term treatment with melatonin on epileptogenesis, neuronal damage and behavioral changes in kainate model of epilepsy in SHR
Zlatina Petkova, Jana Tchkalarova, Daniela Pechlivanova, Valentin Lozanov, Dimitrinka Atanasova, Nikolai Lazarov, Alexander Stoynev (Sofia, Bulgaria)

P06

Heterozygous POLG mutations may predispose patients with Dravet syndrome for acute encephalopathy
Eija Gaily, Anna-Kaisa Anttonen, Ann-Liz Träskelin, Markus Lommi, Leena Valanne, Anna-Elina Lehesjoki (Helsinki, Finland)

P07

Pretreatment with NMDA antagonist dizocilpine abolishes orphenadrine-induced convulsive status epilepticus in rats
Konrad Rejdak, D Nieoczym, M Czuczwar, J Kioe, P WlaŹ, WA Turski (Lublin, Poland)

P08

Nrf2 defense pathway: experimental evidence for its protective role in epilepsy
Manuela Mazzuferi, Gaurav Kumar, Jonathan van Eyll, Benedicte Danis, Patrik Foerch, Rafal M Kaminski (Braine L’Alleud, Belgium)

P09

Early deficits in social behavior and cortical rhythms in pilocarpine-induced mouse model of temporal lobe epilepsy
Daejong Jeon, Jinsoo Seo, Seungmoon Jung, So-Young Lee, Hyunwoo Yang, Byung Sun Kim, Jiye Choi, Minji Bang (Daejeon, Republic Of South Korea)

P10

Synergistic effects of perampanel combined with diazepam in the lithium-pilocarpine rat model of status epilepticus
Takahisa Hanada, Katsutoshi Ido (Ibaraki, Japan)

P11

Perampanel terminates diazepam-resistant status epilepticus in a lithium-pilocarpine rat model
Katsutoshi Ido, Takahisa Hanada (Ibaraki, Japan)

P12

Dysplasias of different genesis switch the brain between tonic or clonic seizure reactivity
Zuzanna Setkiewicz, Kinga Gzielo-Jurek, Lukasz Uram, Krzysztof Janeczko (Krakow, Poland)

P13

Modern spectroscopic methods in the analysis of the biochemical basis of neurodegenerative changes in the epileptic rat brain
Joanna Chwiej, Justyna Kutorasińska, Krzysztof Janeczko, Karen Appel, Rolf Simon, Paul Dumas, Christopher Sandt, Zuzanna Setkiewicz (Krakow, Poland)

P14

Cortical postictal refractoriness after status epilepticus in immature rats
Pavel Mares, Hana Kubova (Prague, Czech Republic)

THERAPY

P15

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IL1**TITLE: THE LONDON-INNSBRUCK STATUS EPILEPTICUS COLLOQUIA 2007-2011, AND THE MAIN ADVANCES IN THE TOPIC OF STATUS EPILEPTICUS OVER THIS PERIOD.**

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Abstract:

In this paper the three previous London-Innsbruck Colloquia on Status Epilepticus are reviewed. The background to the colloquia and the range of topics covered in each colloquium are outlined. The areas in which advances in the study of status epilepticus, and also areas in which advances have been disappointing are highlighted

Text:

Three previous London-Innsbruck Colloquia on the topic of Status Epilepticus have been held, in 2007, 2009 and 2011, organized with the support of the ILAE Commission on European Affairs under the auspices of University College London and the Medical University of Innsbruck. These conferences were designed to invigorate debate and study on the topic of status epilepticus (SE), much as the first medical conference devoted to the topic (the Marseilles Colloquium in 1962) did and the further conferences held in Santa Monica in 1980 and 1997. The current series was conceived to be in direct lineage to these landmark events.

The stated purpose of the first colloquium, held in London in 2007 was: to summarise current knowledge in key clinical and basic science areas; to define optimal clinical practice; to debate controversial issues; and to point to future clinical and scientific research areas. These remained the four objectives of the next two colloquia, the 2009

conference held in Innsbruck and the 2011 conference held in Oxford. The faculties of all the meetings consisted of clinical academics and basic scientists, with an attempt to attract the best in the world, and the emphasis of the congresses has been on debate and discussion. A closed workshop has also been held with each meeting on a different aspect of status epilepticus. The proceedings of all the meetings and the first workshop, have been published as supplements in *Epilepsia* (Shorvon et al 2007, Shorvon et al 2008, Trinka and Shorvon 2009, Shorvon and Trinka 2011).

Certainly, interest in status epilepticus has grown in the last decade or so. The topic which had been herewith to largely absent from the international ILAE congresses, for instance, has appeared now in all the major annual events. As a sign of interest the growth in literature has been striking. The number of articles listing 'status epilepticus' as a keyword on a Medline search, for instance, was 201 in the years 1960-1975, 1165 in the years 1975-1990, 3364 in the years 1990-2005 and in the last 6 years 3355 articles have been published.

A summary of the topics covered in the 3 previous colloquia is shown in Tables 1,2,3. As is immediately clear, a wide range of subjects has been covered, and it is difficult over the relatively short perspective of 8 years or less to pick out the leading advances, which have occurred. The list that follows is inevitably personal and incomplete, and we have divided these into three main categories: molecular and basic science, clinical and therapeutic. In addition, the outcomes of the three workshops will be highlighted,

The main advances in the field over the period 2007-2013**i. Molecular and basic science:**

Major advances include the rapid growth in understanding of:

- The changes occurring in GABA receptors during an episode of status epilepticus, and in particular the role of trafficking of receptors away from the cell membrane, which may be contributing to the drug resistance that occurs as the status proceeds. Also the changes in other receptor types including trafficking of the glutamate receptor to the cell surface and into the synaptic cleft.
- The role of inflammation in the production and maintenance of status epilepticus, both caused by seizure

- activity itself and also as a cause of seizures.
- The role of mitochondrial mechanisms and the genetic control of mitochondrial mechanisms (both mitochondrial genes and also nuclear genes such as POLG1).
 - The basic physiology of status epilepticus and of electroencephalographic burst suppression pattern.

ii. Clinical Science:

The growth in understanding of:

- The EEG patterns on non convulsive status and coma
- New syndromes, such as FIRES and new autoantibody mediated diseases (e.g. NMDA-receptor encephalitis, or limbic encephalitis associated with antibodies against the voltage gates potassium channel/LGI1-complex or GAD
- The importance of uncommon causes of status epilepticus
- Epidemiology of status epilepticus and the range of conditions underlying status in resource poorer countries
- The concept of 'super-refractory' status epilepticus and the setting up of audits and registries of its treatment

iii. Therapeutics:

Major therapeutic advances include:

- The use of benzodiazepines in out-of hospital situations (especially buccal midazolam, and the RAMPART study of IM midazolam)
- The potential for initial polytherapy in early status.
- The use of valproate, levetiracetam and lacosamide at the stage of established status epilepticus
- New drugs in the pipeline for use in refractory status epilepticus and studies of non pharmacological treatment

In addition to the above areas in which significant advances have been made, there are other areas in which progress has been slower and more disappointing. These over this period include: the continued lack of understanding of any genetic influences on status epilepticus, and of the developmental aspects of the condition, the lack of practical benefits from computational modeling, the failure to progress with regulatory aspects of clinical trials, or to improve outcome in refractory and super-refractory status epilepticus.

All three Colloquia hosted closed workshops, dedicated to a specific topic. The first workshop at the First London-

Innsbruck Colloquium 2007 was devoted to the treatments of status epilepticus and the availability of antiepileptic drugs throughout Europe. There was a striking heterogeneity of both, the availability and the use of intravenous antiepileptic drugs. The extensive discussion of the experts led to treatment recommendations, taking into consideration the availability of the drugs of choice in each country (Shorvon et al. Epilepsia 2008).

The Workshop at the Second London-Innsbruck Colloquium 2009 focussed on drug trials, its design, and the medico-legal aspects associated with randomised trials in status epilepticus. Indeed, the trial proposed by a core group (Cock et al. Epilepsia 2011), was later refined by a multinational group from US and Europe (Kapur et al. Salzburg Supplement 2013), and its start in 2013 becomes very realistic.

The Workshop at the Third London Innsbruck Colloquium in Oxford was dedicated to the classification of status epilepticus. At the same time the ILAE Commission of Classification charged a group of participants at the Oxford Workshop, to develop a new proposal for definition and classification of status epilepticus. The new proposal, was exposed for the first time at a Forum at the European Congress on Epileptology in London 2012 (Trinka et al. Abstract ECE 2012). Thus, all three workshops had substantial deliverables, which will further help to improve the better diagnosis and treatment of this devastating condition.

Table 1: Topics covered at the 1st London –Innsbruck colloquium on status epilepticus

Molecular nature of SE

- Relevance of SE in animals to human SE
- Changes in GABA-A receptors in SE
- Impact of receptor changes on treatment
- Inflammation modifies hippocampal injury
- Influence on brain development
- Role of genetic influences in animal models
- Role of mitochondria in SE
- Gene and protein expression

Clinical aspects

- What is nonconvulsive status epilepticus (NCSE)
- EEG criteria for NCSE
- When is epileptic encephalopathy NCSE
- How urgent is therapy for NCSE

- Clinical pharmacology of parenteral drugs
- Valproate and other new AEDs in SE
- Which anaesthetic to use in SE
- Clinical trial design
- ITU management
- Surgical therapy

Outcome of SE

- Neuro-protection
- Neuro-genesis
- Endogenous mechanisms of neuroprotection
- Mechanisms of drug resistance
- Animal experimentation and new drug therapy
- Epidemiology of SE
- Cognitive outcome of SE in adults
- Outcome in children
- Risk of epilepsy after SE
- Out of hospital therapy
- SE treatment guidelines

Table 2: Topics covered at the 2nd London-Innsbruck Colloquium on status epilepticus

Basic physiology of SE

- Endogenous mechanisms of neuroprotection
- Basic physiology of limbic SE
- Physiology of EPC and subcortical mechanism
- Hypo and hyperthermia and other systemic changes in SE
- Experimental SE
- Canine SE
- The receptor trafficking hypothesis revisited
- Drug resistance in SE
- Genetics of SE
- Basic physiology of burst suppression

Developmental and aetiological aspects

- Why is developing brain more susceptible to SE ?
- Long-term effects of febrile SE
- Neuronal plasticity
- SE in the developing brain
- How useful is EEG and EEG monitoring ?
- SE in resource-poor countries
- SE in infection and inflammation
- SE due to paraneoplastic and non-neoplastic encephalitis
- Uncommon causes of SE
- SE in tuberculosis and HIV infection

- SE in other CNS infection

Treatment and medico-legal aspects

- Relative value of standard therapies
- PD and PK of IV antiepileptic drugs
- New drugs in SE
- Novel anaesthetics in SE
- Clinical trials in SE
- Minimum requires for approval of drugs in SE
- Informed consent
- Psychosis and SE: borderland or hidden cause
- SE in the law courts

Table 3: Topics covered at the 3rd London-Innsbruck colloquium on status epilepticus and acute seizures

Fundamental mechanisms of SE

- Developmental changes in receptors and in neurotransmitters
- Mitochondrial function and pathology
- Potentially pathogenic autoantibodies in SE
- Activity dependent trafficking of GABA_A receptors in SE
- Computational modeling of epilepsy and SE
- Light activated channels in SE
- Blood-brain barrier dysfunction in SE
- EEG patterns in coma
- Cellular mechanisms underlining EEG in coma

Clinical aspects and current therapy

- FIRES
- Canine SE for early trials
- Evidence for use of new IV AEDs
- ICU complications in SE
- Anaesthetics in SE
- Multi-model imaging
- RAMPART trial (in the US)
- Prehospital RCT (in France)
- ESETT trial (in Europe) and its tribulations

Future perspectives for therapy

- Super-refractory SE: therapies and outcomes
- Neuro-anatomy of SE value of hypothermia
- Value of anti inflammatory drugs
- Potential for brain stimulation
- New valproic acid derivative
- Mono .vs. poly therapy approaches in SE

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IL2

TITLE: RECEPTOR TRAFFICKING HYPOTHESIS REVISITED: ENHANCEMENT OF AMPA RECEPTOR-MEDIATED NEUROTRANSMISSION DURING ESTABLISHED STATUS EPILEPTICUS.

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Abstract:

Status epilepticus (SE), characterized by continual, self-sustained seizures, is a dynamic and rapidly evolving neu-

rological condition. As SE progresses, electrographic seizures become continuous and Grade V behavioral seizures are observed in rats, benzodiazepines fail to terminate seizures. This is an animal model of established SE (ESE). Understanding synaptic plasticity during ESE will help discover newer targets to treat BDZ-refractory SE. We investigated AMPA receptor (AMPA)-mediated neurotransmission during ESE. We previously found that the expression of the GluA2 subunit of AMPARs in hippocampal principal neurons is dynamically reduced during ESE leading to the expression of calcium-permeable AMPARs. Extending these findings, here we hypothesize that AMPAR-mediated excitatory conductance is progressively enhanced during ESE. To test this hypothesis, SE was induced in lithium-pretreated adult male rats using pilocarpine and the animals were studied either 10 min (early ESE) or 60 min (late ESE) after the onset of the first Grade V behavioral seizure using a combination of electrophysiological and biochemical studies.

Text:

AMPA-mediated excitatory postsynaptic currents (EPSCs) were recorded from CA1 pyramidal neurons (CA1-PN) and dentate granule cells (DGCs) by voltage-clamp technique. Analysis of recordings obtained from CA1-PNs revealed that the frequency of action-potential independent EPSCs (m-EPSCs) increased with increasing seizure duration ($p < 0.0001$, One-way ANOVA). The mean m-EPSC frequency in CA1-PNs of the control group was 0.39 ± 0.05 Hz ($n=14$ cells/ 6 animals), whereas in the late ESE group, it was 1.59 ± 0.4 Hz ($n=12$ cells / 7 animals, $p < 0.05$, Tukey's test). In contrast, the mean m-EPSC frequency in CA1 PNs of the early ESE group was similar to controls (0.22 ± 0.04 Hz, $n = 8$ cells / 6 animals). The amplitude of m-EPSCs in CA1 PNs from both early ESE (11.74 ± 0.8 pA) and late ESE (11.97 ± 0.8 pA) groups were similar to that in the control group (11.40 ± 0.6 pA); however, the net charge transfer of AMPAR-mediated m-EPSCs was significantly greater in the late ESE group (40.25 ± 6.1 pC vs. 138.9 ± 29.9 pC; $p < 0.05$, Tukey's test). Further, when Schaffer collaterals were electrically stimulated to obtain a current-voltage (I-V) relationship, AMPAR-mediated evoked EPSCs (e-EPSCs) recorded from CA1 PN were found to be inwardly rectifying and philanthotoxin-sensitive during early ESE (Rectification Index, $RI = 0.48 \pm 0.08$, $n= 11$ cells / 5 animals) and late ESE ($RI= 0.34 \pm 0.06$, $n=7$ cells / 6 animals). In con-

trast, the I-V relationship of e-EPSCs in control CA1 PNs did not show inward rectification or philanthotoxin sensitivity ($RI= 0.87 \pm 0.04$, $n=7$ cells / 4 animals).

In contrast to CA1 PNs, recordings obtained from DGCs revealed no change in the frequency of m-EPSCs during early ESE (0.54 ± 0.5 Hz, $n=8$ cells/ 5 animals) or late ESE (0.34 ± 0.6 Hz, $n=6$ cells/ 4 animals) compared to that of control DGCs (0.59 ± 0.1 Hz, $n=6$ cells/ 3 animals; $p > 0.05$, ANOVA). Likewise, the amplitude of m-EPSCs in DGCs obtained from early ESE (11.5 ± 0.5 pA) and late ESE (11.31 ± 0.5 pA) animals were similar to that of control DGCs (12.6 ± 0.6 pA, $p > 0.05$, ANOVA). When e-EPSCs were obtained by stimulation of perforant path, the I-V relationship revealed inwardly-rectifying, philanthotoxin sensitive currents only during early ESE (0.56 ± 0.09 , $n=12$ cells / 7 animals) but not late ESE (0.88 ± 0.09 , $n=11$ cells / 7 animals). Control DGC exhibited a linear I-V relationship ($RI = 0.85 \pm 10$, $n=9$ cells / 5 animals). These studies showed that AMPAR-mediated synaptic transmission on CA1 PNs is strengthened from early ESE to late ESE.

We then determined changes in the surface expression of the GluA2 and GluA1 subunits of the AMPAR at early ESE and late ESE using a biotinylation assay to tag surface expressed proteins. Compared to controls, the cell surface expression of the GluA2 subunit was reduced in hippocampi of early ESE ($54 \pm 15\%$, $n=8$, $p < 0.05$, t-test) and late ESE ($53 \pm 6\%$, $n=6$, $p < 0.05$, t-test) animals. In contrast to GluA2 subunit, the cell surface expression of the GluA1 subunit was increased in hippocampi of both early ESE ($145 \pm 6\%$, $n=6$, $p < 0.05$, t-test) and late ESE ($125 \pm 10\%$, $n= 3$, $p < 0.05$, t-test) animals. The increased surface expression of the GluA1 subunit during SE was further confirmed using a BS³ cross-linking assay. In the hippocampi of late ESE animals, the intracellular fraction of the GluA1 subunit was $78 \pm 5\%$ of that in controls ($n= 6$ animals, $p < 0.05$, paired t-test). Since electrophysiological studies revealed distinct differences in the properties of AMPAR-mediated EPSCs between CA1 PN and DGCs during late ESE, a BS3 assay was performed on micro-dissected samples of the CA1 and DGC. The intracellular fraction of GluA1 subunit was unchanged in the DGC subfield ($104 \pm 9\%$, $n= 5$, $p > 0.05$, t-test) whereas it was significantly reduced in the CA1 subfield ($50 \pm 10\%$, $n=7$, $p < 0.05$, t-test). Biotinylation assay of CA1 subfield also con-

firmed the increased surface expression of GluA1 subunit during late ESE ($140 \pm 12\%$, $n=4$, $p < 0.05$, t-test).

An increase in cell surface expression of the GluA1 subunit during ESE indicated potential alterations in the trafficking of AMPARs. Activation of NMDA receptors (NMDARs) can also modulate surface expression of AMPARs; NMDARs are activated during SE. In preliminary studies, treatment of hippocampal slice cultures with NMDA (10 mM) and high extracellular potassium (10 mM) increased the surface expression of GluA1 subunit ($193 \pm 35\%$, $n=2$). Further, treatment of animals with NMDAR open-channel blocker, MK-801 (2 mg/kg) after 10 min of continuous electrographic seizures prevented increase in GluA1 surface expression in the CA1 region ($97 \pm 10\%$, $n=5$, $p > 0.05$, t-test).

Post-translational modification such as phosphorylation can also influence trafficking and conductance of AMPARs. In ongoing studies, we tested whether phosphorylation of the AMPARs at the Ser831 and Ser 845 residue on the C-tail of the GluA1 subunit was increased during late ESE. There were no differences in phosphorylation of either Ser831 ($118 \pm 15\%$, $n=8$, $p > 0.05$, t-test) or Ser845 ($117 \pm 30\%$, $n=8$, $p > 0.05$, t-test) residues in the whole hippocampi of animals during late ESE. These studies indicate that strengthening of AMPAR-mediated neurotransmission on CA1 PN during ESE is associated with an increased surface expression of the GluA1 subunit.

Since our studies demonstrate that glutamate transmission is enhanced during ESE, we tested whether diminishing glutamate release during SE can terminate seizures. Patch clamp recordings obtained from CA1 PNs revealed that the neuropeptide, somatostatin (SST) reduced action potential-dependent EPSCs (s-EPSCs) and Schaffer-collateral stimulated paired pulse facilitation. These effects were inhibited by the SST type 2 receptor (SST2R) antagonist, cyanamid-154806 and were mimicked by the SST2R agonists, octreotide and lanreotide suggesting that SST actions were mediated by SST2Rs. Video-EEG studies revealed that intraventricular administration of SST, within a range of doses, either prevented or attenuated pilocarpine-induced SE or delayed the median time to the first Grade V seizure by 11 min. Similarly, octreotide or lanreotide prevented or attenuated SE in more than 65% of animals. Compared to the pilocarpine model, octreotide was highly potent in

preventing or attenuating continuous hippocampal stimulation-induced SE in all animals within 60 min of SE onset. Together, these studies demonstrate that AMPAR-mediated synaptic transmission is enhanced during ESE and that reducing glutamate release is a potential therapeutic strategy to treat ESE.

IL3

TITLE: ANTAGOMIRS AND MICRORNA IN STATUS EPILEPTICUS

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Abstract:

MicroRNAs are an important class of non-coding RNA which function as post-transcriptional regulators of protein levels within cells. Emerging work has revealed that status epilepticus produces select changes to microRNA levels within the brain which may impact levels of proteins involved in neuronal structure and excitability, gliosis, inflammation and apoptosis. Animal studies show that targeting microRNAs using locked nucleic acid-modified oligonucleotides ("antagomirs") can have potent effects on status epilepticus, seizure-induced neuronal death and the later emergence of recurrent spontaneous seizures. Accordingly, microRNA-based therapeutics may have potential as a future treatment of status epilepticus.

Text:

MicroRNA

MicroRNA (miRNA) is an important class of small non-coding RNA, critical for network-level regulation of gene expression. Biogenesis of miRNAs begins with transcription of a primary transcript (pri-miRNA), mainly from intergenic or intragenic regions of the genome, by the action of DNA polymerases (e.g. pol II). Production of the mature miRNA

results from sequential actions of the RNase III enzymes Drosha and Dicer. One strand of the mature miRNA (~22 nucleotides) is incorporated into the RNA-induced silencing complex (RISC). Within the RISC, the miRNA serves as a guide to direct Argonaute-2 (Ago2) to target messenger RNAs (mRNA). The miRNA works by forming Watson-Crick base pairs with complementary sequences of the mRNA target. This mainly occurs within the 3' untranslated region (UTR), but binding to the 5' UTR or coding sequence is also possible. Reduction in protein levels are predominantly due to the miRNA promoting degradation of the mRNA target, with the remainder accounted for by translation inhibition (Bartel 2009, Krol, et al. 2010).

Multi-targeting effects of miRNAs on pathways

Although there are only ~1500 miRNAs in the human genome these are predicted to regulate over half of all protein-coding genes. This is because a single miRNA is typically able to target ~200 mRNAs. RNA sequencing, ribosomal profiling (sequencing mRNAs during translation by ribosomes) and quantitative proteomics have provided critical insight into the impact of miRNA on protein levels in cells; overexpression or silencing of a miRNA produces changes to hundreds of proteins (Guo, et al. 2010, Selbach, et al. 2008).

miRNA inhibitors

One promising approach to manipulating miRNAs is via chemically-modified antisense oligonucleotides. Termed "antagomirs", these bind the miRNA resulting in its depletion from the cell. Locked nucleic acid (LNA) modification of these oligonucleotides confers long-lasting stability in tissues and biofluids. As a result, LNA-antagomirs can produce miRNA silencing lasting many weeks and are associated with upregulation of large sets (~200) of target mRNAs (Elmen, et al. 2008). A further development has been the design of so-called "tiny LNAs". These are 8-mer LNA oligonucleotides that target shared seed regions of miRNA families, thus producing more extensive silencing of miRNA functions (Obad, et al. 2011). A miRNA-based therapeutic, miravirsen - an LNA-based antagomir that targets miR-122 for the treatment of Hepatitis C - recently successfully completed Phase 2 clinical trials, suggesting manipulation of miRNA can be safe and tolerated in patients. MiRNAs may have unprecedented potential as future treatments of human diseases.

Status epilepticus produces select changes to miRNA levels in the brain

In 2010, the first research showing miRNAs were altered by status epilepticus appeared. Along with subsequent profiling studies, we now have a detailed understanding of the bi-directional spatio-temporal miRNA changes that accompany status epilepticus. Several display consistent change, including miR-34a, miR-132, miR-134 and miR-146a. Some anti-correlated expression between miRNA and mRNA profiles has been noted, consistent with the current model of how miRNAs mainly act to down-regulate their targets. The development of antibodies suitable for Ago2 immunoprecipitation enabled RISC-loaded miRNAs to be identified after status epilepticus, including miR-132 and miR-134 (Jimenez-Mateos, et al. 2011; 2012). Nevertheless, we currently have a poor understanding of which proteins are actually being controlled by miRNAs after status epilepticus. Future efforts must also focus on identifying the mRNAs within the RISC.

Effects of antagomirs on status epilepticus, seizure-induced neuronal death and epileptogenesis

A highly attractive quality of miRNA-based drugs is the long-lasting effects achieved; hippocampal miRNAs can be inhibited for more than one month after a single intracerebral antagomir injection (Jimenez-Mateos, et al. 2012). To date, antagomirs have been used to target four miRNAs in vivo, including miR-34a, miR-132 and miR-134. Of these, inhibition of miR-34a and miR-132 was reported to reduce seizure-induced neuronal death but no effects were found on seizure severity or duration during status epilepticus (Jimenez-Mateos, et al. 2011; Hu, et al. 2012). Silencing miR-134 produced the most remarkable effects. This miRNA is known to target proteins involved in the control of dendritic morphology, and thus potentially of direct relevance to excitatory neurotransmission. We showed that pre-treatment (24 h) with a single intracerebroventricular microinjection of LNA-antagomirs targeting miR-134 reduced kainate-induced status epilepticus by 50-70% (Jimenez-Mateos, et al. 2012). Damage to the hippocampus was also strongly reduced in the mice pre-treated with the antagomirs. Of potential importance as a future anti-epileptogenic strategy, injection of antagomirs after status epilepticus reduced the later occurrence of spontaneous seizures by 90% or more (Figure 1). Silencing miR-134 also reduced progressive damage to the hippocampus.

Summary and future directions

MiRNAs represent an entirely new target for the treatment and prevention of status epilepticus. Important next steps include optimizing doses, formulation and route of delivery. The overall safety of antagomirs and their effectiveness in other models must be established. Undoubtedly, other high-value miRNA targets for status epilepticus exist. Other tools for modulating miRNAs in vivo have also emerged including microRNA "sponges" which may provide even greater capacity to control miRNAs and influence status epilepticus and its harmful effects on the brain.

Acknowledgements:

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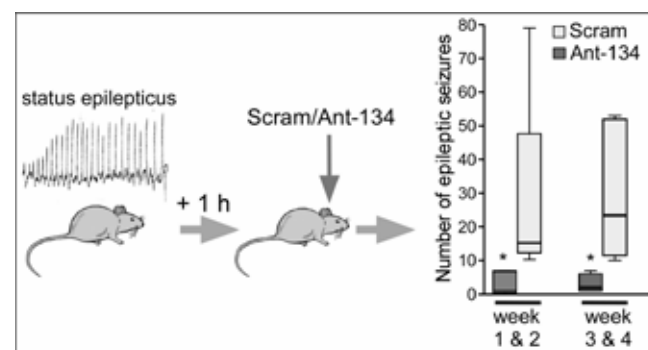
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Figure 1: Post-treatment with antagomirs reduces later spontaneous seizures. Mice were injected with antagomirs targeting miR-134 (Ant-134) or a non-targeting scrambled control (Scram) 1 h after triggering status epilepticus and then epilepsy monitoring commenced. Graph shows box-and-whisker plots of data on telemetry (weeks 1-2) and video-monitored (weeks 3-4) spontaneous seizures in mice (n = 5-6 per group; *p < 0.05). Data are adapted from Jimenez-Mateos et al. (2012)



IL4

TITLE: ROLE OF ADENOSINE IN STATUS EPILEPTICUS – A POTENTIAL NEW TARGET?

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Abstract:

The homeostatic bioenergetic network regulator adenosine is an endogenous anticonvulsant of the brain playing critical roles in seizure termination and postictal refractoriness. Adenosine homeostasis in the adult brain is largely under the control of metabolic clearance through adenosine kinase (ADK), expressed predominantly in astrocytes. The role of adenosine in status epilepticus (SE) appears to be a double-edged sword. We demonstrated that the severity of an SE clearly depends on the expression levels of ADK. A genetic knockdown of ADK prevented SE in a mouse model, whereas transgenic overexpression of the enzyme aggravated the SE. Thus, ADK inhibition or adenosine augmentation might be a therapeutic strategy to terminate or attenuate an SE. On the other hand, SE triggers a surge of endogenous adenosine, which may trigger secondary events leading to epileptogenesis. Two new findings will be discussed: (i) Elevated adenosine triggers changes in the epigenome; and (ii) SE triggers transient changes in ADK expression, which have been linked to neurogenesis. While the ADK/adenosine system is an attractive target for the attenuation of an SE, the same system may also trigger downstream events related to epileptogenesis.

Text:

The purine nucleoside adenosine is an endogenous homeostatic regulator of network activity and adenosine deficiency has been identified as a pathological hallmark of the epileptic brain. Consequently, adenosine augmentation therapies (AATs) constitute an effective strategy to suppress induced and spontaneous seizures, even those that

are refractory to conventional antiepileptic drugs. In the adult brain the ambient concentration of adenosine is under the control of metabolic clearance through astrocytes. Whereas adenosine can be released from neurons or can be derived from the extracellular cleavage of ATP, the astrocyte-based enzyme adenosine kinase (ADK) eliminates adenosine via phosphorylation to AMP. Since astrocytes express two types of equilibrative nucleoside transporters, it is the metabolic clearance through ADK that drives the flux of adenosine into the astrocytes, which thereby form a sink for the metabolic clearance of adenosine. Thereby, the levels and activity of astrocytic ADK control adenosine homeostasis in the brain: High levels of astrocytic ADK correspond to low levels of tissue adenosine, whereas low levels of ADK lead to an increase in adenosine.

Adenosine controls neuronal network function through multiple mechanisms. Adenosine is the endogenous ligand of four types of G protein coupled adenosine receptors designated A₁R, A_{2A}R, A_{2B}R, and A₃R. Activation of the A₁R provides immediate anti-seizure effects through (i) the presynaptic inhibition of glutamate release, and (ii) the stabilization of the postsynaptic membrane potential. Consequently, ADK inhibitors, increased adenosine, or A₁R agonists provide potent seizure control in a multitude of animal models including kindled seizures and spontaneous recurrent seizures in post SE models of epilepsy. In addition to the activation of adenosine receptors, adenosine has additional, evolutionary ancient, receptor independent roles. Adenosine is directly linked to mitochondrial bioenergetics and is an obligatory end product of transmethylation reactions, which also include DNA methylation. These findings suggest a novel role of adenosine as epigenetic regulator. In status epilepticus (SE), three aspects of the ADK/adenosine system warrant further discussion:

1. Susceptibility to SE: As key regulator of endogenous adenosine, the expression levels of ADK determine the brain's susceptibility to an SE. Using mice with genetically altered expression levels of ADK in the brain and a model of focal onset SE triggered by the intraamygdaloid injection of kainic acid (KA), we demonstrated that the global brain-wide overexpression of ADK to levels 140% above normal, led to an aggravation of the SE phenotype as evidenced by increased seizure activity, spread of neuronal injury throughout the hippocampal formation and lethal outcome under con-

ditions, where wild-type animals survived and sowed only focal CA3-selective neuronal injury. Conversely, mice with a reduction of hippocampal ADK to levels of 60% were completely resistant to the intraamygdaloid KA-induced SE. Therefore, ADK expression levels determine susceptibility to SE and seizure spread.

2. Epigenetic consequences of an SE: Like a variety of injuries to the brain, SE triggers a massive surge in adenosine (micromolar concentrations as opposed to baseline concentrations in the 25 to 300 nmolar range), which is linked to the transient downregulation of ADK in astrocytes. We propose that the SE-induced adenosine surge can trigger downstream mechanisms involved in epileptogenesis. New data from our laboratory show that increased adenosine or the downregulation of ADK block DNA methylation in the brain and that this activity leads to a hypomethylated state of the DNA, which might permit the expression of genes that drive epileptogenesis. This novel epigenetic effect of adenosine is directly linked to the transmethylation pathway and the inhibition of methyltransferase enzymes by S-adenosylhomocysteine, a metabolite that increases, when the metabolic clearance of adenosine is reduced by lower ADK activity. These findings suggest that an SE may trigger changes in the epigenome through an adenosine-dependent mechanism.
3. Neurogenesis: SE is known to trigger neurogenesis in the dentate gyrus of the hippocampus and increased neurogenesis may affect the development of epilepsy. While the short cytoplasmic isoform of ADK is almost exclusively expressed in astrocytes and responsible for the regulation of the tissue concentration of adenosine, ADK exists in a second, long, isoform, which is expressed in the nuclei of astrocytes and dentate granular neurons and thought to be involved in cell-autonomous regulatory mechanisms involved in cellular differentiation and plasticity. In pancreas and heart muscle, the nuclear isoform of ADK has been shown to prevent cell proliferation, whereas ADK inhibition promoted cell proliferation. Our data show that ADK in the nucleus of granular neurons of the dentate gyrus is transiently downregulated following an intra-hippocampal KA-induced SE and this transient time window of ADK reduction matches the time-window during which neurogenesis takes place. We thus pro-

pose that nuclear ADK in granular neurons plays a role as 'gate-keeper' for neurogenesis and that SE triggers neurogenesis through a mechanism that involves the transient downregulation of the nuclear isoform of ADK. To address this hypothesis, we generated a new line of mice that lacks the nuclear isoform of ADK in granular neurons of the dentate gyrus. Intrahippocampal KA-induced SE enhanced neurogenesis > 2-fold as compared to normal littermate controls. Those data suggest that SE may regulate neurogenesis through dynamic expression changes of the nuclear isoform of ADK in dentate granular neurons.

Is the adenosine system a new target for SE? It depends. As we have previously shown, life-style choices, including diet, influence the expression levels of ADK in the brain. Thus, a ketogenic diet was shown to reduce ADK expression in the brain in line with seizure suppression. Other life-style choices, such as exercise, have been shown to enhance adenosine levels in the brain. These findings suggest that life-style choices can influence the brain's excitability and thereby the susceptibility to SE. As potent anticonvulsant with effectiveness in a model of pharmacoresistant epilepsy, adenosine augmentation might be a useful therapeutic strategy to terminate refractory and potentially life threatening SE. Under life threatening conditions, the systemic use of adenosine augmenting agents might be justifiable.

A second area of therapeutic interest is the prevention of post-SE epileptogenesis. As discussed here epigenetic factors and neurogenesis might be involved and linked to an SE-associated surge in adenosine. The nuclear isoform of ADK might be a potential target to influence epigenetic mechanisms and neurogenesis in future attempts to prevent epileptogenesis. The therapeutic modulation of ADK expression, e.g. by gene therapy, might be a useful approach to regulate the tissue concentration of adenosine, but also to regulate epigenetic factors and neurogenesis. More knowledge is needed to decide, which isoform of ADK to target, and in which cell types, and in which direction (up- or downregulation). Eventually, the key for successful antiepileptogenic interventions will lie in regional, cell-type, and compartmental specificity of therapeutic approaches.

In summary, the adenosine/ADK system is of therapeutic interest not only for the prevention or termination of SE, but also to influence pathological downstream events triggered by an SE.

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IL5

TITLE: THE NEUROPHYSIOLOGICAL TYPES OF NONCONVULSIVE STATUS EPILEPTICUS - EEG PATTERNS OF DIFFERENT PHENOTYPES

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Abstract:

Proceeding from the proposed classification of status epilepticus syndromes by Shorvon in 1994, we performed a systematic search for reports presenting EEG patterns of nonconvulsive status epilepticus (NCSE) on all syndromes in the classification, where possible. Using the online medical search engine PubMed for 22 different search strategies, EEG patterns supporting a diagnosis of NCSE were sought. From a total of 4,328 search results, 123 cases with corresponding EEG patterns could be allocated to underlying epilepsy syndromes. Based on the characteristic EEG patterns found for the different NCSE syndromes, we present a synthesis of the significant EEG morphologies and evolutions in the individual NCSE syndromes.

Text:

Introduction

There have been many attempts at defining the electroencephalography (EEG) characteristics of nonconvulsive status epilepticus (NCSE) without a universally accepted definition. This lack of consensus arises because the EEG expression of NCSE does not exist in isolation, but reflects status epilepticus under the variety of pathologic conditions that occur with age, cerebral development, encephalopathy, and epilepsy syndrome. Current NCSE definitions include "boundary conditions," in which electroencephalo-

graphic seizure activity occurs without apparent clinical seizures. Furthermore, what appears to one interpreter as status epilepticus, is not to another reader, reflecting the "art" of EEG interpretation. Seizures and epilepsy syndromes have undergone an evolution that has moved beyond a classification of focal or generalized conditions into a syndromic approach. It seems appropriate to make similar changes in the EEG analysis of the syndromes of NCSE. In effect, the literature on epilepsy classification has progressed to incorporate the different NCSE types with clinical descriptions, but the specific EEG evidence for these types is found largely in individual reports, and often by description only. NCSE classification of EEG patterns should derive from the aggregate of published EEG patterns in the respective clinical subtype, supported by an analysis of these EEG studies. The analysis that follows, presents clinical descriptions and EEG patterns of NCSE in the neonatal period, infancy, childhood, adulthood, and late adulthood from a syndromic perspective based on age, encephalopathy, cerebral development, etiology, and syndrome.

Methods

Proceeding from the proposed classification of status epilepticus syndromes (Table 1) in "Status epilepticus: its clinical features and treatment in children and adults", we have performed a systematic search for reports presenting EEG patterns of NCSE using the online medical search engine PubMed (<http://www.ncbi.nlm.nih.gov/sites/entrez>) for the following 22 different search strategies:

- For neonatal and infantile epilepsy syndromes "nonconvulsive status epilepticus", "West syndrome", "Ohtahara syndrome", and "Dravet syndrome".
- For childhood epilepsy syndromes "Panayiotopoulos syndrome", "Ring chromosome 20 syndrome", "Angelman syndrome", "Rett syndrome", "myoclonic astatic epilepsy", "electrical status epilepticus", and "Landau-Kleffner syndrome".
- For epilepsy syndromes in childhood and adult life "Lennox-Gastaut syndrome", "absence status epilepticus", and "tonic status epilepticus".
- For epilepsy syndromes in adulthood and late adult life "limbic status epilepticus", "complex partial status epilepticus", "late-onset nonconvulsive status epilepticus", "late-life nonconvulsive status epilepticus", "coma/nonconvulsive status epilepticus", "epileptic psychosis", "drug-induced status epilepticus", and

"metabolic status epilepticus".

EEG patterns were reviewed by two EEG readers who reached consensus regarding presence of NCSE. The following criteria were used for the diagnosis of NCSE in early life as proposed in the section "Diagnosis of NCSE in children" of the Oxford conference report in 2005. "A continuous or virtually continuous dysrhythmia or paroxysmal activity on the EEG is necessary. Furthermore, a continuous, abnormal electrical dysrhythmia may occur on the EEG and be difficult to equate with the clinical state. Such electrical status that occurs every time the child goes to sleep is seen in the Landau-Kleffner syndrome and some cases of Lennox-Gastaut syndrome. These continuous dysrhythmias may be acute or chronic.

The diagnosis of NCSE ideally must consist of a combination of clinical and EEG features. Therefore, the following four clinical and electroencephalographic criteria for the diagnosis of NCSE in early life were used:

1. Clear clinical change in behavior (manifested as changes in cognition, memory, arousal affect, ataxia, motor learning and motor behavior) that lasted at least 30 minutes. The word "clear" in the context of NCSE would imply that an adequate description of behavior before the onset of NCSE was available for comparison and the time of onset could have been defined given that the onset can be gradual and the duration of the NCSE prolonged.
2. There must have been confirmation by clinical or neuropsychological examination of a clinical change.
3. Continuous or virtually continuous paroxysmal episodes must have been present on the EEG.
4. Continuous major seizures either tonic or clonic must have been absent.

All of the above criteria had to be fulfilled for the diagnosis of NCSE in early life. A clinical response to anticonvulsant medication such as intravenous/oral benzodiazepines with simultaneous improvement in the EEG and clinical symptoms added further support to the diagnosis if positive, but did not exclude the diagnosis if negative as proposed by Livingston and Brown.

For NCSE in adults and late adult life the definition from the Oxford conference on NCSE was used as follows: "The diagnosis of NCSE was primarily dependent on the pre-

sence of electrographic seizure activity. This allowed the inclusion, within the rubric of NCSE of a range of "boundary conditions" in which such activity occurred but in which there were no obvious clinical "seizures". (ii) Electrographic seizure activity can take various forms, some of which clearly denote NCSE (clear-cut criteria) and some of which are less easy to interpret and probably denote NCSE only in some cases (equivocal criteria). The six "clear-cut" criteria included:

1. Frequent or continuous focal electrographic seizures, with ictal patterns that wax and wane with change in amplitude, frequency and/or spatial distribution.
2. Frequent or continuous generalized spike wave discharges in patients without a prior history of epileptic encephalopathy or epilepsy syndrome.
3. Frequent or continuous generalized spike wave discharges, which showed significant changes in intensity or frequency (usually a faster frequency) when compared to baseline EEG, in patients with an epileptic encephalopathy/syndrome.
4. PLEDs or BIPEDs that occurred in patients in coma in the aftermath of a generalized tonic clonic status epilepticus (subtle status epilepticus). EEG patterns, which were less easy to interpret included:
5. Frequent or continuous EEG abnormalities (spikes, sharp waves, rhythmic slow activity, PLEDs, BIPEDs, GPEDs, triphasic waves) in patients whose EEG showed no previous similar abnormalities, in the context of acute cerebral damage (e.g., anoxic brain damage, infection, trauma).
6. Frequent or continuous generalized EEG abnormalities in patients with epileptic encephalopathies in whom similar interictal EEG patterns were seen, but in whom clinical symptoms were suggestive of NCSE.

Categories 3 and 6 reflect the problem of deciding the significance of spike-wave discharges in the setting of epileptic encephalopathy (e.g., Lennox-Gastaut syndrome) in which the ictal and interictal EEG patterns may be very similar. The differentiation of the two is problematic. Category 5 reflects the difficulty of differentiating patterns of epileptic discharges that may lie along an ictal-interictal continuum.

Results

From a total of 4,328 search results, 123 cases with corresponding EEG patterns could be allocated to underlying

epilepsy syndromes. Typical characteristic EEG patterns were found for the different NCSE syndromes. A synthesis of the significant EEG morphologies and evolutions of the individual NCSE syndromes arranged according to the classification of NCSE syndromes by Shorvon is provided in table 2. The corresponding EEG figures upon which our synthesis is based, can be found in the recent publication entitled “Electroencephalographic criteria for nonconvulsive status epilepticus: Synopsis and comprehensive survey”.

Conclusion

This study identifies and provides the various EEG patterns seen in NCSE from a syndromic perspective. A caveat is that published figures supporting the particular type of status epilepticus may be of inconsistent quality, warranting newer reports with better illustrations of several of the syndromes. Further, some SE types lack any adequate illustrative figures. Included are borderline patterns, and associations with seizures. The compendium provides clinical and illustrative electroencephalographic descriptions that enable clinicians to approach and categorize NCSE within the context of specific syndromes with their clinical features and subtypes, rather than using previous descriptions and distinctions into complex partial (focal) and absence (generalized)

subtypes. It is hoped that this compendium may help in moderating semiologic borderline disputes on NCSE.

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Table 1: NCSE etiology or clinical context, forms, and response to treatment (adapted from the revised classifications of status epilepticus in children and adults)

NCSE in the neonatal and infantile epilepsy syndromes			
Syndrome	Etiology or clinical context	Clinical form	Response to treatment or prognosis
West syndrome	Various	Infantile spasms with periods of NCSE with no clinical signs of ongoing epileptic activity	Poor
Ohtahara syndrome	Various	Tonic spasms	Poor
Severe myoclonic epilepsy of infancy (Dravet syndrome)	Genetic	Nonspecific	Poor
NCSE in other forms of neonatal or infantile epilepsy	Various	Nonspecific	Various
NCSE in childhood			
Syndrome	Etiology or clinical context	Clinical form	Response to treatment or prognosis
Early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)	Idiopathic	Autonomic status epilepticus	Excellent
NCSE in other forms of childhood epileptic encephalopathies, syndromes, and etiologies, (eg, ring chromosome 20, Angelman syndrome, myoclonic-astatic epilepsy, other childhood myoclonic encephalopathies)	Various, usually genetic or cryptogenic	Atypical absence and other nonspecific forms	Generally poor

Electrical status epilepticus in slow-wave sleep	Various, usually cryptogenic	No clinical signs but ongoing electrographic activity in sleep	NCSE usually remits but may leave intellectual deficits
Landau Kleffner syndrome	Various, usually cryptogenic	Clinical correlate of electrographic activity is severe speech disturbance	NCSE usually remits but may leave intellectual deficits
NCSE in adult life (and childhood) <u>with</u> epileptic encephalopathy			
Syndrome	Etiology or clinical context	Clinical form	Response to treatment or prognosis
NCSE in Lennox-Gastaut syndrome	Various, often cryptogenic	Atypical absence status epilepticus and tonic status epilepticus	Poor
NCSE in other forms of disrupted cerebral development (cryptogenic or symptomatic)	Various, often cryptogenic	Various	Variable
NCSE in adult life (and childhood) <u>without</u> epileptic encephalopathy			
Syndrome	Etiology or clinical context	Clinical form	Response to treatment or prognosis
Typical absence status epilepticus	Idiopathic generalized epilepsy	Generalized absence	Excellent
Complex partial status epilepticus (limbic and nonlimbic origin)	Various -symptomatic or cryptogenic	Complex partial	Good
NCSE in the postictal phase of CSE	Various	Confusion state with psychiatric features	Good
Subtle status epilepticus	Various	Coma with small irregular myoclonic jerks	Variable
Aura continua	Various -symptomatic or cryptogenic	Simple partial (sensory, special sensory, cognitive)	Good
NCSE in late adult life			
Syndrome	Etiology or clinical context	Clinical form	Response to treatment or prognosis
De novo absence status epilepticus	Psychotropic drug withdrawal or idiopathic generalized epilepsy	Generalized absence	Excellent
Boundary syndromes			
Coma with epileptiform EEG changes			
Epileptic behavioral disturbance or psychosis			
Drug-induced or metabolic confusion state with epileptiform EEG changes			

NCSE = nonconvulsive status epilepticus; CSE = convulsive status epilepticus; EEG = electroencephalography

Table 2: Prominent electrographic elements and EEG patterns for NCSE syndromes

NCSE in the neonatal and infantile epilepsy syndromes	
Syndrome	Prominent EEG patterns and evolution
West syndrome	Generalized continuous or waxing and waning high-voltage polymorphic slow wave discharges (> 200 µV) with interspersed multifocal, irregular spikes and sharp waves usually followed by voltage attenuation and irregular 2 to 4 Hz slow wave discharges. There may be periods of suppression of background activity or a continuous burst-suppression pattern.
Ohtahara syndrome	Continuous burst-suppression pattern with repetitive bursts of high-voltage slow waves (200 to > 400 µV) interspersed with multifocal, irregular spikes followed by periods of near isoelectric suppression.
Severe myoclonic epilepsy of infancy (Dravet syndrome)	Continuous or waxing and waning periodic or pseudoperiodic frontal or fronto-temporal spikes, which may be followed by slow waves in the awake tracing. Spikes tend to be triphasic instead of biphasic and subclinical discharges are slower than in Lennox-Gastaut syndrome. There are no polyspikes in sleep, and discharges that mimic tonic discharges show no recruiting pattern. No clinical tonic or electromyographic features on video EEG awake and sleep records. Usually background activity is slow and/or suppressed.
NCSE in other forms of neonatal or infantile epilepsy	Various forms as defined from the Oxford conference on NCSE .

NCSE in childhood	
Syndrome	Prominent EEG patterns and evolution
Early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)	Waxing and waning low-voltage fast and rhythmic epileptic activity of 1 to 2.5 Hz predominantly in the occipital regions, increasing in voltage (>200 μV) and decreasing in frequency with rapid bilateral fronto-temporal spreading that is followed by rhythmic spike-and-wave discharges with occipital predominance. Usually background activity is slow and desynchronized.
NCSE in other forms of childhood epileptic encephalopathies, syndromes, and etiologies	<u>Ring chromosome 20</u> : Generalized continuous or waxing and waning repetitive irregular spikes with frontal predominance, followed by rhythmic or irregular high-amplitude slow waves at 3 to 4 Hz with interspersed multifocal, irregular spikes. Usually the frequency of the spike-and-wave discharges increases, and the slow waves can get polymorphic. Usually background activity is slow and/or suppressed. <u>Angelman syndrome</u> : Generalized continuous or waxing and waning rhythmic sharp wave discharges with fronto-central predominance. Usually background activity is slow and/or suppressed. <u>Rett syndrome</u> : Continuous or waxing and waning unilateral, multifocal or generalized spikes usually during 50% of slow wave sleep. Usually background activity is disorganized and desynchronized. <u>Myoclonic-astatic epilepsy syndrome</u> : Generalized continuous or waxing and waning slow wave discharges of 2 to 3 Hz with interspersed multifocal, irregular spikes, polyspikes, and slow wave complexes. Electromyographic channels showed multifocal, erratic myoclonic jerks on a background of mild tonic contraction. The ictal activity then may blend into a burst-suppression pattern.
Electrical status epilepticus in slow-wave sleep	Generalized continuous rhythmic or irregular spike-and-wave discharges of up to 3 Hz during slow-wave sleep with a fronto-central, or posterior-temporal predominance. Usually background activity is slow and/or suppressed.
Landau Kleffner syndrome	Focal, multifocal or generalized continuous or nearly continuous repetitive high-voltage spike or spike-and-wave discharges, which are activated in slow-wave sleep. The epileptic activity usually involves the dominant temporal area. Usually background activity is slow and/or suppressed.
NCSE in adult life (and childhood) <u>with</u> epileptic encephalopathy	
Syndrome	Prominent EEG patterns and evolution
NCSE in Lennox-Gastaut syndrome	<u>Atypical absence status epilepticus</u> : Generalized continuous or waxing and waning irregular 2 to 2.5 Hz spike and polyspike-slow-wave discharges predominantly fronto-temporal and usually with normal background activity. <u>Tonic status epilepticus</u> : Generalized repetitive runs of polyspikes at high frequencies of 16 to 20 Hz, beginning with low-voltage and increasing high-voltage (100 μV) and a 10 Hz recruiting rhythm of high-voltage from onset. The runs of polyspikes can be interspersed with slow waves. Background activity may be disorganized and desynchronized.
NCSE in other forms of disrupted cerebral development (cryptogenic or symptomatic)	Various forms as defined from the Oxford conference on NCSE .
NCSE in adult life (and childhood) <u>without</u> epileptic encephalopathy	
Syndrome	Prominent elements or sequential arrangements
Typical absence status epilepticus	Generalized continuous or waxing and waning rhythmic 3 to 4 Hz spike and polyspike-slow-wave discharges predominantly anterior and usually with normal background activity.
Complex partial status epilepticus (limbic and nonlimbic origin)	<u>Limbic</u> : Continuous or waxing and waning periodic or pseudoperiodic sharp wave discharges interspersed with low-voltage spikes and polyspike-and-waves with uni- or bilateral fronto-central predominance and usually generalized slow and/or suppressed background activity. Waxing and waning rhythmic delta activity, only. <u>Nonlimbic</u> : Continuous or waxing and waning periodic or pseudoperiodic sharp waves and spike-and-wave discharges with unilateral, focal onset and frequent seizure progression into generalized sharp wave and slow, and/or suppressed wave discharges usually with frontal predominance and generalized slow background activity.
NCSE in the postictal phase of CSE	Generalized or partial continuous or waxing and waning periodic epileptic discharges that resemble PLEDs or GPEDs with a frontal predominance and usually generalized slow background activity.
Subtle status epilepticus	Generalized continuous or waxing and waning periodic epileptic discharges resembling GPEDs that may be interrupted by short periods of nearly isoelectric suppression over 3 to 5 seconds. Usually background activity is slow and/or suppressed.
Aura continua	Unilateral continuous or waxing and waning rhythmic spike-and-wave or high-voltage slow-wave discharges (>200 μV) usually with generalized slow and/or suppressed background activity.

NCSE in late adult life	
Syndrome	Prominent elements or sequential arrangements
De novo absence status epilepticus	Generalized continuous or waxing and waning rhythmic 3 to 4 Hz spike, polyspike-slow-wave discharges predominantly anterior and usually with normal background activity.
Boundary syndromes	
Syndrome	Prominent elements or sequential arrangements
Coma with epileptiform EEG changes	Generalized waxing and waning periodic epileptic discharges that resemble GPEDs with periods of nearly isoelectric suppression. Usually background activity is slow and/or suppressed.
Epileptic behavioral disturbance or psychosis	Various forms as defined from the Oxford conference on NCSE .
Drug-induced or metabolic confusion state with epileptiform EEG changes	Various forms as defined from the Oxford conference on NCSE .

NCSE = nonconvulsive status epilepticus; PLEDs = periodic lateralized epileptiform discharges; GPEDs = generalized periodic epileptiform discharges; CSE = convulsive status epilepticus; EEG = electroencephalography

IL6

TITLE: A ROLE FOR INFLAMMATION IN STATUS EPILEPTICUS IS REVEALED BY A REVIEW OF CURRENT THERAPEUTIC APPROACHES

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Abstract: A significant number of epileptic patients fail to respond to currently available anti-epileptic drugs. This suggests a need for alternative approaches to reduce the occurrence of seizures in these patients. Methods to pharmacologically reduce blood-brain barrier permeability and reduce inflammation have emerged as means to reduce seizure

activity. For example, corticosteroids and magnesium sulfate have been shown to reduce seizures and may be able to further reduce seizure burden in conjunction with currently prescribed anti-epileptic drugs. Further, emerging evidence suggests that some anti-epileptic drugs may increase inflammatory responses in epileptic patients; these effects may perhaps paradoxically increase seizure activity.

Text: A wind of change characterizes ongoing epilepsy research efforts. The traditional approach based on a neurocentric view of seizure generation promoted understanding of the neuronal mechanisms of seizures. These efforts resulted in the development of potent anti-epileptic drugs (AEDs) and triggered refined surgical approaches to treat multiple drug resistant seizures. The fact that a significant number of epileptics still fail to respond to available AEDs restates the need for an alternative approach.

Two emerging players hold the lion’s share of “unconventional” epilepsy research. On one hand, inflammation is becoming an essential topic linking the immune system to neuronal dysfunction. On the other, altered blood-brain barrier (BBB) permeability plays an important etiological role in seizure generation. The BBB has recently been targeted to develop new pharmacological approaches aimed at restoring homeostasis and normal function. Combination therapies utilizing an AED in conjunction with BBB-stabilizing corticosteroid therapy may control seizures better than AED therapy alone {8162}. Direct evidence from

the pilocarpine model of status epilepticus (SE), together with clinical data supporting the use of anti-inflammatory drugs to treat seizures have been published and reviewed (e.g., (Janigro 2012)). This short article will use an indirect approach in an attempt to further the notion that seizures can be prevented or treated by targeting systemic inflammation and its gate keeper, the BBB. In particular, we will focus on SE and its management.

In status epilepticus the role of BBB-immune interactions is poorly understood but if one considers the therapeutic approaches to treat SE, a surprising overlap with anti-inflammatory maneuvers becomes apparent (Marchi et al., 2012). These therapeutic options span from drugs acting on GABA receptors (benzodiazepines, anesthetics and barbiturates), to anti-inflammatory drugs (corticosteroids) and to other maneuvers with direct or indirect, documented or unknown, mechanisms of action on neurons.

One extreme of the spectrum of treatments for SE are GABA-ergic drugs or anesthetics which quickly (<1 hr.) achieve the desired anti-SE effect. For these, a direct effect on neurons and modulation of inhibitory synapses is the unquestionable *modus operandi*. However, anesthetic drugs also have immunomodulatory effects partially overlapping with those of corticosteroids. For instance, propofol or thiopental exert potent anti-inflammatory effects mediated by decreased NF- κ B expression (Roesslein et al., 2008; Sanchez-Conde et al., 2008). Sevoflurane, which has similar anesthetic potency but lacks anti-inflammatory action, is not the first choice among halogenated anesthetics for SE. Furthermore, sevoflurane may actually have an epileptogenic effect (Jaaskelainen et al., 2003). These anti-inflammatory mechanisms are comparable to what is observed with corticosteroids and aid in the prevention, or recovery of BBB integrity (Marchi et al., 2009; Marchi et al., 2011; Verhelst et al., 2005).

An emerging therapeutic approach to refractory SE (reviewed by Shorvon and Ferlisi 2011) is the use of intravenous infusion of magnesium sulphate. Magnesium has negligible BBB permeability and, in healthy individuals, brain levels exceed serum concentrations (Amtorp & Sorensen 1974). When the BBB is disrupted (e.g., during seizures), brain Mg^{++} may decrease due to brain-to-blood leakage. This causes a partial, seizure-promoting NMDA receptor

disinhibition. Thus, systemic administration to achieve high magnesium levels in blood may prevent leakage or restore brain levels of this ion, with a pronounced effect on excitatory synapses and thus on neuronal excitability.

Last but not least, traditional AEDs exert immunological effects. While an ample array of contradictory data exists, AEDs interfere with normal immunological responses leading to the activation of proinflammatory pathways that may lead to or exacerbate seizure activity (Beghi & Shorvon 2011).

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IL7

TITLE: INTRINSIC EPILEPTOGENICITY OF DYSPLASTIC CORTEX: CONVERGING DATA FROM EXPERIMENTAL MODELS AND HUMAN PATIENTS

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Abstract:

Focal cortical dysplasia (FCD) are brain malformations as-

sociated with particularly severe drug-resistant epilepsy often requiring surgery for seizure control (Blümcke et al., 2011). The molecular basis of such enhanced propensity to seizure generation in FCD is not as yet elucidated. It is similarly unknown whether these highly frequent seizures may be a pathogenic co-factor in the generation of further seizures. To investigate cellular and molecular basis of epileptogenic mechanisms and possible effect of severe epilepsy on the malformed cortex we have here performed a parallel analysis of a rat model of acquired cortical dysplasia previously established in our laboratory (MAM-PILO rats; Colciaghi et al., 2011) and surgical samples from patients with type IIB FCD.

Data from the MAM-PILO rat model and the human FCD samples reveal in both conditions: i) that SE and/or seizures can further modify the cellular and molecular settings of the malformed cortex; ii) excitation/inhibition imbalance, and dysregulation of the NMDA/MAGUK expression; iii) activation of cell death in neurons and glia. The data therefore highlight the mechanistic relevance of glutamate/NMDA hyperactivation in FCD epileptogenesis and suggest that epilepsy is a pathologic process capable of affecting structure and function of both neurons and glia.

Text:

Introduction

Malformations of cortical development result from pathologic events of different nature occurring during the process of cortical ontogenesis (Barkovich et al., 2012). They are the neuropathologic substrate of quite a number of drug-resistant epileptic patients. In particular, focal cortical dysplasia (FCD) is the more common brain malformation in patients undergoing epilepsy surgery for the relief of intractable seizures (Fauser et al., 2006; Lerner et al., 2009). The classification of FCD has been recently re-evaluated by a task force from ILAE to further define clinical, imaging and neuropathology features of affected patients (Blümcke et al., 2011). Among the different forms, type IIB FCD, which was first described in a seminal paper by Taylor and colleagues (Taylor et al., 1971), is characterized by distinctive clinical features: early age of onset, EEG patterns of continuous interictal spiking activity, severe seizures, and frequent episodes of epileptic status (Palmini et al., 1995; Tassi et al., 2001).

Mechanisms of hyperexcitability in the malformed brain

The mechanisms underlying such severe epilepsy are not completely understood (Schwartzkroin and Wenzel 2012). However, many data indicate that dysmorphic neurons are strictly related to FCD epileptogenesis. First, stereo-EEG demonstrated that both ictal discharges and interictal rhythmic spiking activity originated from the dysplastic areas where dysmorphic neurons were located (Chassoux et al., 2000). Second, electrocorticographic recordings from FCD patients demonstrated seizure onset from cortical areas characterized by the presence of dysmorphic neurons and not ballooned cells (Boonyapisit et al., 2003; Marusic et al., 2002). Third, electrophysiological studies in vitro on cortical slices or dissociated neurons from surgery specimens of pediatric FCD patients confirmed that cytomegalic neurons displayed abnormal electrophysiologic properties thus possibly playing a relevant role in sustaining epileptic discharges in FCD (Cepeda et al., 2003; 2005).

It is also possible that an imbalance between glutamatergic excitatory and GABAergic inhibitory inputs may be at the origin of the intrinsic hyperexcitability of the FCD areas. This hypothesis is supported by data indicating N-Methyl-D-Aspartate (NMDA) receptors as important determinants of FCD-related epilepsy (Ying et al., 1998 and 1999; Takase et al., 2008). NR2A/2B NMDA subunits are increased and epileptogenic activities are sensitive to NR2B-specific inhibitors in surgical specimens from epileptic FCD patients (Crino et al., 2001; Moddel et al., 2005). In keeping with these data, we demonstrated a selective increase of NR2B in cortical specimens of FCD human patients (Finardi et al., 2006). Thus, dysregulation of NMDA receptor complex expression and function likely plays a role in FCD hyperexcitability.

MAM-PILO rats: a model for human FCD

To better investigate the issue of why the malformed cortex is highly epileptogenic, we have recently developed a rat model of human FCD (Colciaghi et al., 2011) based on prenatal methylazoxymethanol (MAM) treatment (inducing cortical malformations) and post-natal pilocarpine (PILO) treatment (leading to status epilepticus - SE - and epilepsy). This model recapitulates both pathological conditions of human FCD, i.e., abnormal cortical structure and highly recurrent spontaneous seizures. Behavioral and EEG

analysis of seizures shows that MAM-PILO rats develop severe epilepsy. The morphologic and molecular analysis of the model demonstrate that SE and epilepsy are able to induce in MAM-PILO rats the presence of abnormally large cortical pyramidal neurons with neurofilament over-expression and recruitment of NMDA regulatory subunits at the post-synaptic membrane. These neurons bear similarities with the dysmorphic pyramidal neurons observed in human FCD. We have more recently further exploited our MAM-PILO model by analyzing epileptic rats at different time-points after epilepsy onset (18 hours after SE onset, as acute SE stage; 3-5 days after the first spontaneous seizure, as early chronic stage; 3 and 6 months after epilepsy onset, as two stages of chronic epilepsy). As appropriate controls, we used MAM rats receiving diazepam (DZP) before PILO, not experiencing either SE or spontaneous seizures (MDP rats). Our analysis has shown that: i) epilepsy duration is positively associated with progressive cortical and hippocampal atrophy; ii) dysmorphic cortical neurons over-expressing neurofilaments and NMDA receptors increase in number and become more widespread in the course of epilepsy; iii) recurrent seizures significantly reduce dendritic branching and spine density of dysmorphic pyramidal neurons in both neocortex and hippocampus, as demonstrated by Golgi-Cox analysis; iv) despite the loss of dendritic spines, the glutamatergic input to large cortical and hippocampal pyramidal neurons (soma size $\geq 400 \mu\text{m}^2$) is maintained (and that to granule cells even increased) whereas the GABAergic input to the same neurons is decreased, thus creating a statistically significant imbalance between excitatory and inhibitory synapses in both neocortex and hippocampus; v) there is a steady activation of the NMDA NR2B regulatory subunits, which at least in the neocortex is progressive during the course of epilepsy. Therefore, data from MAM-PILO rats indicate that the extent of architectural and molecular alterations in both hippocampus and neocortex are related to the duration of epilepsy, thus supporting the intriguing hypothesis of progressive epilepsy-dependent brain abnormalities.

FCD in human patients: the glutamate hypothesis.

We have next extended our investigation in FCD patients to verify the possible effects of severe epilepsy also on the malformed human cortex. To this, we have analyzed surgical samples from eight FCD IIB patients with different epilepsy duration and nine non-dysplastic controls. Pati-

ents were surgically treated either at the Epilepsy Surgery Center "C. Munari" of the Niguarda General Hospital or at the Neurosurgery Department of the Neurological Institute "C.Besta" in Milano. In the epileptic patients, high-resolution MRI and electroclinical analysis including SEEG or video-EEG recordings were used to carefully define the areas of epilepsy onset. In every FCD patient we have compared the dysplastic areas at the origin of epileptic discharges with adjacent areas involved in the epileptic circuitry but not at the origin of seizures. Our results demonstrate that the epileptogenic/dysplastic areas of all patients are characterized by larger dysmorphic neurons, reduced neuronal density and increased glutamatergic inputs if compared to adjacent areas. These features are likely the result of abnormal cell proliferation and differentiation during brain development of the epileptogenic/dysplastic areas analyzed (Orlova et al., 2010; Blümcke et al., 2011). However, the comparison between patients with longer (>10 years) vs shorter (<10 years) epilepsy history revealed that in the epileptogenic/dysplastic areas epilepsy duration was positively correlated with dysmorphic neurons of further larger size, further reduced neuronal cell density and increased reactive gliosis with altered astrocytic morphology. Thus, in line with what demonstrated in the MAM-PILO model, these data in FCD patients provide support to the intriguing hypothesis that epilepsy per se can trigger pathologic plasticity of both neurons and glia exacerbating or inducing cytological abnormalities within the malformed FCD cortex. In addition to the increased glutamatergic input, our western blot data demonstrate that the NMDA regulatory subunits 2A and 2B and related membrane-associated guanylate kinase (MAGUK) proteins are consistently altered in all FCD patients examined. Therefore, the increased glutamatergic input and altered NMDA/MAGUK expression are major determinants in the epileptogenic mechanisms of human FCD, not only contributing to hyperexcitability but also possibly triggering intracellular mechanisms capable of deeply altering brain structure.

Cell death in the dysplastic cortex

The progressive cortical and hippocampal atrophy of MAM-PILO rats and the reduced neuronal cell density observed in the epileptogenic/dysplastic areas of human FCD patients suggest that in both the experimental model and human patients SE and/or severe recurrent seizures can activate

cell death pathways. We have therefore investigated cell death pathways in MAM-PILO rats at the different epilepsy stages considered (see above). Fluoro Jade B staining (FJB) confirmed that SE was associated with diffuse labeling of degenerating neurons in the neocortex, hippocampus and thalamus, as already reported by different groups (Narkilahti et al., 2003; Wang et al., 2008). Surprisingly, however, we found FJB⁺ degenerating neurons at all epilepsy stages considered. In particular, we found FJB⁺ neurons in: i) superficial and deep neocortical layers at early stages, and deep layers at 3 and 6 months of chronic epilepsy; ii) CA pyramidal neurons at all stages, and dentate gyrus (hilar neurons only) up to 3 months of chronic epilepsy; iii) ventrolateral/ventrobasal and intralaminar thalamic nuclei at all stages. At chronic epilepsy stages, some neocortical (entorhinal and perirhinal) and thalamic regions were diffusely necrotic. We have also verified the presence of reactive gliosis during the course of epilepsy. As expected, marked increase in GFAP immunoreactivity was found in neocortical, hippocampal and thalamic regions. In all areas considered, astrocyte morphology changed during the course of epilepsy: larger cell bodies, thicker processes, and eccentric nuclei became evident. Hypertrophic astrocytes, with very large opalescent cytoplasm and eccentric nucleus, possibly representing the final morphologic stage of reactive astrogliosis, were evident in the hippocampus of some MAM-PILO rats. We next verified the activation of intracellular death pathways by means of double labeling confocal IF for activated caspase or c-Jun and neuronal and glial markers. Our data demonstrate that at chronic stages CA pyramidal neurons were positive for both active caspase3 and p-c-Jun, whereas neocortical pyramidal neurons (including large hypertrophic pyramidal neurons with neurofilament over-expression) were positive for p-c-Jun only. By contrast, GFAP⁺ astrocytes were frequently labeled for active caspase3 but not for p-c-Jun, suggesting that different pro-death pathways are preferentially activated in neurons and glia following SE and seizures. Since GFAP⁺ astrocytes were never FJB⁺, the presence of caspase3 could also signify a non-apoptotic role of caspase3 in cytoskeletal remodeling leading to astrogliosis (Acarin et al., 2007; Aras et al., 2012). In any case, these results clearly indicate that in the dysplastic cortex not only SE but also chronic seizures may induce both neuronal and glial cell death.

Concluding remarks

Data from the MAM-PILO rat model and the human surgical FCD samples reveal common features shared by both conditions: i) SE and/or seizures can further modify the cellular and molecular settings of the malformed cortex; ii) there is imbalance between glutamatergic excitation and inhibition, and dysregulation of the NMDA/MAGUK expression; iii) SE and seizures can induce cell death by activating specific intracellular pathways in neurons and glia. The comparative analysis of rat model and human patients therefore highlights the mechanistic relevance of glutamate/NMDA hyperactivation in FCD epileptogenesis. In addition, both sets of data suggest that, within the specific context of the epileptogenic malformed brain, epilepsy can be viewed as a maladaptive process affecting the cellular structure and the molecular function of both neurons and glia (i.e., epilepsy can damage the brain).

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IL8

TITLE: STATUS AS A SYSTEM DISTURBANCE: IS STATUS DUE TO SYNCHRONIZATION OR DESYNCHRONIZATION?

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Abstract:

The traditional view of seizure activity is one in which there is extreme hypersynchronization. Although what is meant by hypersynchronization is rarely explicitly and fully defined it is understood to imply large numbers of neurons firing together essentially simultaneously. In this discussion we will explore the possibility that seizures – both self-terminating and sustained in status - are not purely synchronous in time or in space. We will investigate the alternative possibility that much seizure activity represents spatiotemporal desynchronization. Furthermore, we will discuss the possibility that, in contrast to canonical views of epileptic activity, a high degree of synchronization is a pre-requisite for termination of the seizure rather than a marker of early and ongoing seizure activity. These ideas will be discussed with reference to results from our collaborative group based on microelectrode recordings in patients with epilepsy as well as to the many studies done by others in both patients and animal models. Finally, we will explore implications for these hypotheses in the treatment of patients with epilepsy and in status epilepticus.

Text:

Despite many decades of research in both clinical neurophysiology and basic neuroscience our understanding of the mechanisms of epileptiform activity remains crude. Two general principles of neuronal activity have come to dominate our thinking about what is a seizure or how a seizure occurs. The first is that seizure activity arises from

an imbalance of inhibitory and excitatory neuronal action. The second is that ictal activity represents a form of hypersynchrony within neural behavior. These descriptions of neuronal action have been enormously powerful in helping formulate ideas about seizure progression and in the explanation and even design of therapeutic interventions – primarily pharmacological ones. Particularly in the last decade, however, these simplifications have been increasingly recognized as just that – simplifications that, while useful in many regards, do not fully describe the spatiotemporal dynamics of neuronal activity during seizures. Instead, an emerging body of work suggests that both self-limited seizures and status epilepticus evolve through different phases during which there are different degrees of spatio-temporal synchrony (reviewed recently in {Jiraska, 2013 #4939}).

To begin, we need to be clear about what is synchrony and desynchrony. They can be variously defined. At one extreme, at the level of individual neurons and with the most conservative definition, we can establish synchrony only when neurons are firing action potentials truly simultaneously. Desynchrony occurs when the normal degree to which neurons are firing simultaneously is disrupted. At the other extreme we could imagine synchrony to be present when either action potentials or any other neuronal activity (e.g. post-synaptic potentials) are maintaining a consistent relationship over short periods of time— closer than is the case under ‘normal’ conditions. This could be true over the time span of 10s of milliseconds or even more.

A major confound in this scheme is the overall degree of neuronal activity. As action potential firing rate increases, for example, there is necessarily a greater degree of synchrony for firing between any two neurons in any given bin of time. Is this truly increased synchrony or merely an epiphenomenon of the increased rate of activity? The answer will depend essentially on how synchrony is defined and it is currently both possible and reasonable to use either end of the spectrum to make that definition. What is perhaps most important is to be clear about what degree of synchrony is being measured and, ultimately, what are the mechanistic causes / effects of that synchrony. With this major, semantic, caveat present we can then proceed to look for evidence that seizures, and status in particular, demonstrate either synchronization or desynchronization.

Evidence for desynchrony at the microscale

Seizures, by definition, go through an evolution in time. Different phases of the seizure demonstrate different activities at whatever level of analysis one chooses to examine. This is particularly true for focal seizures but also true for generalized events. None-the-less, the degree to which this change represents changes in levels of synchrony has been unclear. To explore this issue specifically at the level of individual neurons, our group examined the behavior of neuronal populations in small cortical regions inside and outside of the seizure focus in patients with intractable focal epilepsy. Surprisingly, the early and middle phases of the seizure appear to be characterized by heterogeneity in firing activity {Truccolo, 2011 #4595}. Similar findings are present using other methods of recording unit activity {Bower, 2012 #4884}. In addition, these findings parallel earlier work done in a slice model of epilepsy. Netoff and Schiff used intracellular recordings to demonstrate that synaptic inputs to pairs of neurons were less correlated during initiation and maintenance of the seizure than during interictal periods {Netoff, 2002 #3503}. In theoretical work it was predicted that when the spiking rate is at its maximum neurons would desynchronize and this is likely to occur at the height of the seizure {Ermentrout, 1998 #4904;Gutkin, 2005 #4938}. Finally, even brief epileptiform discharges seem to display a similar degree of heterogeneous activity which is not consistent with the notion of pure hypersynchrony {Keller, 2010 #4549}. This heterogeneity in neuronal behavior argues against homogeneous and hypersynchronous runaway excitation or widespread paroxysmal depolarization as the primary mechanism underlying seizure initiation and spread. Instead, the seizure appears to result from a complex interplay among groups of neurons with different spiking behaviors which evolve at multiple temporal and spatial scales.

Evidence for desynchrony at the macroscale

Seizures, by definition, go through an evolution in space as well. Measures of activity across that spatial domain also demonstrate that there is greater heterogeneity in inter-areal interactions than might be expected from a model of pure hypersynchrony. For example specific measures may show a decrease in synchrony in the minutes to hours preceding a seizure {Le Van Quyen, 2001 #3530} or a spatial decorrelation during the low voltage fast activity that is seen at the beginning of certain seizures {Wendling,

2003 #3728} or changes in the degree of synchronization as recorded with MEG for many different types of seizures {Garcia Dominguez, 2005 #3725}. To be sure, there are many examples of analysis which show higher macroscale synchronization during seizures or at rest in the seizure focus. But, the aforementioned studies (and many others) point out that the notion of hypersynchrony is certainly misleading in its most pure form.

Furthermore, these and other studies also clearly demonstrate that the degree of synchrony or desynchrony is dynamic during the seizure. Using functional network measures based on correlation, for example, our group has observed a sequence of mildly increased synchronization at the start of the seizures, followed by desynchronization in the middle of the seizure only to see truly heightened synchronization at the end of the event {Kramer, 2010 #4548}. Similar results have been observed using other methods of measuring coupled activity {Schindler, 2007 #3847; Schindler, 2008 #4620}.

Greatest synchrony in self-terminating seizures may be present at the end of the event.

In fact, the different methods for measuring or describing synchrony seem to demonstrate that it is at the end of a typical focal seizure that generalizes that synchrony at both the scale of individual action potentials and local field potentials becomes most synchronous. As mentioned, in examining seizure networks with either eigenvalue decomposition {Schindler, 2008 #4620} or correlation measures {Kramer, 2010 #4548} it is just before the seizure terminates that synchrony appears to be greatest. The same is true at the level of the single neuron {Truccolo, 2011 #4595}. This has led to the hypothesis that seizure termination that occurs normally is the result of this truly hypersynchronous activity. In cases of status (albeit few that they are), the dynamical changes presumably essential for seizure termination do not appear to be present and, perhaps as a result, the seizure is unable to cross a critical transition to post-ictal behavior {Kramer, 2012 #4807}.

Implications for understanding and treating status epilepticus

The vast majority of these studies exploring the true role of synchrony / desynchrony in the initiation, propagation and termination of seizures have been done with respect to fo-

cal, self-terminating seizures. Little of the work has directly explored the neurophysiology of status epilepticus per se. Yet, it is likely that the dynamics present at both the micro and macrophysiological levels are at least similar. Perhaps not all of the now classical phases of status {Treiman, 1990 #4947} show the same degree of synchrony or desynchrony that is seen in a single seizure but the possibility that a failure to reach high enough synchrony may prevent the seizure from terminating is certainly intriguing and may provide an entirely novel approach to trying to prevent status from evolving or in shifting a patient from the status state to a, presumably, more benign post-ictal state.

Acknowledgements:

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IL9

TITLE: NEUROGENESIS AND NEURONAL REGENERATION IN STATUS EPILEPTICUS

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Summary

Neurogenesis in the adult central nervous system has been well documented in several mammals including humans. By now, a plethora of data has been generated with the aim to understand the molecular and cellular events directing neurogenesis providing the basis for modulation of neurogenesis for therapeutic purposes, in particular in

neurodegenerative diseases. Here, we review the current knowledge on neurogenesis, in particular in the frame of epilepsy, since seizures have massive effects on neurogenesis. Vice versa, some studies suggested that aberrant neurogenesis might contribute to the development or manifestation of epilepsy and, moreover, chronic inhibition of neurogenesis in epilepsy might contribute to comorbidities of epilepsy such as cognitive deficits. Thus, a better understanding of neurogenesis in the context of epilepsy is still required for future therapeutic purposes.

Adult neurogenesis

While neurogenesis, i.e. the generation of new neurons in the adult central nervous system has been documented in several mammalian species already in the mid 1960s (Altman and Das 1965), the real awareness for neurogenesis in the adult brain arose following the findings that this process also takes place in the adult, even elderly, human brain (Eriksson, et al. 1998). Neurogenesis occurs predominantly in two brain regions, the subgranular zone (SGZ) of the dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles. While SGZ-derived newly born neurons stay within the DG of the hippocampal formation and functionally integrate into the preexisting neuronal network, SVZ-derived immature neurons migrate along the rostral migratory stream into the olfactory bulb, where they functionally integrate and acquire electrophysiological characteristics of mature DG granule cells (Carleton, et al. 2003, van Praag, et al. 2002). Adult hippocampal neurogenesis has been shown to be relevant for learning and memory and vice versa (Kempermann 2002). Moreover, defects in neurogenesis might contribute to psychiatric disorders such as depression, anxiety and schizophrenia (Sah, et al. 2012). While a lot of knowledge on neurogenesis has been created in animal models, the functional relevance of neurogenesis in the adult human brain and the contribution to neurological and psychiatric diseases is still of hypothetical nature. At present, progress in this area is primarily limited by the lack of methods to image adult neurogenesis in the human brain. Nevertheless, studies on material derived from hippocampal resections along the course of an anti-epileptic treatment suggested a role of hippocampal neurogenesis in cognition (Coras, et al. 2010).

Adult neurogenesis and epilepsy

It is well established that in animal models of temporal lobe epilepsy prolonged seizures dramatically elevate the levels of SVZ- as well as hippocampal neurogenesis, at least transiently over a period of several weeks (Parent, et al. 1997). Here, neurogenesis is quantitatively enhanced at the level of progenitor proliferation as well as accelerated at the level of maturation and integration of the newly generated neurons. The initial rise in neurogenesis is followed by a long-lasting low level of neurogenesis (Hattiangady, et al. 2004). For example, cell proliferation is reduced in the hippocampus of children with frequent seizures (Mathern, et al. 2002).

Besides the quantitative changes in neurogenesis after epilepsy, major qualitative alterations, in particular at the level of spatial integration of new neurons have been noticed. Typically, newly generated neurons in the adult hippocampus migrate only a short distance into the granule cell layer, where they integrate. Surprisingly, after seizure, new neurons migrate either the opposite direction into the hilus or all through the granular layer into the molecular layer (Parent, et al. 2006). The molecular reasons for the displacement of newly generated neurons are unknown at present. Nevertheless, their highly excitability, their synaptic input from mossy fibers and their little inhibitory input suggests a critical role of displaced new neurons in the manifestation of epilepsy. Thus, seizure-induced neurogenesis might contribute to the formation of an epileptic hippocampus.

Another well-described qualitative feature of neurogenesis in epilepsy is the persistence of hilar basal dendrites. These basal dendrites are typical for immature hippocampal neurons, which in comparison to mature neurons are known to be hyperexcitable. Therefore, an attractive hypothesis might be that in epilepsy some of the newly generated neurons remain highly excitable for a protracted period of time and thus contribute to the manifestation of epilepsy (Ribak, et al. 2000).

Newly generated DG neurons, as well as their mature counterparts, extend their axon along the mossy fiber pathway into the CA3 region of the hippocampus. While mossy fiber sprouting after epilepsy is a well-known feature since decades, it became only recently clear that apparently only the new neurons respond to epilepsy with axonal sprouting. Moreover, such axons synapse on the displaced hilar neurons (Pierce, et al. 2007). These data

suggest that other mechanisms in addition to mossy fiber sprouting might contribute to enhanced hippocampal excitability during epileptogenesis.

Does neurogenesis contribute to comorbidities of epilepsy?

Although intriguing, it is difficult at present to assign a causal role of seizure-induced neurogenesis to the manifestation of epilepsy. However, the reduced levels of neurogenesis in chronic epilepsy might have a strong contribution to cognitive deficits and mood disorders such as depression associated with epilepsy. Adult neurogenesis has a key role in learning and memory formation and deficits of neurogenesis are associated with cognitive dysfunction, depression and anxiety. Neurogenesis-associated cognitive deficits in epilepsy might arise at different levels. First, the low rate of neurogenesis in chronic epilepsy might reduce the hippocampal network's ability for learning and memory formation. Second, ectopically (hilar) displaced neurons may disturb normal network function. Thus, a biphasic modulation of neurogenesis, i.e. inhibition of seizure-induced neurogenesis during the early phase and a stimulation of neurogenesis in the chronic phase might be an interesting therapeutic concept for the future treatment of cognitive disabilities in epilepsy.

Acknowledgements

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IL10

TITLE: GENE THERAPY IN STATUS EPILEPTICUS

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Abstract:

Gene therapy in human disease has expanded rapidly in recent years with the development of safer and more effective viral vectors, and presents a novel approach to the treatment of epilepsy. Studies in animal models have demonstrated that over expression of inhibitory peptides can modify seizure threshold, prevent the development of epilepsy and modify established epilepsy. More recently, there has been a flurry of studies using optogenetics in which light activated channels expressed in neurons can transiently change neuronal excitability on exposure to light, enabling the development of closed loop systems to detect and stop seizure activity.

The treatment of status epilepticus presents its own challenges. Because of both the delay in gene expression following transfection and also the necessity of using focal transfection, there are a limited number of situations in which gene therapy can be used in status epilepticus. One such condition is *epilepsia partialis continua* (EPC). We have used gene therapy in a model of EPC and have shown that we can "cure" the condition.

Recent evidence, suggesting that gene therapy targeting subcortical regions can modify generalized or more diffuse epilepsies, indicates that the range of situations in status epilepticus in which gene therapy could be used may expand.

Text:

The initial concept of gene therapy involved the replacement of a defective gene, using active or inactive viruses or virus-like particles carrying the "healthy" DNA (Friedmann & Roblin, 1972). There are very few genetic conditions

for which such an approach was considered suitable, and deaths from the use of pathogenic viral vectors (in particular adenovirus) stifled early research (Romano, 2006). In the last decade, gene therapy has undergone a resurgence, largely as a result of the development of effective and safe means of transfecting cells. To date, there have been over 1800 clinical trials approved for gene therapy (Ginn et al., 2013), and such therapy has expanded from replacing defective genes to overexpressing or "knocking down" healthy genes in order to treat disease.

Gene therapy in epilepsy

Gene therapy in epilepsy is still in its infancy. Initial studies overexpressing inhibitory peptides such as galanin or NPY were shown to increase seizure threshold or to modify the development of epilepsy (Haberman et al., 2003; Noè et al., 2008). A decrease in galanin was proposed to be a mechanism by which seizure activity progressed to status epilepticus; administering galanin to the hippocampus prevented such a progression from occurring. Decreases in adenosine or its receptors have also been proposed to be a mechanism leading to the progression from seizures to status epilepticus (Mazarati et al., 1998). Loss of adenosinergic mechanisms has also been shown to be important for the progression to status epilepticus (Young & Dragunow, 1994; Hamil et al., 2012). Although gene therapy resulting in increased adenosine release has not yet been used, a similar approach in which stem cells are genetically engineered to release adenosine has met with some success in treating seizures (Boison, 2009).

There is growing evidence that such approaches may prevent the development of epilepsy and can also be used to treat established epilepsy, but gene therapy to treat status epilepticus brings with it particular hurdles. Foremost amongst these is the time over which gene expression occurs. Gene expression using viral vectors takes days to weeks. This is completely at odds with the rapid time scale over which emergency treatment of status epilepticus takes place. Furthermore, gene therapy is usually accomplished either *ex vivo* in which case cells are modified and then placed *in vivo*, or by focal application of a vector *in vivo*. Both of these approaches use focal treatment, and would therefore be ideally aimed at a focal status epilepticus. Gene therapy would ideally treat a chronic focal status epilepticus such as *epilepsia partialis continua* (Wykes et al., 2012). *Epilepsia partialis continua* (EPC) is chronic, drug-

resistant and usually affects eloquent cortex(Cockerell et al., 1996), making the risks of surgery high with a high chance of a focal deficit.

Gene therapy in Epilepsia Partialis Continua

We developed a rodent model of EPC by injecting tetanus toxin into the motor cortex(Nilsen et al., 2005). Tetanus toxin decreases neurotransmitter release and predominantly affects inhibitory, GABAergic synapses. The loss of inhibition results in focal seizure activity, which progresses over about 3-7 days. After time, the tetanus toxin is cleared but the seizure activity continues. Neurophysiological studies demonstrate that neuronal excitability increases after injection of tetanus toxin and this increased excitability endures(Wykes et al., 2012). The clinical phenotype consists of tonic posturing of the limb (similar to that observed in human epilepsy partialis continua), but clonic movements are not so obvious. There is a dose effect, such that at high dose of tetanus toxin, there is marked limb posturing, weight loss and occasional sudden death associated with a more severe seizure. Lower tetanus doses result in almost continuous EEG seizure activity but with much subtler clinical manifestations, and far fewer adverse effects(Wykes et al., 2012). We continuously monitored seizure activity for weeks using a wireless transmitter sampling at 512 Hz, permitting monitoring of activity up to 160 Hz(Chang et al., 2011).

We used three different strategies to treat this model of status epilepticus(Wykes et al., 2012). In the first we used an optogenetic strategy to overexpress the light-activated chloride-pump, halorhodopsin, in pyramidal cells. Such a strategy had been previously used in ex vivo tissue and cell cultures(Tønnesen et al., 2009). In that study, activating halorhodopsin reduced pyramidal cell excitability and terminated stimulation induced epileptiform bursts and seizure-like activity induced with the GABA(A) receptor antagonist picrotoxin. We extended this method to our in vivo model of EPC. The second strategy was to determine if permanently reducing the excitability of a subset of pyramidal cells in the focus during the epileptogenic process prevented the occurrence or severity of seizures. This approach is not so relevant to the clinical problem (i.e. treatment of established EPC). Therefore, we pursued a third strategy of using the same method of reducing the excitability of a subset of pyramidal cells in the focus in previously established epilepsy.

There are a number of different viral vectors for efficient transfections of neurons(Warnock et al., 2011). Adeno-associated viral vectors (AAVs) are modified adeno-associated viruses. Adeno-associated viruses are small, non-pathogenic, DNA viruses which insert into the genome at a specific location. AAVs are modified so that they do not insert but form episomes, avoiding the putative problems of insertional mutagenesis. AAVs have a predilection for neurons. Two main handicaps face AAV therapy; the first is that they can only be used to insert a limited amount of genetic material (i.e. small genes), and the second is that AAVs are immunogenic and their usefulness can be restricted by the presence of neutralizing antibodies (this is less of a problem with injection into the immune privileged CNS). There have also been some concerns that gene expression may be time-limited. An alternative vector is a lentivirus vector. Lentiviruses are retroviruses that can transfect non-dividing cells. They contain RNA which is reversed transcribed and inserted into the genome. Although insertional mutagenesis is a concern, increasing numbers of studies have revealed the risks are vanishingly low. The lentivirus is modified so that it is non-replicating, and more recent modifications render the virus self-inactivating, so that active infection cannot take place. The advantages of lentivirus vectors are: persistent transfection, and the ability to transfect a larger amount of DNA. Lentivirus vectors also diffuse less far than AAVs. By selecting the appropriate gene promoter, it is possible to restrict gene expression to particular subsets of neurons (e.g. pyramidal cells). We used lentiviral vectors to transfect predominantly pyramidal neurons with either halorhodopsin or the potassium channel Kv1.1(Wykes et al., 2012). We had previously shown that Kv1.1 overexpression in neurons in culture is an effective strategy for reducing neuronal excitability. Lentiviral transfection in vivo resulted in persistent gene expression for at least 6 months.

More than a week after tetanus toxin injection into the motor cortex, when seizure activity was well established, we were able to suppress this activity using light activation of halorhodopsin transfected into pyramidal cells in the focus. This provides a method of regulating seizure activity but is probably more relevant to a means of terminating or preventing individual seizures using a closed loop system. Such an approach has been successfully used in a model of temporal lobe epilepsy by reducing the excitability of

pyramidal cells using halorhodopsin or by increasing the activity of interneurons selectively expressing the light-activated channel, channelrhodopsin(Krook-Magnuson et al., 2013). Such an approach is unlikely to be used in EPC in which a more permanent reduction of neuronal excitability is required.

Using focal overexpression of Kv1.1, we were able both to prevent the development of EPC and also, more importantly, to stop seizure activity after it had become established. Thus, we demonstrated a potential treatment for EPC. Importantly, our strategy reduced the excitability of pyramidal neurons but permitted normal function. There was, therefore, no adverse effect (e.g. limb weakness) of our treatment.

Could such an approach be expanded to other forms of refractory status epilepticus? The observations that optogenetic reduction of excitability of thalamic neurons using halorhodopsin can interrupt more generalised seizure activity(Paz et al., 2013) and that genetic manipulation of thalamic delta GABA(A) receptor-subunit expression using oligodendronucleotides can inhibit generalized spike-wave activity (Cope et al., 2009) indicate that gene therapy manipulation of subcortical structures may be an approach that could be used to target generalized refractory status epilepticus.

Conclusion

In conclusion, we have shown how different gene therapy approaches could be used to treat a chronic, refractory, focal status epilepticus. At present, our methods of gene transfection mean that such approaches are only suitable for refractory or chronic status epilepticus. However, targeting subcortical structures may expand the use of this treatment from very focal status epilepticus to more diffuse or generalized refractory status epilepticus.

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IL11

TITLE: AUTOIMMUNITY, SEIZURES, AND STATUS EPILEPTICUS

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Abstract:
The recent discovery of a category of autoimmune encephalitis associated with antibodies against neuronal cell-surface and synaptic proteins has renewed interest for autoimmune causes of epilepsy. The identification of autoimmune encephalitis has changed paradigms in the diagnosis and management of several novel and treatable syndromes that occur with seizures and status epilepticus previously attributed to viral or idiopathic etiologies. This review focuses on the novel group of autoimmune encephalitis and also discusses some classical paraneoplastic syndromes that constitute another group of autoimmune disorders that may result in seizures.

Text:
The autoimmune encephalitides that occur with seizures and status epilepticus can be divided into limbic and diffuse encephalitis, and may have a paraneoplastic or non-paraneoplastic etiology. Table 1 shows the most frequent autoantigens of these disorders grouped according their clinical relevance, likelihood of being paraneoplastic, location of the antigen, and response to immunotherapy (Lancaster & Dalmau, 2012).

TABLE 1: Autoantigens of encephalitis associated with seizures and status epilepticus

	Syndrome	Clinical significance	Location of epitopes	Frequency of systemic tumor	Response to immunotherapy
INTRACELLULAR PARANEOPLASTIC ANTIGENS					
Hu	Limbic, cortical encephalitis	High	Intracellular	>90%	Infrequent
CV2/CRMP5	Limbic encephalitis	High	Intracellular	>90%	Infrequent
Ma2	Limbic, diencephalon, upper brainstem encephalitis	High	Intracellular	>90%	Moderate
Amphiphysin	Limbic encephalitis, Stiff person-syndrome	High	Intracellular	>90%	Poor
CELL-SURFACE OR SYNAPTIC ANTIGENS					
NMDAR (NR1)	Psychosis, dyskinesias, autonomic instability, hypoventilation	High	Extracellular	Varies with age, gender and ethnicity	Frequent
LGI1	Limbic encephalitis, tonic seizures (faciobrachial dystonic seizures)	High	Extracellular	<10%	Frequent
Caspr2	Encephalitis, Morvan's syndrome, neuromyotonia	High	Extracellular	~40%	Frequent
GABA(B) receptor	Limbic encephalitis, early and prominent seizures	High	Extracellular	70%	Frequent
AMPA (GluR1/2)	Limbic encephalitis (frequent relapses)	High	Extracellular	70%	Frequent
mGluR5	Limbic encephalitis	High	Extracellular	>90%	Frequent
DPPX(subunit of Kv4.2 K+ channel)	Encephalitis, frequent relapses	N/A	Extracellular	N/A	Frequent
GAD	Limbic encephalitis, refractory epilepsy, stiff-person syndrome, cerebellar dysfunction	High (may occur with cell-surface antibodies)	Intracellular	<5%	Moderate
ANTIGENS OF UNCLEAR CLINICAL SIGNIFICANCE					
AMPA (GluR3)	Rasmussen's encephalitis	Unclear	Extracellular?	No tumor association	Infrequent
VGKC-protein complex antibodies different from LGI1/Caspr2	Multiple neurological symptoms, from neuropathy to encephalitis with seizures	Low	?	?	Variable
Thyroid peroxidase	Hashimoto's encephalitis	Low	Intracellular	No tumor association	Frequent

CRMP5: Collapsin response mediator protein-5; GAD: glutamic acid decarboxylase; NMDAR: N-methyl-D-Aspartate receptor, LGI1: leucine rich glioma inactivated protein 1, Caspr2: Contactin-associated protein-like 2, GABA(B) receptor: g-Aminobutyric acid-B receptor, AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, mGluR5: metabotropic glutamate receptor 5, DPPX: dipeptidyl-peptidase-like protein-6
N/A: not available, too early to assess significance.

Encephalitis and antibodies against intracellular paraneoplastic antigens
Although most of the immune responses shown in Table 1 can associate with an underlying tumor, there are some that almost always are paraneoplastic (e.g., >90% of patients have cancer). Any paraneoplastic encephalitis involving the limbic system or cerebral cortex may result in seizures and status epilepticus. The associated antibodies include, Hu, Ma2, CV2/CRMP5, and amphiphysin. While there is strong evidence that the first three immune res-

ponses are mediated by cytotoxic T-cells responses, there are studies indicating that amphiphysin antibodies may be directly pathogenic (Geis et al., 2010). Of these 4 immune responses, anti-Hu antibodies are those most frequently described with seizures, epilepsy partialis continua, and status epilepticus. The underlying tumors are small-cell lung cancer (all antibodies), germ-cell tumors of the testis (Ma2), and thymoma (CRMP5). Most of these disorders show limited response to immunotherapy.

Encephalitis and antibodies against cell-surface or synaptic antigens

A frequent feature of these immune responses (except for GAD antibodies) is that the autoantigens are extracellular and therefore accessible to circulating antibodies. In some patients the presence of an underlying tumor that expresses synaptic proteins, or a previous viral infection appear to be involved in triggering the immune response, but in many instances no trigger is identified. The spectrum of symptoms, frequency of associated tumors, mechanisms of disease, treatment, and outcome varies according to the target antigen. Using in vitro or in vivo models, the antibodies of all the disorders studied to date (NMDAR, AMPAR, mGluR5, LGI1) have direct structural or functional effects on the target antigen. On the other hand, it is unclear whether antibodies against GAD are able to penetrate the cell and result in neuronal dysfunction as shown in some experimental models. The poor response of anti-GAD associated seizures or encephalitis to immunotherapies directed at depleting the antibodies or antibody-producing cells, compared with the more favorable response of disorders related to cell-surface antigens, suggest that anti-GAD cytotoxic T-cell mechanisms are also pathogenically involved (Lancaster & Dalmau, 2012).

Antibodies to the NR1 subunit of the NMDAR associate with a syndrome different from limbic encephalitis, that characteristically occurs with behavioral change or psychosis and usually progresses to a decline of the level of consciousness, catatonia, dyskinesias, autonomic instability, and frequent hypoventilation (Titulaer et al., 2013). Seventy percent of the patients develop seizures and/or status epilepticus. About 40% of the patients are younger than 18 years; their clinical picture does not differ significantly from that of adults, but approximately 30% of children and teenagers present initially with seizures or sta-

tus epilepticus. The combination of epileptic seizures and complex, elaborate orofacial and limb movements without EEG correlates complicates the clinical recognition of the seizures. About 50% of women older than 12 years have an underlying ovarian teratoma. Younger patients and men rarely have tumors. Despite the severity and duration of the disorder, patients often respond to immunotherapy and when appropriate tumor removal; some patients improve spontaneously. The recovery is slow and may take many months. After recovery, most patients remain free of seizures.

Antibodies to LGI1 associate with a form of limbic encephalitis that usually affects older individuals causing memory deficits and several types of seizures, including myoclonic-like or tonic seizures (Lai et al., 2010). The recognition of the seizures (named by some as facio-brachial-dystonic seizures) as an autoimmune disorder should lead to prompt immunotherapy that may prevent symptom progression to severe limbic encephalitis (Andrade et al., 2011; Irani et al., 2011). Interestingly, LGI1 is a secreted protein that forms a trans-synaptic complex that interacts with the pre-synaptic VGKC through ADAM23. LGI1 null-mice die within the first 2 weeks of life due to tonic seizures. Mutations of LGI1 result in autosomal dominant temporal lobe epilepsy, a benign condition in humans. About 60% of patients with antibodies against LGI1 have hyponatremia.

Antibodies to Caspr2 may occur in patients with Morvan's syndrome, diffuse encephalitis, and less frequently in cases of classical limbic encephalitis or neuro-myotonia (Irani et al., 2010; Lancaster et al., 2011b). In patients with Morvan's syndrome the association with thymoma, seems to be more frequent than in patients with other symptoms, who rarely have tumors.

Antibodies to GABA(B) receptor associate with limbic encephalitis with early and prominent seizures (Lancaster et al., 2010). These antibodies occur in most patients with limbic encephalitis and SCLC who are Hu antibody negative. While patients with Hu antibodies rarely have substantial responses to immunotherapy, those with GABA(B) receptor antibodies usually respond to steroids, IVIg and other immunotherapies.

Antibodies to AMPAR also associate with classical limbic encephalitis that is responsive to immunotherapy (Lai et al., 2009). As with the other cell-surface autoantigens, this disorder can occur with or without a tumor association. The tumors more frequently involved are cancer of the breast, lung and thymus. Patients with this disorder often have clinical relapses and may harbor other auto-antibodies (TPO, N-type VGCC), suggesting a tendency to autoimmunity.

Antibodies to mGluR5 have been reported in a few patients with limbic encephalitis and Hodgkin's lymphoma (Ophelia syndrome) (Lancaster et al., 2011a). Although the disorder is rare, the consistency of the presence of these antibodies suggests they are the dominant etiology of this syndrome. Patients respond dramatically to treatment of the tumor and immunotherapy, such as steroids and IVIg.

Antibodies to DPPX have recently been described in a few patients with encephalitis characterized by symptoms of CNS hyperexcitability, including agitation, myoclonus, tremor and seizures (Boronat et al., 2013). At symptom presentation patients often have diarrhea or gastrointestinal dysfunction, which may be accompanied by substantial weight loss leading to suspect Whipple's disease or a paraneoplastic disorder. The disorder usually responds to steroids and other immunosuppressants with a tendency to relapse when steroids are discontinued.

Antibodies to GAD usually associate with non-paraneoplastic stiff-person syndrome and cerebellar dysfunction, but there are an increasing number of reports showing that these antibodies also associate with subtypes of limbic encephalitis and refractory epilepsy (Malter et al., 2010). The response to immunotherapy is usually poor.

Encephalitis and antibodies against antigens of unclear clinical significance

While antibodies to well-defined antigens, such as the NR1 subunit of the NMDAR, LGI1, Caspr2, AMPAR, GABA(B) receptor, mGluR5, or GAD specifically associate with a limited set of syndromes and thus are useful in diagnostic testing, the clinical significance of other antibodies is unclear. For example, most patients with Rasmussen's encephalitis do not have antibodies against GluR3 and therefore the utility of these antibodies as a diagnostic test and their po-

tential role in the pathogenesis of the disorder are unclear. Similarly, the significance of "VGKC-complex antibodies different from LGI1 or Caspr2" is at this time uncertain; the identity and location of the antigens are unknown, these antibodies occur in association with symptoms that vary widely from patient to patient, and responses to immunotherapy are variable.

A substantial number of patients with disorders currently known to be associated with relevant cell surface or synaptic proteins are misdiagnosed with Hashimoto's encephalitis due to the limited diagnostic criteria of this disorder (e.g., encephalopathy associated with TPO antibodies that respond to steroids). However, TPO antibodies are encountered in 10% of normal individuals, including children and, as shown in this review, many other disorders associated to well-defined cell surface antigens or inflammatory disorders of unknown etiology can also respond to steroids.

Common features of autoimmune encephalitis with cell-surface or synaptic antigens

Patients of any age who develop rapidly progressing symptoms presenting or accompanied by seizures or status epilepticus, usually including behavioral change and memory deficits, with CSF lymphocytic pleocytosis and/or oligoclonal bands of unclear etiology, EEG findings of encephalopathy and/or epileptic activity, should have serum and CSF studied for antibodies. About 30% of patients with anti-NMDAR encephalitis develop a characteristic EEG pattern named extreme delta brush. In some forms of encephalitis [LGI1, AMPAR, GABA(B) receptor] the MRI often shows increased T2-FLAIR signal in medial temporal lobes, but in other disorders the MRI is often normal or with mild transient cortical-subcortical changes. The diagnosis is established by demonstrating antibodies in serum and CSF, keeping in mind that sometimes antibodies are only detectable in CSF. Detection of antibodies should prompt treatment with immunotherapy, such as steroids, IVIg or plasma exchange. If these fail, the use of second line therapies, such as rituximab and cyclophosphamide are often effective. The process of recovery can be very slow, resulting in admission to hospitals and rehabilitation centers for many months. The reasons for this remain unclear, but many patients have high levels of CSF antibodies for long time, the effects of antibodies on neuronal circuitry are likely prominent, and there is evidence that for some of

these disorders the antibodies are produced in the CNS by plasma cells that are long-lived and difficult to eliminate.

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IL12

TITLE: STATUS EPILEPTICUS IN SUB-SAHARAN AFRICA: NEW FINDINGS

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Abstract:

Status epilepticus (SE) is common in sub-Saharan Africa, particularly in children. Most cases in children are caused by infections, particularly malaria in endemic areas. The outcome is worse than in the West, probably because of delays in initiating treatment, lack of skills and facilities for the management of SE. However some of the causes e.g. falciparum malaria offer challenges in the diagnosis and the treatment of SE. Exposure to parasites such as *Toxocara* species increases the risk of SE. Much of the SE in Africa could be prevented by reducing the incidence of infections. The outcome could be improved through education, development of locally appropriate guidelines and provision of appropriate facilities.

Text:

Status epilepticus (SE) occurs either in the context of febrile seizures, acute symptomatic seizures or as a complication of epilepsy. In sub-Saharan Africa (SSA), acute symptomatic seizures and epilepsy are more common than in the West; and in each of these conditions, SE appears to be more frequent, although there is little data. Infections are important causes. This paper briefly reviews recent studies on status epilepticus in SSA, with a particular emphasis on the role of parasitic infections.

Burden of epilepsy in SSA

The prevalence of epilepsy in SSA is twice that of Euro-

pe, Asia and North America (Ngugi et al. 2010; Preux and Druet-Cabanac 2005). The larger burden is thought to be caused by an increase in the incidence of risk factors (Newton and Garcia 2012). A recent study of five sites across Africa has identified neonatal insults and parasitic infections as major risk factors for epilepsy on this continent (Ngugi et al. 2013), and these factors may be responsible for a third of the cases in children and adults respectively.

Burden of status epilepticus

In the multi-centre cross-sectional study in 586,607 people (Ngugi, et al. 2013) in SSA 36% of the people with active convulsive epilepsy had a history of status epilepticus (Kariuki et al. in preparation). The frequency of SE in the people with epilepsy differed significantly across the sites, although in some sites the recall and/or documentation of SE was poor. In this study 69% of the SE was reported to be associated with a febrile illness and 88% of patients occurred in established epilepsy (Kariuki et al. in preparation). Status epilepticus was significantly more common in generalized epilepsy than focal epilepsy.

There are few epidemiological studies of status epilepticus in SSA. One study in Kilifi on the coast of Kenya, recorded a minimum incidence of convulsive SE (CSE) as 35/100,000/year in children (0-13 years) based upon hospital admissions (Sadarangani et al. 2008), which is 2-8 times (depending upon the definition used) to that found in London (Chin et al. 2006). This rate is the minimum incidence since a proportion of children will die in status epilepticus before reaching hospital, and others will be treated in private clinics. In this study, 15% died in hospital, but 21% died after being discharged from hospital (Sadarangani et al. 2008), often from another episode of status epilepticus (Prins et al. in preparation). Seventy-one percent of the cases of SE were caused by infections, mainly falciparum malaria (58%), but only 3% were previous cases of epilepsy.

In a more recent study of active convulsive epilepsy in adults and children living in Kilifi, Kenya, only 40% of patients who reported SE in the community was admitted to Kilifi District Hospital (Kariuki et al. in preparation). About 88% of the reported SE occurred with epilepsy, and 58% of SE was associated with a febrile illness. Seizures in SE occurred significantly earlier in those with a history of feb-

rile seizures compared to those without, and later in those with epilepsy compared to those without. Focal seizures and focal electroencephalographic features were present in 54% and 36% of those with SE, respectively. Important risk factors were perinatal complications, parasitic infections, history of seizures in the family, neurological impairments and visit to traditional healers. In particular, previous exposure to toxocara species increased the risk of SE.

In a study in Ugandan children admitted with acute seizures, 25% of children did not have their seizures stopped within 10 minutes with either rectal diazepam or buccal midazolam (Mpimbaza et al. 2009). Focal seizures, cerebral malaria and blood glucose ≥ 11 mmol/l at presentation were independent predictors of treatment failure defined as seizures lasting >10 minutes or recurrence within one hour of treatment.

Malaria and status epilepticus

In malaria endemic areas, falciparum malaria is the most common cause of status epilepticus, particularly in the context of acute symptomatic seizures in children. Attribution of SE to malaria in endemic areas is problematic, since up to 70% of asymptomatic children in the community will have a peripheral parasitaemia. Furthermore, there is debate as to whether children with malaria have febrile seizures or acute symptomatic seizures, since malaria is the most common cause of febrile illness in children aged 6 months to 6 years in malaria endemic areas.

In Kilifi, we have calculated the malaria attributable fraction using logistic regression to estimate the proportion of CSE that can be attributed to malaria (Kariuki et al. 2011). In these models, we estimated that 93.6% (95% confidence interval 90.9–95.9%) of children, who were admitted to hospital with convulsive SE and falciparum parasitaemia, could be attributed to malaria. This estimation was confirmed by the monitoring the reduction in the incidence of CSE attributable to malaria with the decrease in the incidence in malaria that occurred in this area over a 7-year period.

The pathological hallmark of falciparum malaria is the sequestration of parasitized red blood cells in the microvasculature of the deep organs, particularly the brain. Although the parasites are rarely seen within the parenchyma

of the brain, the sequestration causes a wide range of inflammatory and metabolic perturbations which affect the brain function. Seizures associated with malaria are different from the febrile seizures seen in non-malaria endemic areas, in that the proportion of focal seizures, repetitive seizures and prolonged seizures are much more common in the malaria associated seizures than febrile seizures (Kariuki, et al. 1996).

Treatment of status epilepticus

The mortality of SE is higher in SSA than in the resource rich countries. This may be caused by the delay in presenting to hospital, poor management of SE in hospital and underlying aetiology (Wilmshurst et al. 2011). Patients who have SE may be taken to traditional healers first, and/or their presentation to hospitals may be delayed even further by lack of infra-structure or transport. Many hospitals in SSA lack facilities such as infusion pumps, ventilators and staff to manage SE appropriately (Wilmshurst et al. 2011).

The pharmacological management of SE is problematic in SSA. The anti-epileptic drugs available for the treatment of SE are limited in many African hospitals, mainly to diazepam and phenobarbital. Furthermore the supply of parenteral phenobarbital has been erratic in some countries (Wilmshurst and Newton 2005), and this lack of supply has initiated studies or the administration of oral phenobarbital in the management of SE (Wilmshurst et al. 2010). Also some of the recommended anti-epileptic drugs appear to be less effective in SSA than elsewhere (Ikumi et al. in preparation). This may occur as result of the prolonged duration of seizures before treatment is started, or the cause of the seizures. Thus seizures caused by falciparum malaria appear to be resistant to diazepam, possible due to decrease in the binding capacity of Gamma-aminobutyric acid-A receptors in malaria (Ikumi et al. 2008). Since intravenous access is often difficult in low-resource settings, alternative routes of administration have been examined. Thus intra-nasally lorazepam is more effective than intramuscular paraldehyde (Ahmad et al. 2006) in Malawian children, and buccal midazolam was more effective than rectal diazepam in Ugandan children without malaria (Mpimbaza et al. 2008).

Conclusion

Status epilepticus is common in SSA, particularly in children in whom it often caused by infections. The outcome is worse, possibly due to delays in treatment and lack of skills and facilities. Falciparum malaria is important cause of SE in endemic areas, but presents unique problems in defining malaria associated SE and treatment.

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TITLE: FIRES AND IHHE – DELINEATION OF THE SYNDROMES

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Abstract:

IHHE and FIRES are rare epileptic syndromes that are characterized by the occurrence of status epilepticus in a previously healthy child during or closely after fever. In both syndromes, there is no evidence of central nervous system infection (encephalitis) and the etiology remains unclear. Treatment is disappointing particularly in FIRES except for a response to KD in half of patients. In IHHS, children develop hemispheric brain atrophy with contralateral hemiplegia, epilepsy and a variable degree of cognitive deficit. Patients with FIRES develop refractory epilepsy with severe cognitive deficit affecting the temporal and frontal lobes functions. The role of inflammation is hypothesized with a vicious circle involving inflammation and seizure activity facilitated by brain maturation putting them under the concept of “acute encephalopathy with inflammation-mediated status epilepticus”.

Text:

IHHE and FIRES are rare childhood epileptic syndromes. They are characterized by the occurrence of refractory status epilepticus during or after fever without evidence of central nervous system infection. Their incidence could be underestimated in the literature since there are no epidemiological studies considering these two entities. However, they are recognized worldwide and were both included in the last proposition for classification of the ILAE (Berg et al., 2010).

Idiopathic hemiconvulsion hemiplegia and epilepsy syndrome (IHHE):

Hemiconvulsion-hemiplegia epilepsy syndrome (HHE) is characterized by the combination of unilateral convulsive status epilepticus (SE), mainly clonic, followed by transient or permanent ipsilateral hemiplegia. It occurs in infants during the course of a non-specific febrile illness, mainly in the first two years of life and in any case before the age of four years (Gastaut et al., 1960). SE is usually long and might persist for hours if not treated. In order to differentiate this condition from the more common unilateral deficit after a “complex” febrile seizure, a minimum duration of hemiplegia of one week is required (Chauvel et al., 2005). In opposition to the sequence of stroke seizure where seizure occur several hours after onset of the motor deficit, in HHS, the seizure(s) itself generates brain edema cell death with motor defect and often later epilepsy as additional sequel. Several months following the status pharmacoresistant partial epileptic seizures recur (Gastaut et al., 1960). This sequence is stereotyped and HHS with or without Epilepsy (HHS±E) has been introduced as an epileptic syndrome in the first ILAE classification of epilepsies (1989) and was included among epilepsy syndromes and epilepsies in the recent report of the ILAE Taskforce on Classification and Terminology (Berg et al., 2010).

HHE was reported as “symptomatic” in many instances since it complicates the course of pre-existing brain disorder: i.e. Sturge-Weber disease, agenesis of the corpus callosum or tuberous sclerosis. However, many cases are idiopathic (IHHS) and occur in apparently healthy infants who exhibit neither clinical nor imaging evidence of pre-existing brain lesion. In addition to the role of fever, specific viruses have been advocated but are not found in the CSF. Moreover, CSF comprises neither pleiocytosis nor oligoclonal profile excluding an infection of the CNS. Three quarters of patients remain with epilepsy (Roger et al., 1982). IHHS was hypothesized to represent the end of the spectrum of febrile status epilepticus and that its incidence has decreased with the use of benzodiazepines as rescue therapy in long lasting FS. However, modern radiological series of febrile status might not support this hypothesis (Shinnar et al., 2012). Seizures start with rhythmic unilateral. They predominate on one side and last several hours, up to 24. Ictal EEG shows high amplitude 2-3 Hz rhythmic slow wave activity with low amplitude fast activity and rhythmic spikes contralateral to the predominating jerks (Chauvel et al., 2005). MRI shows

increased diffusion on one side mainly in the peri-sylvian and parieto-occipital areas followed by atrophy.

Febrile infection related epilepsy syndrome (FIRES):

Previously described as DESC (devastating epilepsy in school age children) (Mikaeloff et al., 2006), FIRES is characterized by the development of seizures in a healthy children during or a few days following non-specific febrile infection (Van Baalen et al., 2009). Seizures rapidly aggravate and turn to status epilepticus followed by pharmacoresistant epilepsy and cognition functions deficit (Mikaeloff et al., 2006, Van Baalen et al., 2009).

In almost half of patients, fever has disappeared when the first seizures occur. Seizures semiology points to a focal onset with lateral deviation of the head, chewing movements and some autonomous features suggesting a mesial temporal lobe involvement. Clonic jerks of the mouth extending to the limbs sign the opercular extension. Several seizures, up to 100 may occur each day rising from both hemispheres. The EEG between seizures shows slow waves over the whole brain that neurophysiologists tend to qualify as an “encephalitis” pattern (Mikaeloff et al., 2006, Van Baalen et al., 2010).

Investigations to search for some viral or autoimmunity contributions remain negative: there are a few cells in the CSF, polymerase chain reaction is negative and electrophoresis of CSF proteins shows no oligoclonal bands. VGCK, NMDAR, AMPAR and GABABR antibodies are negative and although some “neuroin” antibodies are reported in a few case reports, the cause or consequence role of these antibodies is not clear and this syndrome is considered as an encephalopathy rather than an encephalitis (Van Baalen et al., 2010, Nabbout et al., 2011).

Early magnetic resonance imaging (MRI) might be disappointing since at most bulging of the mesial temporal structures during the first weeks of the disease, with T2 hypersignal.

Status epilepticus persists usually whatever the conventional antiepileptic schedule and the use of general anaesthesia is not only disappointing but might be a negative cognitive prognosis factor (Kramer et al., 2011). Only Ketogenic diet showed an efficacy in almost half of patients when tried even late in the course of the disease (Nabbout et al., 2010, Kramer et al., 2011). In the most refractory cases, death may occur after 4-8 months of ongoing seizures and post-mortem examination performed in a few patients only revealed

cell loss with but no lymphocyte infiltration, adding to the concept of encephalopathy rather than encephalitis.

After several weeks or months, seizures finally decrease with progressive recovery of consciousness but patients are left with major cognitive deterioration and intractable. At that chronic stage, seizures tend to occur in clusters every 2-4 weeks and ictal EEG shows that they involve the same regions as during the status epilepticus. Cognitive functions are affected with a severe episodic memory, speech and frontal lobe functions deficit (Mikaeloff et al., 2006).

MRI after 6 months or more may show bilateral mesial temporal atrophy and T2 hypersignal in almost half of cases however, in all, positron emission tomography scan identified a very large area of hypometabolism involving bilaterally orbito-frontal and temporo-parieto regions, with a good correspondence to the specific cognitive troubles that each child exhibited (Mazzucca et al., 2011). Genes involved in epilepsy with fever sensitivity (SCN1A, PCDH19) or in refractory status epilepticus often initiated in the setting of febrile illness as in Alpers disease (POLG) did not show any mutation or rare copy number variations (Appenzeller et al., 2012).

Refractory status epilepticus following a common febrile infection in the absence of identified infectious agent is reported in few small series and case reports in the literature and we suggested with others (Nabbout et al., 2011, Kramer et al., 2011) that these entities with different names might share a common pathophysiology based on a vicious circle with inflammation inducing seizures evolving to status and status entertaining the inflammation process (Nabbout et al., 2011). We proposed to group these entities under the concept of acute “encephalopathy with inflammation-mediated status epilepticus” (Nabbout et al., 2011). This hypothesis questions the place of specific anti-inflammatory and immunomodulatory therapies in these devastating syndromes (Nabbout, 2012).

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IL14

TITLE: MULTIMODAL INVASIVE MONITORING IN STATUS EPILEPTICUS – WHAT IS THE EVIDENCE IT HAS A PLACE

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Abstract:

Underlying pathophysiological of status epilepticus (SE) mostly remain invisible to the clinician in the ICU setting. In animal studies associated hemodynamic and brain neurochemical changes have been well described. In the last decade, bedside invasive neuromonitoring techniques allow the assessments of changes in focal and global cerebral physiology associated with ictal activity on the tissue level in humans. Recent studies demonstrate, that laboratory research insufficiently replicates the complexity of the human condition. Here we summarize the current knowledge gained from human studies integrating cortical electrographic and brain tissue metabolic and hemodynamic information into the current pathophysiological concept of

SE in humans. With increasing experience gained by the use of extended neuromonitoring we are more and more able to understand associated hemodynamic and brain neurochemical changes in patients with SE. In future, this information can potentially provide integrated pathophysiological endpoints into SE treatment concepts.

Text:

Status epilepticus (SE) is accompanied by complex pathophysiological changes most of which are undetectable by standard clinical examination and imaging techniques alone that are currently employed in the ICU setting. Invasive neuromonitoring including intracortical and subdural electroencephalography, partial brain tissue oxygen tension ($P_{bt}O_2$), cerebral blood flow (CBF), and cerebral microdialysis allows assessments of changes in focal and global cerebral physiology associated with ictal activity. This information can potentially be combined with current techniques to provide integrated pathophysiological endpoints measured at the brain tissue into SE treatment concepts. There are no studies or clinical trials to support this approach but the following review will summarize the conceptual framework and supportive literature for this approach.

Surface EEG combined with invasive neuromonitoring.

Continuous scalp EEG monitoring is commonly used in comatose patients revealing a high incidence of NCSz and NCSE in medical and neurological/neurosurgical ICU patients. Few studies correlated surface EEG findings to intracranial measurements of brain physiology. Seizure associated brief episodes of brain tissue hypoxia have been known for many years from patients with temporal lobe epilepsy. Similarly, blood flow changes typically visualized using imaging techniques are used in clinical practice to characterize seizure onset. After TBI increases in intracranial pressure and brain chemistry (i.e., lactate pyruvate ratio) have been reported. Recently, one small study did not find an association of partial brain tissue hypoxia (based on nursing records of $P_{bt}O_2$ drops below 20mmHg) with scalp recorded nonconvulsive seizures (NCSz). However, the authors objective was to determine if $P_{bt}O_2$ measurements could be used to detect nonconvulsive seizures with adequate sensitivity and specificity to alert clinicians. Their study demonstrated both, that EEG is required to diagnose seizures and that interpreting multimodality mea-

surements requires access to high density, non-stationary monitoring data.

Intracortical mini depth electrode combined with invasive neuromonitoring.

In the ICU setting, surface EEG monitoring is commonly artifact contaminated which is a major obstacle for automated seizure detection. Recently, a new method of invasive EEG monitoring, a mini-depth electrode, was placed in the cortex of 16 patients with brain injury through a bur hole. Intracortical seizures were detected in 10 patients and only half had a surface (scalp EEG) correlate. The phenomenon of neurovascular coupling has been well described in animal studies and represents increased oxygen supply through cerebral blood flow augmentation to metabolically active neurons. A recent report using invasive neuromonitoring techniques in a patient with frequent seizures after cardiac arrest showed drops in $P_{bt}O_2$ despite increases in CBF associated with cortical electrographic seizures. This observation supports the notion that at times and possibly particularly in acutely brain injured patients the metabolic demand inflicted by the seizure activity outmatches the substrate supply via increased cerebral blood flow. In a study of 48 comatose SAH patients with surface and cortical EEG monitoring, compensatory mechanisms involving increased CBF were only observed in patients with scalp seizures with a delay of 10min while increases in mean arterial blood pressure leading to an increase in cerebral perfusion pressure were seen rapidly following seizure onset. These findings were most prominent for seizures detected not only on the depth electrode but also on the scalp, suggesting that the amount of involved brain tissue is important for this phenomenon in humans. Animal work further suggests that vasodilation may only be seen in actively seizing brain while surrounding brain tissue will have vasoconstriction. These observations however require a spatial resolution which will be difficult to achieve in humans with existing technology.

As mentioned above, compensatory vasodilatory mechanisms may still be insufficient especially in patients with brain injury where repetitive seizures, SE and cortical spreading depolarizations are common. The increased metabolic demand reflected in the cerebral metabolic rate of oxygen (CMRO₂) may result in an imbalance between energy supply and demand. Associated metabolic changes

of increased cerebral glutamate, glycerol, higher lactate/pyruvate ratio, and decreased cerebral glucose levels have been previously described in humans in both surface- and intracortical detected seizures using cerebral microdialysis. The sensitivity of this invasive method in detecting seizure/SE associated brain metabolic changes is currently limited by the sampling time of at least 20 minutes. In the line with that, profound metabolic changes were not observed in the series of 48 comatose SAH patients following seizures detected on scalp or intracortical EEG, however the authors did not report cerebral glutamate levels. Only baseline cerebral glucose levels were lower in intracortical detected seizures that typically did not evolve to detectable seizures on scalp EEG. Suggesting that glucose may be fundamental as energy supply to allow progression of seizures. Newer methods of cerebral microdialysis may overcome these limitations and provide near-real time metabolic information of the seizing brain.

Subdural strip electrodes.

Continuous electrocorticography (ECoG) is another important tool of invasive neuromonitoring and was recently reinvented as research tool in severely brain injured patients. Cortical spreading depolarizations are frequent in patients with acute brain injury including subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and malignant hemispheric stroke and associated with poor outcome in TBI patients. Although more research is needed, the detection of spreading convulsions in SAH patients and their association with electrographic seizures in ECoG recordings, secondary neuronal injury and post-hemorrhagic seizures suggests a pathophysiologic role of CSD in the initiation of seizures, evolution to SE and post-injury epilepsy. Scalp EEG may not be sensitive enough in detecting single spreading depolarizations and depressions of spontaneous activity in humans but when CSD occur in clusters slow potential changes may be detected on surface EEG.

New directions.

In addition to routine biochemical monitoring (glucose, lactate, pyruvate, glutamate, glycerol), in vivo brain microdialysis permits sampling of other stable biochemical compounds in the extracellular fluid of the human brain that pass the dialysis membrane. This technique provides the possibility to further investigate on neuronal excitability (glutamate), and associated inflammatory responses

(Interleukin 1, IL-6, TNF alpha) in patients suffering of repetitive seizures or SE as previously shown in patients with SAH and TBI. Moreover, it provides a method of measuring interstitial concentrations of various drugs (i.e. antiepileptic drugs) and even performing quantitative pharmacokinetic studies. These methods are currently limited by the variable recovery rate, however new approaches may overcome some existing limitations and may provide techniques to monitor drug metabolism and even allow the delivery of low molecular weight drugs into the extracellular compartment in future. Lastly, multimodal neuromonitoring devices may prove beneficial to guide decisions about intensity and duration of therapy in patients with SE i.e. to titrate sedatives in order to achieve the optimal level of sedation, ensure sufficient energy supply (glucose, oxygen) to the vulnerable brain tissue, and evaluate the optimal time to titrate patients off sedatives drugs suffering from SE. Future trials are conceivable that would utilize multimodality monitoring endpoints to guide treatment intensity and duration.

On a meta level these preliminary observations illustrate the complexity of acute human brain injury and the major limitations of directly translating existing seizure models to humans. With increasing experience gained by the use of extended neuromonitoring we are more and more able to understand associated hemodynamic and brain neurochemical changes in patients with status epilepticus. Trials founded in these pathophysiological observations made in the acute human brain injury model will likely lead to treatment trials with a higher chance of positive outcome than those that directly translate observations made in the animal laboratory that insufficiently replicate the complexity of the human condition.

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IL15

TITLE: THE MULTIFACETED CARE OF STATUS EPILEPTICUS

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Abstract:

After seizures have been controlled, long-term care of status epilepticus may be needed and collectively involves every major organ. First, as a result of rapid escalation of antiepileptic drugs, there are initial concerns with hypotension, acid-base abnormalities, and cardiac arrhythmias. Second, refractory status epilepticus and the continuous need for intravenous administration of anesthetic drugs will lead to a multitude of systemic complications which require long-term complex care. Most anticipated problems are infectious complications with a high risk of pneumonia and sepsis, but thromboembolism due to immobilization and catheter placement are also common. If a good outcome is possible or anticipated in a patient with refractory status epilepticus physicians should plan for a surveillance and treatment protocol to adequately support these patients.

Text:

Seizures not only damage the brain but also other organs. Status epilepticus results in a dramatic physiological re-

sponse, and some of it causes an unstable medical condition. There is a need for rapid seizure control and that involves the transition to a large dose of an intravenously administered antiepileptic drug (or a combination of drugs) and such an approach often is at the expense of serious side effects (Smith 2011). In patients with super refractory status epilepticus who are held in a pharmacologic coma (and frighteningly close to suspended animation), long-term mechanical ventilation and immobilization may collectively lead to a multitude of systemic complications requiring complex critical care (Shorvon and Ferlisi 2012). This brief review touches on some of the major medical issues.

Side Effects of Anesthetic Drugs

The medical problems may start early and some of the used drugs have side effects within days after their administration. These side effects are usually easily handled but some are severe or even life threatening. An example is the so-called propofol infusion syndrome and is usually only found in patients treated with a high dose -starting at >5 mg/kg/h- or an infusion time for 3 days or more. Risk factors are young age, any critical illness, high fat and low carbohydrate intake, concomitant catecholamine infusion, and concomitant corticosteroid use (Diedrich and Brown 2011). Many neurointensivists have become cautious with using the drug after experiencing this syndrome that often results in rapid cardiovascular collapse (Iyer, et al. 2009). It is therefore unsettling that many reviews on status epilepticus still allow a high dose of propofol, up to 10 mg/kg/h. There is no good treatment for propofol infusion syndrome other than stopping propofol, improving gas exchange, and sometimes cardiac pacing and renal replacement therapy. Extracorporeal membrane oxygenation may be the only option in some cases.

Another major and immediately noted side effect is propylene glycol toxicity (Bledsoe and Kramer 2008). Propylene glycol is a vehicle in lorazepam, barbiturates, etomidate, and its absorption peaks within an hour in most patients. The diagnosis is suspected in any patient who has developed lactic acidosis, but this potentially worrisome acid-base imbalance is often misattributed to ongoing seizures (Miller, et al. 2008) and not detected because it requires calculation of an osmolar gap—measured serum osmolality minus calculated osmolality. There is a good corre-

lation between osmolar gap and propylene glycol levels (Barnes, et al. 2006).

Long term effects of prolonged use of anesthetic drugs are not precisely known and if found may be difficult to separate from brain injury associated with the excitotoxic state. Inhaled anesthetic agents such as isoflurane can be demonstrable toxic, but with disappearance of MRI abnormalities when it is discontinued (Fugate, et al. 2010)

Systemic Manifestations of Status Epilepticus

Metabolic acidosis occurs because of excessive muscular contraction, which results in glycogen depletion and anaerobic glycolysis, promoting lactic acid formation from pyruvic acid. Metabolic acidosis— but mostly with pH values of about 7.2—was not significantly associated with potential life-threatening cardiac arrhythmias in one study (Wijdicks and Hubmayr 1994). However, a pH value of 6.8 has been recorded soon after a generalized seizure and most physicians may feel compelled to administer sodium bicarbonate. In many patients respiratory acidosis is found, and increased arterial PCO₂ can be caused from lung injury from aspiration but also due to decreased respiratory drive and increased mechanical load of respiratory muscles. Mechanical ventilation (reducing hypercarbia) and bronchoscopy (clearing secretions) will correct this abnormality. Many of the initial concerns in super refractory status epilepticus are pulmonary and physicians have to continuously correct episodes of pulmonary effusions and consolidation. Both rapid development of atelectasis or mucous plugging of a main bronchus is common. Acute atelectasis is basically an airless part of the lung created by resorption after obstruction. Pleural effusions develop frequently in acutely ill neurologic patients and may require thoracentesis.

Health-acquired pneumonia or ventilator-associated pneumonia increasingly is caused by multidrug-resistant or extremely drug-resistant pathogens. This includes *Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae* and carbapenems containing *Enterobacteriaceae* (Sutter, et al. 2012). The use of oral gastric decontamination in combination with parenteral antibiotics is often considered but there is a great likelihood this will lead to more antibiotic resistance in the ICU.

Another major systemic manifestation after refractory status epilepticus is fever. Any combination of fever and seizures is underappreciated by clinicians who should find ways to effectively cool the patient (Corry, et al. 2008). Cooling can be achieved in controlled hospital settings with well-designed practice protocols, but quick cooling can also be achieved by large-volume (20 ml/kg), cold (refrigerator cold; 4° Celsius) saline, but its effect is short (less than 30 minutes) and may need to be repeated (with 10 ml/kg) until more long-lasting effective measures are available. Cooling may lead to shivering and if it occurs, the best intervention is dexmedetomidine titrating up to 1.5 mcg/kg/hr.

Cardiac arrhythmias are quite common after any status epilepticus and more than two-thirds require a cardiac intervention (Hocker, et al. 2012, Hocker, et al. 2013). Moreover, any use of a high dose of intravenous anesthetic drugs will result in hypotension and, in some patients, this may become refractory. Causes other than the IV drugs must be considered and apical ballooning cardiomyopathy (i.e., Takotsubo cardiomyopathy) described in more than 50 cases after status epilepticus may be the cause of hypotension in refractory status epilepticus (Lemke, et al. 2008, Shah, et al. 2012, Stollberger, et al. 2011, Weeks, et al. 2007). An echocardiogram will easily characterize the disorder and will show a very significant reduction in ejection fraction.

Most of Takotsubo cardiomyopathy can be treated with inotropes, that may include dobutamine or milrinone, but intra-arterial balloon pump has been needed in some cases. Damage to the heart has been further corroborated by cardiac pathology studies in patients who died after refractory status epilepticus. Microscopy showed contraction bands and coagulative necrosis in a high proportion of samples, suggesting a massive hyperadrenergic response during seizures (Manno, et al. 2005). Whether this cardiomyopathy can be predicted by EKG abnormalities is unlikely.

Other clinical concerns are due to the massive increase in catecholamine that can lead to hyperglycemia and damages the brain through worsening lactate acidosis. Glucose control is standard ICU practice with preferably insulin infusion starting at a threshold not higher than 180 mg/dL and – at least – maintaining a blood glucose target between 140 -180 mg/dL. A blood glucose of <110 mg/dL is not considered safe.

Tonic-clonic seizures may damage muscle. A slight increase in serum creatine kinase concentration is invariably found after a single seizure, but creatine kinase levels may reach enormous proportions within a day. Some laboratory values may already point to rhabdomyolysis. These are metabolic acidosis not entirely explained by lactate accumulation, hyperkalemia, increased serum aldolase, hypocalcemia, and certainly myoglobinuria. Most cases associated with status epilepticus reported in the literature are mild and temporary. Acute nonoliguric renal failure from rhabdomyolysis may become apparent with acutely rising serum creatinine, hyperkalemia, and hyperphosphatemia. Initial treatment is to change intravenous fluids from normal saline to D5W with 3 ampules of bicarbonate at 200 cc/hr to maintain urinary output of more than 100 cc/hr. Phosphate binders (calcium acetate) are needed until laboratory values normalize.

Long-Term Medical Issues with Induced Coma

Approximately 30% of the patients with status epilepticus will require tracheostomy, but this decision is often already made 2-3 weeks after treatment. This is often also combined with a gastrostomy to facilitate nutrition.

Any patient who is in a prolonged immobilized state is at risk of multiple systemic complications. Most noticeable are infectious complications that include high risk of pneumonia, sepsis, pseudomembranous colitis, and urinary tract infections. Gastrointestinal problems may be seen and often lead to adynamic ileus. Many of the drug effects can produce significant colonic standstill that would lead to temporary parenteral nutrition.

The risk of deep venous thrombosis is markedly increased in these immobilized patients. Antithrombotic and thrombotic therapy includes the use of subcutaneous heparin, low molecular weight heparin, or intermittent compression devices. Deep venous thrombosis and pulmonary emboli and thrombus may form spontaneously or at central lines. Each of these complications would require heparinization often invariably in patients who have been treated for several months for refractory status epilepticus.

The most common problems are skin lesions. We have found massive tongue swelling with barbiturates, and the skin is often at high risk of breakdown in patients who have been on long-term barbiturates (Ji, et al. 2009). Skin might also become abnormal as a result of drug rashes with polypharmacy during the management of these com-

plex patients. Skin care has a high priority in immobilized patients. Decubital ulcers or, more often, patches of demarcated painful erythema indicative of developing ulcers may appear, even with meticulous care. Two-thirds of the patients with pressure sores acquire them within the first week of admission and therefore frequent turning in bed, lanolin creams, and dry patting of the skin are essential. Use of air-fluidized mattresses is critical. Oral candidiasis, recognized as creamy white patches on the pharynx or tongue, should be anticipated in patients receiving broad-spectrum antibiotics, corticosteroids, or total parenteral nutrition; but the probability is increased in any preceding debilitating state. Fluconazole, 100 mg orally per day, may treat this infection rapidly before it becomes invasive.

Conclusions

With every minute that passes there must be an urge to quickly control seizures. Such an approach is necessary, but it may lead to more side effects of these drugs and some are substantial. After seizures are temporarily controlled the care of these patients is complex and multifaceted and involves virtually every major organ. Poor outcome is often seen in patients with prolonged mechanical ventilation, pneumonia at any time, or cardiac arrhythmias. There are many laboratory abnormalities, including acid-based abnormalities, seen throughout the course of treatment of these patients. A carefully designed treatment protocol is warranted to better support these patients.

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IL16

TITLE: THE EVOLUTION OF THERAPY FOR STATUS EPILEPTICUS

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Abstract:

The modern treatment of status epilepticus dates from about 1860, and prior to this the condition was treated in the same way as other forms of epilepsy. The early emphasis was on sedation and then anaesthesia. By 1940, a variety of antiepileptics, sedative and anaesthetics were being used. In the 1970s, the introduction of the benzodiazepines revolutionised therapy. Advances in therapy since that time include: an appreciation of the nature of the status-induced cerebral damage, the recognition of the need for early therapy, the introduction of rectal and other

non-IV forms of therapy for out-of-hospital use, the use of blood monitoring, the advances in neuroimaging and clinical investigation, the development of ITU technologies, the development of staged protocols, the use of randomised controlled trials, the introduction of buccal therapy, the focus on therapy for refractory and the concept of super-refractory status epilepticus.

Text:

Treatment when status epilepticus was first defined.

A study of the evolution of therapy in status epilepticus is necessary to understand the current position of therapy and the reasons for the current approach. It is convenient to date the history of modern therapies to the mid-nineteenth century, for it was then that the condition ‘status epilepticus’ was differentiated from the rest of epilepsy, and then that there was a focus on the particularities of its therapy. Up until this time, therapy of epilepsy and of status epilepticus were similar. The list of Delasiauve is a useful summary of contemporary treatment, with categories of therapy divided into four: 1. Debilitating therapies (such as bleeding, tepid baths); 2. Evacuant therapies (including emetics and purgatives); 3. Sedative therapies (including ether); 4. Specifics (including valarian and opiates) (see Hunter 1959/60; Shorvon 1994; Neligan and Shorvon 2009).

The early antiepileptic drugs in status epilepticus and the role of sedation

The age of effective antiepileptic drugs ushered in new therapies, with a realization that inducing ‘sedation’ was often the best approach. The antiepileptics used included bromide (introduced in 1861) sometimes hypodermally, rectally or even by injection into the stomach, amyl nitrate, apomorphine, atropine, chloral, chloroform, ether, hyoscyne, morphia, opium, quinine, strophanthus, and valerian. Gowers, writing in 1881 commented “In the status epilepticus, and where bromide, even in large doses was useless, I have found small hypodermic injections of morphia of great service.” Turner in 1907 wrote: “During the height of a status attack nothing will arrest the seizures except the inhalation of chloroform”. Physical therapies were also used including the use of enemata, CSF drainage, cold baths and venesection. At the turn of the century, there was an strong emphasis on cleansing the bowel, and Shannahan (1915) for instance stated: “the most urgently indi-

cated procedure in status is a free irrigation of the lower bowel, using gallons of water given at frequent intervals to completely empty the bowel of faecal matter. After the bowel irrigation, choral hydrate or amylene hydrate should be given by enema in sufficient quantity for sedation”.

The introduction of intravenous barbiturates changed rapidly the approach to therapy. The first barbiturate was somnifene, introduced in 1921 and then hexobarbitone in 1932 and thiopentone in 1934. The first reference to the use of intravenous phenobarbitone was in 1923. Pentobarbital was introduced in the 1930s, but used then largely in veterinary medicine and more latterly for euthanasia and capital punishment. Barbiturates were used initially in sub-anaesthetic doses, and subanaesthetic phenobarbital remains the mainstay of treatment of established status to this day in many countries and institutions.

Anaesthesia in status epilepticus

Ether, nitrous oxide (discovered in 1772) and chloroform (discovered in 1831) anaesthesia were also used, at least since 1860, and the potential for anaesthesia was well recognized at this time. The anaesthesia was used to the level of induction of ‘twilight sleep’ and clearly any deeper level of anaesthesia would have been dangerous to manage without the paraphernalia of modern ITU care, and it is no wonder that there was a significant mortality. Direct laryngoscopy was introduced in years before the first world war, and positive pressure ventilation in the years after the second war. The use of barbiturate anaesthesia became widespread when curarisation, IV anaesthesia and positive pressure ventilation were introduced in 1958. IV propofol was introduced in 1977 and IV midazolam in 1978. Propofol, midazolam and thiopental/pentobarbital remain the anaesthetics of choice throughout the world today in the treatment of refractory and super-refractory status epilepticus.

Advances in antiepileptic drug therapy for status epilepticus 1940-1970

Phenytoin was first used IV in status epilepticus in 1958. By then paraldehyde was the most widely used sub-anaesthetic antiepileptic (and also used for anaesthesia) and was thought, for instance, by Lennox in 1960 to be “The drug of choice in status epilepticus by rectum, muscle or vein”. Lennox though did not have long to wait

for the introduction of another class of drugs which would eclipse the effects of phenytoin, and these were the benzodiazepines, introduced into clinical practice for anxiety and then epilepsy from 1960. The first reports for use in status epilepticus were in 1965. Gastaut et al (1965) described the treatment of status epilepticus with diazepam as: "outstanding for the reliability and rapidity of action, which together make it a more effective drug than others we have used in the past, among which have been: injectable phenobarbital, somnifene, chloral hydrate, eunocet, sodium bromide, rectanol, novocain and hemineurin." And by 1971, Gastaut wrote of clonazepam "We do not hesitate to affirm that [clonazepam] is by far the most effective agent which we have at present for the treatment of status epilepticus of whatever form or aetiology" (Gastaut et al 1971). The use of benzodiazepines as first line therapy in status is now universal practice, with lorazepam, diazepam, clonazepam or midazolam.

Advances in therapy since 1970

Since then, the drugs and drug classes used in therapy remained largely unchanged until the last 5-10 years, when levetiracetam, valproate and more experimental drugs were introduced. The exact place of the newer drugs remains uncertain. The type of drug used may not have changed much, but in recent years there have been very important advances in the principles of therapy and the approach to therapy and these have been extremely important in improving management and outcome. These therapeutic advances have been predicated on a much greater understanding of the molecular, physiological and basic science of status epilepticus. Amongst the more important developments are:

1. The recognition that status epilepticus causes cerebral damage via excitotoxicity and that early therapy is important in preventing this brain damage (derived from the experiments of Meldrum and colleagues in the 1970s; Meldrum 1991; Meldrum et al 1973a,b)
2. The recognition that urgent therapy of febrile status will prevent longer-term neurological damage through the work of Aicardi and his colleagues in the 1970s (Aicardi and Chevrie 1970)
3. The introduction of rectal diazepam (Knudsen and Vestermark 1979) for out of hospital therapy of acute seizures.
4. The use of blood level monitoring of phenobarbital

and phenytoin particularly for the control of dosing in status epilepticus (in the 1970s)

5. The rapid advances in neuroimaging and clinical investigation to improve the detection of the underlying causes of status epilepticus and the recognition that the effectiveness of treatment is dependant to a great extent on underlying cause (1980s onwards)
6. The development of ITU technologies and therapies for the care of patients anaesthetised for long periods of time (1990s onwards; Walker et al 1995)
7. The first staged protocols for the treatment of SE, dividing the therapy of the condition into early, established and refractory stages, and the recognition of the 'prodromal phase' (early 1990s; EFA Working Group, 1993, Shorvon 1994).
8. The first RCT in status epilepticus (the Veterans study; Treiman et al 1998) comparing diazepam/phenytoin, phenytoin, phenobarbital, lorazepam
9. The introduction of buccal midazolam (following the study of Scott et al 1999, McIntyre et al 2005)
10. Other large scale RCTs - notably the study comparing lorazepam, diazepam and placebo in an out-of-hospital setting (Alldredge et al 2001) and the RAMPART study of IM midazolam (Silbergleit et al 2012)
11. The introduction of the concept of super-refractory status epilepticus and treatment protocols for therapy at this stage (Ferlisi and Shorvon 2011)

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IL17

TITLE: SURGICAL TREATMENT OF STATUS EPILEPTICUS

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Text:

Status epilepticus (SE) or prolonged seizures represent a serious medical and neurologic emergency. SE has been defined through the International Classifications of Epileptic seizures as a seizure lasting for more than 30 minutes or intermittent seizures lasting for more than 30 minutes from which the patient does not regain consciousness, and when the unconsciousness is due to the seizure activity. This definition applies to any seizure type. The mortality rates in SE was investigated in several studies in the past 20 years and have varied from as low as 8% to as high as 50%. Recent advances in the treatment of SE have improved the prognosis. Although status epilepticus does not resemble a domain for neurosurgical indications in single occasions a microneurosurgical procedure in patients with catastrophic epilepsy and status epilepticus should be considered as an ultima ratio-choice in these patients. A palliative approach in epilepsy surgery is presented in this publication.

Methods:

From a personal series of over 600 epilepsy surgery procedures in a period from August 1, 1993 till March 13, 2013 22 patients were identified with catastrophic epilepsy and all of them with at least one episode of status epilepticus. Some of them were operated under ongoing status epilepticus. Eight patients received palliative primary incomplete resections of the epileptogenic lesions, thirteen patients received unilateral resections of bilateral lesions. In one patient both bilateral lesions were removed.

Results:

Twelve patients became seizure free, two patients showed over 90% seizure reduction, seven patients over 50% seizure reduction, one patient resulted unchanged. No surgery related complications in terms of permanent morbidity were ascertained in the presented series.

Discussion of the literature:

In the literature different modalities over the years were proposed as an alternative and as an ultimate approach in patients with catastrophic epilepsy and status epilepticus. Single case reports were described in the literature applying resections of epileptogenic focus, multilobar resection, tumor resection and callosotomy. In a total and cumulative number of 24 patients a resection of the epileptogenic foci was achieved. The multiple subpial resections (MST) were described in two cases with moderate results. The vagal nerve stimulation (VNS) was carried out in seven cases with encouraging results. There are some patient outcome data suggesting that vagal nerve stimulator allowed early cessation of SE and discharge from ICU. Available follow up demonstrated that the patients experience significant seizure reduction in long-term. There are no valid data of larger series about deep brain stimulation (DBS) and alternative methods in the treatment of SE. For DBS in summary with the targets and stimulation parameters investigated so far, the effects of electrical brain stimulation on seizure frequency have been moderate at best. A different subgroup of nine patients resembles the children suffering from electrical status epilepticus in sleep and cognitive impairment. Six of eight patients in one series became seizure free after functional hemispherectomy. The Landau-Kleffner syndrome (LKS) shows a bitemporal status epilepticus during sleep (BTESES) in all cases. This phenomenon was described in a series of 11 patients affected by LKS. Four of them presented a shift from a BTESES towards an intercalated electrical status epilepticus during sleep accompanied by a global regression of cognitive and behavioural functions in three of four cases. It is important for the prognosis to utilize antiepileptic treatment and possibly neurosurgical techniques to eliminate EEG paroxysmal abnormalities.

Conclusions:

Patients suffering from catastrophic epilepsy including status epilepticus can benefit from resective epilepsy surgery

even with incomplete resection of the epileptogenic lesion. In the analyzed group, more than 50% of the patients enjoyed freedom from seizures. However, surgery resulted in a marked improvement in quality of life even for patients without complete seizure relief. These preliminary results are encouraging and need further intensive research and investigations.

IL18

TITLE: WHAT CAN WE LEARN FROM STATUS EPILEPTICUS REGISTRIES?

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Abstract:

There is a remarkable dearth of information about the various therapies used, often widely so, to control refractory or super-refractory status epilepticus despite its high mortality and morbidity. As pointed out by recent literature reviews, there are no controlled studies, and information is based almost entirely on open, often small and retrospective, case series or case reports. Randomized or controlled studies that are sufficiently powered are not feasible in relation to the many therapies and treatment approaches available. For this reason, we proposed an international case registry of therapies used in refractory and super-refractory cases and their outcome. Clinicians from different countries will be asked to complete an online questionnaire when they treat a patient with refractory or super-refractory status epilepticus. Information gathered from this database will summarize the spectrum of etiologies, treatments and outcomes of this challenging condition and may even form the bases for treatment guidelines or future targeted treatment trials.

Text:

Tonic-clonic status epilepticus is an important neurological emergency potentially associated with significant mortality and morbidity rates. Immediate treatment is required, aimed at stopping seizures largely in order to avoid cerebral damage and other morbidity.

The treatment of the earlier phases of tonic-clonic status epilepticus has been well studied and discussed in recent years. There are a number of similar guidelines and protocols published: all contemporary protocols take a staged approach to treatment. Typically, in the early stage of status epilepticus, therapy is with benzodiazepines. If seizures continue despite this therapy, the patient is said to be in Stage 2 (established status epilepticus) and therapy consists of intravenous anti-epileptic drugs such as phenytoin, phenobarbital or valproate. Although based on an inadequate evidence base, these stages of treatment are widely accepted and practiced.

If seizures continue despite this treatment for up to 2 h, the patient is said to be in refractory status epilepticus, a stage where general anaesthesia is required. However, there are no comparative trials, and the anaesthetic is usually chosen on the basis of the prior experience and usual practice of the intensive care unit medical team, at a dose that results in EEG burst suppression (a level of anaesthesia at which most seizure activity is controlled). In most patients, this treatment regimen is sufficient to control the seizures. In some though, seizures continue or recur. Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases that recur on the reduction or withdrawal of anaesthesia. It was a term first used in the Third London-Innsbruck Colloquium on status epilepticus held in Oxford on 7–9th April 2011 (Shorvon & Trinka, 2011).

Although constituting a minority of cases of status epilepticus (~15% of all those presenting to hospital in status epilepticus; Novy et al, 2010), refractory and super-refractory status epilepticus are serious conditions and appropriate therapy of these cases is poorly studied.

The mortality rate is substantial, reported in various series between 30 and 50%. Yet, despite the fact that it remains an important clinical problem in all neurology centres worldwide and all neurologists and intensivists are likely

to be involved with the care of patients with refractory and super-refractory status epilepticus, for many therapies there is a remarkable lack of published data concerning effectiveness, safety or outcome.

A great number of therapies are in current usage and the literature reporting these therapies has been reviewed recently (Shorvon & Ferlisi, 2011; Ferlisi & Shorvon, 2012). 180 papers were found, and they form the evidence base for therapy. The therapies reported include thiopental, pentobarbital, midazolam, propofol, ketamine, inhalational anaesthetics (isoflurane, desflurane), antiepileptic drugs (topiramate, lacosamide, pregabalin, levetiracetam), hypothermia, magnesium, pyridoxine, immunotherapy, ketogenic diet, emergency neurosurgery, electroconvulsive therapy (ECT), CSF drainage, vagal nerve stimulation and deep brain stimulation. It is salutary to note that there is only one randomized or controlled study of any of these therapies (a trial comparing thiopental and propofol) requiring 150 patients for adequate power but which managed to recruit only 24 patients and therefore failed to reach any conclusions (Rossetti et al., 2011). Apart from this study, the evidence base consists entirely of single case reports or small series. Furthermore, none of the widely recommended drugs or procedures has been subjected to an adequate systematic review, despite their adoption worldwide. This is an unsatisfactory state of affairs.

Assessing outcome of individual therapies is even more difficult due to the complete lack of controlled data, the fact that all super-refractory patients are on multiple therapies, the tendency for authors to report effects days after the therapy is started and which can therefore be difficult to securely attribute to the therapy and the fact that outcome fundamentally depends on the underlying aetiology, which differs in different studies (Neligan & Shorvon, 2010). Control of refractory and super-refractory status epilepticus was reported in 74% of the cases treated with anaesthetics and variable rates of control were achieved with other therapies (Ferlisi & Shorvon, 2012).

The lack of evidence and the lack of outcome data in this situation require urgent remediation. Randomized or controlled studies that are sufficiently powered are not feasible in relation to the many therapies and treatment approaches discussed above. For this reason we have proposed

a multinational database of therapies used in refractory and super-refractory cases and their outcome. Only with such a database can evidence of effectiveness be gathered and progress made in this uncommon but difficult clinical situation.

Intensivists and neurologists from around the world are being asked to take part in a multinational audit in order that we may better understand the range of therapies, relative frequency of their usage and outcome as well as information about the etiology of refractory status epilepticus. This is a prospective multicentre case audit using 'active surveillance', run by a Steering Committee comprised of neurologists and neurointensivists from around the world.

The aim is to collect information on the treatment of 1000 cases over 12 months. As it is an audit of physician's practice, with no intervention and no collection of protected health information, in most countries there is no need for ethics approval or patient consent. The audit will not have access to patient names or any other identifiable information. Physicians who agree to participate are asked to prospectively complete the online audit form for all patients they treat with the stage of refractory or super refractory status epilepticus.

Every month, each participant will be sent a standard email, asking if a case has been seen in the previous month. If they have, they will be sent an online form which should take less than 5 minutes to complete. After a case is reported, biweekly questionnaires are sent (taking 1-3 minutes to complete), until the physician indicates that the patient is no longer in the ICU, at which time an outcome questionnaire is sent. Recorded information includes basic demographic information, history of epilepsy, type, etiology and duration of status epilepticus, choice, order and duration of antiepileptic and anesthetic therapy, use of non-pharmacologic therapies, duration of ICU stay, whether active therapy was withdrawn, outcome on discontinuation of anesthesia and modified Rankin scale at 6 months.

As with any registry, the validity of this audit will depend on the range of participation. Thus, we have enlisted a Steering Committee of physicians from around the world in order that we may capture the wide range of treatment practices used in refractory status epilepticus as well as information on outcomes. To participate, please register your interest at <https://www.status-epilepticus.net/>.

This exercise will form the basis for the formulation of clinical guidelines and point to areas of future research.

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IL19

TITLE: LESSONS FROM THE RAMPART STUDY – AND WHICH IS THE BEST ROUTE OF ADMINISTRATION OF BENZODIAZEPINES IN STATUS EPILEPTICUS

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Abstract:

Early treatment of prolonged seizures with benzodiazepi-

nes given intravenously by paramedics in the prehospital setting had been shown to be associated with improved outcomes, but the comparative efficacy and safety of an intramuscular (IM) route, which is faster and consistently achievable, was previously unknown. RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) was a double-blind randomized clinical trial to determine if the efficacy of IM midazolam is noninferior by a margin of 10% to that of intravenous (IV) lorazepam in patients treated by paramedics for status epilepticus (SE). In children and adults with >5 min of convulsions and who are still seizing at paramedic arrival, midazolam administered by IM autoinjector was non-inferior to IV lorazepam on the primary efficacy outcome with comparable safety. Patients treated with IM midazolam were more likely to have stopped seizing at emergency department (ED) arrival, without EMS rescue therapy, and were less likely to require any hospitalization or admission to an intensive care unit. Lessons from the RAMPART study's findings and potential implications on clinical practice, on the potential role of other routes of administration, on the effect of timing of interventions, and on future clinical trials are discussed.

Text:

Early treatment of SE by paramedics reduces the number of patients with persistent seizures on ED arrival and the number admitted to the intensive care unit (ICU) for refractory status. Traditionally, diazepam has been the agent used most frequently by Emergency Medical Services (EMS) to treat patients with seizures despite evidence that intravenous lorazepam may be more effective. Lorazepam has proven impractical for EMS use because of its short shelf life without refrigeration. More recently, midazolam has been adopted in a limited number of EMS systems because it is more rapidly absorbed by intramuscular and transmucosal routes than diazepam or lorazepam, and has excellent stability. The safety and efficacy of intramuscular midazolam, however, had not until recently been studied in a randomized controlled trial, and the optimal agent for prehospital treatment of SE was unknown. In RAMPART (the Rapid Anticonvulsant Medication Prior to Arrival Trial) we hypothesized that in the prehospital treatment of SE, the efficacy of IM midazolam would be non-inferior to that of intravenous (IV) lorazepam, as determined by the proportion of subjects with termination of clinically evident seizure at arrival in the ED after a single dose of study

medication and without use of rescue medication.

Methods

RAMPART was a double-blind randomized noninferiority clinical trial of the efficacy of IM midazolam versus IV lorazepam in the prehospital treatment of SE by paramedics. The trial was conducted in the Neurological Emergencies Treatment Trials (NETT) network, a multidisciplinary clinical trials infrastructure funded by the National Institute of Neurological Disorders and Stroke (NINDS). RAMPART involved more than 4,314 paramedics, 33 EMS agencies, and 79 receiving hospitals across the United States.

Subjects enrolled in RAMPART were all administered study medication by IM autoinjector followed by rapid placement of a venous catheter and IV study medication. All subjects received active treatment. In half of the subjects the active treatment was in the IM study medication and in half active treatment was in the IV study medication. Children over 40 kg and all adults randomized to active IM therapy were treated with 10 mg midazolam IM followed by IV placebo. Children over 40 kg and all adults randomized to IV active therapy were treated with IM placebo followed by 4 mg lorazepam IV. The weight of children was estimated from their length using a length-based weight-estimation tape. Active therapy in children estimated to be <40 kg was either 5 mg midazolam IM or 2 mg lorazepam IV. Children estimated to be <13 kg were not enrolled.

A specially designed study box incorporated a voice recorder activated by opening the box. Study personnel used the device to identify the following events: IM treatment, IV access obtained, IV administered, administration of any rescue treatments, when and if convulsions are observed to stop, and whether the subject is seizing on arrival at the ED. The recorders' time code allowed each event to be time-stamped. When starting an IV was difficult, medics attempted placement for at least 10 minutes, or were allowed to place an intraosseous (IO) line in lieu of IV access. Rescue therapy, as dictated by local EMS protocol, was used in subjects who were still convulsing 10 min after the last study medication was administered.

The study was conducted under 21 CFR 50.24, U.S. Food and Drug Administration (FDA) regulations governing emergency clinical research performed with exception

from informed consent (EFIC). The Institutional Review Board (IRB) at the coordinating center and at each site reviewed and approved the trial. Each site IRB reviewed local community consultation and public disclosure activities. Subjects or their legally authorized representatives were notified about enrollment in the trial by the study team as soon as possible, usually while the subject was still in the ED, and were asked for their consent for continued data collection through the subject's end of study.

Results

Eight hundred ninety three subjects were enrolled over 19 months. Subjects were well balanced between treatment groups on demographic and clinical characteristics, dose tier, prior history of epilepsy, accuracy in diagnosis of status epilepticus (versus a discharge diagnosis of seizure mimic or pseudoseizure), and in the diagnosis of the underlying cause of status epilepticus. Among subjects with a prior history of epilepsy, status epilepticus was most commonly from noncompliance with, or withdrawal from, anticonvulsant medication, but idiopathic precipitants and other breakthrough seizures were also common. Status epilepticus resulting from lowering of the seizure threshold by identifiable acute co-morbidities was much less common.

Seizures were absent without rescue therapy at ED arrival in 329 of 448 (73.4%) subjects allocated to active IM treatment and in 282 of 445 (63.4%) allocated to active IV treatment (difference: 10.1%, 95% CI: 4.0%, 16.1%; $p < 0.001$ for non-inferiority and $p < 0.001$ for superiority). Among the 119 subjects in the IM group and the 163 in the IV group that failed the primary outcome, 47 (39.5%) and 57 (35.0%) respectively received rescue medications and were not seizing on arrival, and 22 (18.5%) and 42 (25.8%) received rescue medications and were still seizing on arrival.

The secondary and safety outcomes were consistent with and reinforced the finding of non-inferiority for the primary outcome. In IM and IV treatment groups, the frequency of endotracheal intubation (14.1% v. 14.4%), recurrent seizures (11.4% v. 10.6%), and other predefined safety outcomes were similar by group. In those admitted, the ICU and hospital length of stay did not vary with treatment group, but the proportion of subjects admitted was significantly lower in the IM group (57.6%) as compared to the

IV group (65.6, $p = 0.01$).

Time interval data included those subjects meeting the primary outcome in whom time of active treatment and seizure cessation were captured ($n = 317$). Time to administration of drug by the IM route was significantly shorter than by the IV route, but the onset of action (seizure termination) after IV administration was shorter than after IM administration. The overall interval until seizure termination was similar in both groups.

Intramuscular midazolam is the best option for the prehospital treatment of status epilepticus.

The superiority of IM midazolam over IV lorazepam in RAMPART indicates that early administration of IM midazolam is the best option for the prehospital treatment of SE by paramedics. While early administration of adequate doses of IV lorazepam is the preferred initial treatment for SE in the emergency department and other controlled clinical environments, it has limitations that make it less preferable for use by EMS. The need to rapidly establish IV access in a convulsing patient may delay benzodiazepine administration in the prehospital environment, and lorazepam's short shelf life out of refrigeration is not pragmatic for EMS use. The ability to use an IM route with midazolam allowed more reliable and rapid administration and ultimately led to better clinical outcomes as reflected in lower rates of hospital admission, and lower rates of ICU admission.

Implications for other non-intravenous routes of administration

Some EMS systems that use midazolam for the prehospital treatment of SE use transmucosal routes of administration (buccal, nasal, or rectal) as an alternative to IM administration. Such routes are less invasive and are potentially similarly rapid. Advocates for these routes were disappointed that RAMPART did not directly compare alternative non-intravenous routes of midazolam administration to each other and to intravenous lorazepam. Based upon what is known about the pharmacodynamics of transmucosal midazolam, the RAMPART investigators feel that the differences among various non-intravenous routes are likely to be small, and that the trial successfully answered the key question: whether a non-IV route can be non-inferior to an IV route. In the context of status epilepticus, the clinical importance of avoiding the invasiveness of an IM injection

per se is unclear, and there are potential limitations to each non-intravenous route. These include the relatively low concentrations of midazolam that are commercially available for atomized administration, and that have most often been studied in nasal administration, as well as the occasional problem of seizing patients spitting or blowing out medication during administration. However, we feel that the RAMPART results should be taken to be generally supportive of non-intravenous midazolam administration.

Implications for the timing of interventions for status epilepticus

With regard to mechanism, the time interval data in RAMPART are consistent with the expectation that the medication given by the IM route is administered more rapidly after arrival than medication given IV, but that the onset of action after IV administration is more rapid than after IM administration. The administration time saved by using the IM route appears to more than offset the delay in onset of action. It is interesting to speculate that the earlier administration in the IM group, of just a few minutes, may have been enough of a difference to drive the slight superiority of IM seen in the primary outcomes.

Implications for future clinical trials in the emergency treatment of status epilepticus

While RAMPART definitively identified the best route of administration and optimal benzodiazepine for initial treatment of seizures and status epilepticus, it also suggests many opportunities and questions for future investigation. Primary among these is recognition that 26.5% had SE that remained refractory to benzodiazepines at emergency department arrival. Identification of the most effective second line anticonvulsant therapy for this population is thus a research priority. Furthermore these clinical data indicating that earlier treatment may work synergistically to improve anticonvulsant efficacy, taken in combination with pre-clinical animal data, suggest that future clinical trials should examine collapsing or accelerating the traditional serial progression of emergency treatments of SE, including the possible use of additional agents in prehospital treatment.

Acknowledgments:

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Stroke (NINDS), the Office of the Director, National Institutes of Health (OD), BARDA, and the NIH CounterACT program. This trial is registered with Clinical Trials.gov (NCT00809146).

References:

IL20

TITLE: INITIAL THERAPY OF STATUS EPILEPTICUS – POLY-THERAPY?

Author: Claude Wasterlain

Abstract not received

IL21

TITLE: ESTABLISHED STATUS EPILEPTICUS TRIAL

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Text:

Objectives:

The primary objective of ESETT is to determine the most effective and/or the least effective treatment of benzodiazepine-refractory SE among patients older than 2 years. There are three active treatment arms being compared:

fosphenytoin (fPHT), levetiracetam (LVT), and valproic acid (VPA). Certain adverse effects of drugs such as hypotension; and the mortality and etiology of SE vary with age, therefore secondary objective is a subgroup analysis to determine the most effective and/or the least effective treatment for benzodiazepine-refractory SE in each age group; Final objective is comparison of three drugs with respect to secondary outcomes.

Primary outcome is clinical cessation of status epilepticus, without recurrent seizures, life-threatening hypotension or cardiac arrhythmia, or use of additional anti-seizure medications within 60 minutes of the start of study drug infusion. Clinical cessation of SE consists of absence of clinical seizures and improving responsiveness. The study will also compare treatment arms on the following secondary outcomes: time to termination of clinical seizures, intubation, admission to ICU, mortality; and cessation of SE and occurrence serious adverse effects analyzed separately.

Methods:

This is a multicenter, randomized, double-blind, Bayesian adaptive, Phase III comparative effectiveness trial of three active treatments in patients with status epilepticus who have failed benzodiazepines (established status epilepticus -ESE). Response-adaptive randomization will be used to allocate patients to fPHT, LVT, or VPA for the treatment of SE in the emergency department with the goal of focusing randomization preferentially on the treatment arms with the highest response rates. Response adaptive randomization will occur after 300 patients have been recruited and allocated in 1:1:1. Randomization will be stratified by three age groups, 2-18, 19-65, and 66 and older. Each subject will be followed until discharge or 30 days from enrollment. This trial will be monitored for early success and futility.

Inclusion:

Patient older than 2 years of age, who is witnessed to have a clinically apparent seizure in the ER, 5-30 minutes after already having received at least an adequate dose of benzodiazepines for generalized, tonic-clonic convulsion(s). Adequate doses of benzodiazepines for this study are: diazepam 10 mg IV, lorazepam 4 mg IV, or midazolam 10mg IV or IM for subjects above 40 kg, and diazepam 0.3mg/kg IV, lorazepam 0.0.1 mg/kg IV or midazolam 0.3mg/kg IV or IM for subjects between 10-40 kg. These drugs may have

been administered in two or more divided doses, including in the out-of-hospital setting.

Interventions and Duration:

The required concentrations of the study drugs, fPHT 16.66 mg/ml, VPA 33.33 mg/ml and LVT 50 mg/ml, will be produced, packaged and labeled by the University of California, Davis, Good Manufacturing Practice (GMP) facility and shipped to the study sites. These drugs (along with the Itouch study device and tubing) will be placed in pre-randomized study boxes labeled "use next" kept in ED drug refrigerator. Any patient witnessed to have seizures in the emergency room (ER) will be evaluated for enrollment based on inclusion and exclusion criteria. Enrollment will occur under exception from informed consent rules (EFIC) due to emergent and life-threatening nature of SE. Randomization is stratified by age groups: 2-18, 19-65 and 66 and older. Pre-randomized study boxes labeled "use next ESETT" with appropriate drug vials inside will be available for rapid use in the study. This is an intention to treat study. Enrollment occurs when the infusion pump connected to study drug vial and patient's IV catheter is switched on and the time of enrollment recorded on the study device. The device is an Apple Itouch loaded with ESETT study app. The assigned treatment dose (fPHT 20 mg/Kg, LVT 60 mg/Kg or VPA 40 mg/Kg) will be infused over 10 minutes. The patients will be observed for 20 minutes, when the duration of clinical seizures and response to verbal or painful stimuli will be recorded. At 60 minutes from enrollment a study team member will record whether a clinically apparent seizure requiring intervention and improvement in responsiveness have occurred since last observation; and whether life-threatening hypotension or arrhythmia requiring intervention have occurred since enrollment. Primary outcome will be determined and recorded at this time. A subsequent chart review will determine duration of clinical seizures, admission to ICU or floor, whether patient was intubated and final disposition.

Sample Size and Analysis:

This is a response adaptive study designed to recruit a maximum sample size is 795 patients total. The expected response rate for fPHT, LVT and VPA are based on the ret-

spective analysis of 279 episodes of ESE in adults, who were treated with PHT, LVT or VPA. The study reported worst response rate of 52% and best response rate 75%. Based on this study and expert evaluation of all currently published data on the treatment of ESE, we expect that the worst drug will be effective in 50% of the patients. The recently completed RAMPART study for the initial treatment of SE was conducted with the assumption that a difference of less than 10% would be considered non-inferior. Thus an absolute difference of 15% would this be clearly indicative of superiority of one of the drugs over others, and will be sufficient to change clinical practice, therefore the study is powered to detect a 15% difference on the whole study population.

We expect to recruit a total of 795 patients (including 336 children) over 4 years, an accrual rate of approximately 16.5 patients per month; patients will be recruited by two national networks of emergency departments: Neurology Emergency Treatment Trials network (NETT) and Pediatric Emergency Care and Action Network (PECARN). Each network has successfully undertaken a SE treatment trial under EFIC rules.

Interim analyses will be performed after 300, 400, 500 and 600 patients have been recruited. The posterior probabilities that each treatment is the most and least effective treatment will be calculated using Bayesian methods. More patients will be allocated to the treatment with a higher probability being most effective. This trial will be considered a success if the probability that a treatment is the most effective is greater than 0.975 or the probability that a treatment is the least effective is greater than 0.975 for any treatment. When the total sample size is 795, there will be 90% power to identify the most effective and/or the least effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (as determined by simulation). Secondary goal is to detect an absolute difference in proportions as small as 20% between treatments in children with at least 80% power. In order to detect this difference a sample size of 336 children is required.

TITLE: TREATMENT OF RECURRENT ELECTROGRAPHIC NONCONVULSIVE SEIZURES (TRENDS) STUDY

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Abstract:

Nonconvulsive seizures (NCSs) and nonconvulsive status epilepticus (NCSE) are electrographic seizures (ESz) that are not associated with overt clinical seizure activity. NCSs are distinct ESz, while NCSE has ongoing, continuous electrographic seizure activity. Both are common in critically ill patients admitted to hospital intensive care units (ICU), and studies have shown that about 20% of ICU patients undergoing cEEG monitoring will have NCSs/NCSE. Though the treatment for convulsive SE is well established, there is no clear consensus for the treatment of NCSs/NCSE. Antiepileptic drugs (AED), such as phenytoin (PHT) and fosphenytoin (fPHT), used in convulsive SE are also used to treat NCSs/NCSE despite lack of data for their appropriateness for these conditions. Recent studies have shown that very aggressive treatment of NCSs/NCSE can lead to worse outcomes as the AED used can have significant adverse effects. Recently, several IV AEDs have become available for substitution therapy when their oral use is not possible. There are retrospective case reports and case series that suggest that these AED may be beneficial for treatment of NCSs/NCSE. The Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENDS) study will compare the efficacy and tolerability of fPHT and LCM in patients having NCS as noted by cEEG monitoring. The study is currently open to recruitment and has 13 sites in the United States. A total of 200 subjects will be randomized, 100 to each treatment arm.

Text:

Nonconvulsive seizures (NCS) are seizures that have only subtle clinical phenomena and alteration of consciousness. Clinical features described with NCSs include agitation, facial or limb muscle twitching, nystagmus, sustained eye deviation, catatonia, and psychosis. NCS are often noted in critically ill patients who are already encephalopathic. In this group of patients, up to 90% of seizures may be nonconvulsive, making their detection difficult. NCS are detected with continuous electroencephalographic (cEEG) monitoring, and appear as electrographic seizures (ESz; seizures that do not have a clinical correlate). The terms NCS and ESz are used interchangeably when referring to seizures detected on cEEG that do not have an obvious clinical correlate.

Several studies have noted that the frequency of NCS in neurologic intensive care units (NICU) and other ICU is high. One of the first studies noted that 33.9% of patients undergoing cEEG monitoring in the ICU had ESz, and almost half of them were in nonconvulsive status epilepticus (NCSE). More recent studies have noted that about 20% of critically ill patients undergoing cEEG monitoring have ESz. After treatment of convulsive seizures, some patient stop having the overt manifestation of seizure activity but continue to have ESz.

NCS are intermittent, and between seizures the EEG will show variable periods of intervening interictal activity. NCSE, on the other hand, has continuous, ongoing electrographic epileptiform activity. When ESz activity persists for greater than 30 minutes, it is considered NCSE. Because NCS are intermittent, a 20-30 minute EEG may not detect them. Though it is widely believed that cEEG is needed to assess for NCS, there is some uncertainty about how long cEEG monitoring should be continued to exclude the possibility of NCSs in comatose patients. One study noted that 95% of patients with NCSs had their first seizure within the first 24 hours of monitoring. However, only 15% of these patients were seizing at the start of the EEG, and only about 50% had their first seizure within the first hour of monitoring. Another area of some uncertainty is how long monitoring should be continued after seizures have been controlled. A recent survey of neurologists who perform cEEG monitoring noted that most respondents (47%) continue monitoring for 24 hours after control of seizures.

Patients noted to be in convulsive SE are aggressively treated with AEDs and sedative agents such as pentobarbital. How aggressively NCSE and NCSs should be treated is much less clear as the long-term complications of these conditions are not as clear as with convulsive SE. A systematic review comparing treatment of convulsive SE and NCSE with intravenous (IV) AEDs and pentobarbital noted 50% mortality regardless of the treatment. Pentobarbital was more effective in stopping the ESz but more often resulted in medical complications such as hypotension, leading to overall comparable mortality. Another study compared treatment of NCSE with IV benzodiazepines in the ICU to less aggressive treatment outside the ICU. Despite no difference in disease severity, patients receiving benzodiazepines had a higher mortality. The realization that aggressive treatment of NCSs with sedative IV medications may be detrimental for patients is reflected in a recent survey of neurologists, which noted much more frequent use of nonsedating AEDs (such as phenytoin [PHT] and levetiracetam) as compared with IV benzodiazepines for the treatment of NCSs.

The Treatment of Recurrent, Electrographic, Nonconvulsive Seizures (TRENDS) study is designed to compare the efficacy and tolerability of fosphenytoin (fPHT) and lacosamide (LCM). This study became possible because of the existence the Critical Care EEG Monitoring Research Consortium (CCEMRC). This is a consortium of like-minded investigators and facilities that came together to study EEG patterns in critically ill patients. Members of this consortium have the facility to perform cEEG monitoring in the ICU and have an interest in, among other things, studying the treatment and outcomes of NCS and NCSE.

Rationale

The largest randomized, double-blind study of convulsive SE demonstrated that lorazepam was more efficacious than phenytoin (PHT) alone in controlling convulsive SE. The other 2 arms of the study, phenobarbital and diazepam followed by PHT, were not significantly different from lorazepam or PHT alone. Because of the sedation and complications associated with IV phenobarbital, it is currently used as a second- or third-line agent. A benzodiazepine followed by PHT is often recommended as the first-line therapy for convulsive SE.

Unfortunately there are no randomized, multicenter treatment trials for NCS. Treatment recommendations for con-

vulsive SE are often extrapolated to NCSs despite lack of data confirming the appropriateness of this practice. Several studies have shown that aggressive treatment of NCSs with sedating AEDs may lead to more complications and worse outcomes than if they were managed less aggressively. Fosphenytoin (fPHT) is used in this patient population routinely without data confirming its utility. Small retrospective studies have suggested that the new AED lacosamide (LCM), available in IV formulation, is effective in this patient population.

The TRENDS study is a phase II, prospective, multicenter, open-label, randomized study comparing the efficacy of IV LCM with IV fPHT in controlling frequent NCSs using cEEG monitoring. The on-site EEG reading physician will interpret the cEEG in real time for treatment purposes, and central reviewers providing final cEEG interpretation for study purposes will review the data at a later date. Both will be blinded to treatment. The treating physician responsible for the clinical care of the subject will not be blinded to treatment.

Clinical Experience with Study Drugs

PHT has been available for several decades. There is extensive experience with the use of PHT in the NICU. The only randomized convulsive SE study, referred to above, confirmed the utility of PHT when combined with a benzodiazepine. The IV formulation contains 40% propylene glycol and 10% ethanol to maintain PHT solubility. Extravasation of IV-administered PHT can cause phlebitis and "purple glove syndrome." Other common side effects of PHT include cardiotoxicity, hypotension, hepatotoxicity, leukopenia, thrombocytopenia, pancytopenia, and hepatic enzyme induction. Despite these complications, PHT has been used as a first-line treatment for seizures and SE in the ICU because of familiarity with the compound and lack of other suitable IV AEDs. With the introduction of fosphenytoin (fPHT), a water-soluble PHT prodrug, IV administration became safer with a lower risk of phlebitis; however, many of the other complications still persist. When used in SE, fPHT is administered as a bolus ("loading dose") of 18 to 20 mg PE/kg, followed by 5 mg PE/kg/day. The efficacy of PHT and fPHT in controlling NCSE or NCSs in the ICU is uncertain. There is no large, multicenter trial documenting efficacy of PHT or its superiority to any other AED in this condition.

Adverse events reported with fPHT are similar to those seen with PHT, with nystagmus, dizziness, headache, somnolence, and ataxia being most common. Additionally, pruritus is seen more often with fPHT. During the infusion, however, the incidence of pain, burning, erythema, tenderness, and swelling is lower with fPHT. In one study, the infusion of PHT had to be slowed or stopped more often than the fPHT infusion. Studies have suggested that fPHT is a safer alternative to PHT, and in most situations when IV PHT is needed, fPHT is used. However, a recent white paper commissioned by the Food and Drug Administration (FDA) noted that the frequency of cardiovascular (arrhythmia and hypotension) and dermatologic (Stevens Johnson syndrome and pruritis) complications was similar for PHT and fPHT.

Lacosamide has undergone 3 pivotal, double-blind, placebo-controlled trials involving patients with uncontrolled partial-onset seizures. A total of 1092 subjects were studied across the 3 trials. In all studies subjects were started on a LCM dose of 50 mg twice daily and force-titrated to target dose in 6 weeks. Target doses were 200 mg/day, 400 mg/day, and 600 mg/day. The pooled analysis of all 3 trials showed that the percent seizure reduction was 18.4% for placebo, 33.3% for LCM 200 mg/day, and 36.8% for LCM 400 mg/day. The LCM 600 mg/day dose showed a 40% and 38% reduction in seizure frequency in 2 trials. All 3 doses were statistically superior to placebo, but there was no significant difference between the 400-mg/day and 600-mg/day treatment arms. The 600-mg/day treatment arm had a higher incidence of side effects; therefore the FDA has approved only the 200-mg/day and 400-mg/day doses.

In clinical trials LCM was well tolerated and most treatment-emergent adverse events (TEAEs) were mild or moderate. The most common TEAEs were headache, nausea, and dizziness. Discontinuation rates of LCM were 5.2% in the placebo group, 9.6% in the 200-mg/day group, and 17.2% in the 400-mg/day group, and the TEAEs leading to discontinuation were most often dizziness, vomiting, and diplopia. The incidence of rash was not significantly elevated in the LCM arms. Electrocardiographic (ECG) evaluations revealed a slight increase in the PR interval of 1.5 milliseconds and 3.1 milliseconds in the 200-mg/day and 400-mg/day groups, respectively. First-degree at-

rioventricular (AV) block was noted in 3 patients, and no patient had second- or third-degree AV block. However, 2 case reports have noted second- and third-degree heart block in 1 patient each, the latter with a very high dose of LCM. Hematology and serum chemistry values did not change significantly in the LCM-treated groups.

Bioavailability of IV LCM has been noted to be the same as oral LCM when administered over 30 or 60 minutes. A multicenter, double-blind, double-dummy, randomized trial of subjects enrolled in an open-label LCM study (patients were already taking LCM) was performed to evaluate the safety and bioavailability of IV LCM 200 to 600 mg/day. Thirty- and 60-minute infusions showed bioavailability comparable to oral LCM, and no additional adverse events (AEs) were noted. Specifically no significant ECG changes were noted. A subsequent study evaluated safety of IV LCM boluses of 200 mg, 300 mg, and 400 mg administered over 15 minutes to outpatient subjects with epilepsy but naïve to LCM. These subjects were then administered oral LCM 100 mg twice daily, LCM 150 mg twice daily, or LCM 200 mg twice daily for 6.5 days. The percentages of subjects who withdrew from the study due to AEs were 0% for the LCM 200-mg group, 6% for the LCM 300-mg group, and 16% for the LCM 400-mg group. Only 1 subject had a serious adverse event (SAE), chest pain. This subject was in the 400-mg group. No ECG changes were reported. A retrospective study done at Duke University Medical Center found that 60% of patients receiving LCM for NCSE or NCSs achieved control of their seizures. Patients with NCSs responded more frequently than those who were in NCSE. A recent review of the retrospective use of LCM in treatment of refractory SE showed improvement in 76 of 136 (56%) patients. These favorable studies and properties of LCM suggest that it may have a role in patients with frequent NCSs.

Objectives

The primary objective of this study is to evaluate the efficacy of LCM compared with fPHT in the treatment of NCSs as measured by cEEG monitoring in critically ill subjects. The secondary objectives are: 1) to evaluate the safety and tolerability of LCM compared with fPHT, and 2) To compare the functional outcomes of subjects treated with LCM compared with fPHT

Subject Selection

All subjects undergoing cEEG monitoring and having ESz will be considered for enrollment. To qualify for randomization, subjects must have at least 1 ESz lasting at least 10 seconds, with or without a clinical correlate. If a new AED has been started, the subject must have an ESz after starting that AED.

Subjects will be excluded if they are already being treated with or have a contraindication for the use of one of the study medications. Additionally, if the subject is having ongoing generalized convulsive SE or NCSE (defined as at least 30 minutes of ESz activity per hour of cEEG activity) they will not be eligible for participation. Subjects with generalized absence seizures or absence status epilepticus will not be eligible either. Those subjects admitted for epilepsy surgery evaluation or spell characterization will also not be eligible. Finally, subjects who have ESz following cardiac arrest and anoxic brain injury or those undergoing therapeutic hypothermia are not eligible.

Overview of Study Design

This trial will include a pre-acute-treatment period, an acute-treatment period, a post-acute-treatment period, and a long-term follow-up period.

In the pre-acute-treatment period consent for study participation will be obtained, a pregnancy test will be performed on all women of childbearing potential and the baseline seizure count/frequency will be established. All subjects must be on cEEG monitoring during this period. Subjects will be randomized, and study drug will be administered, marking the beginning of the acute-treatment period.

In the acute-treatment period, cEEG monitoring will be continued, and the primary and most secondary endpoints will be assessed. Subjects will initially be randomized to either fPHT or LCM. A bolus of fPHT 20 mg PE/kg at a rate no greater than 75 mg PE/minute will be used. Subsequent twice-daily maintenance doses will be 2.5 mg PE/kg. Lacosamide will be administered as a bolus of 400 mg IV. The daily maintenance dose will be 200 mg twice daily. If a breakthrough seizure occurs after the bolus, a rebolus of the same AED will be given. A rebolus of 5 mg PE/kg IV fPHT will be given to subjects receiving fPHT; their daily maintenance dose will be 5 mg PE/kg. A rebolus of 200 mg IV LCM will be given to subjects receiving LCM; as

a result of the rebolus, their daily maintenance dose will be 300 mg twice daily. The acute treatment phase will end once the subject has not had an ESz 24 hours after bolus or rebolus of study medication.

If a seizure occurs within 24 hours after a rebolus has been administered, the subject will be crossed over to the second treatment arm. In the second treatment arm, the subject will receive the study drug that was not administered first. The same bolus and rebolus paradigms will be used as were used for the first treatment arm. Once again, the acute treatment phase will end once the subject has not had an ESz 24 hours after bolus or rebolus of second study drug. If the subject has a seizure within this time frame, the acute treatment phase will be terminated and the subject treated per best medical practice.

In the post-acute-treatment period, functional outcome will be assessed. Ongoing maintenance AED therapy during the post-acute-treatment period is at the treating physician's discretion, so efficacy of ongoing maintenance AED therapy will not be assessed in this study.

In the long-term follow-up period, subjects or their families will be contacted by telephone at 6 months, 12 months, and 24 months post-randomization, to determine if the subject is alive and if so, whether the subject has continued to have seizures since participation in the study and is continuing with AED therapy.

Endpoints

The primary endpoint will be no recurrence of seizures for 24 hours following initial study drug bolus/rebolus with LCM vs. fPHT, as measured by cEEG monitoring with blinded review. There are several secondary endpoints as well, including percentage of subjects who require a second AED to control NCSs and functional outcomes.

Current Status of Study

The study is actively recruiting subjects.

The TRENdS study is projected to last for another 12-18 months. It will be the first study in which two AEDs have been studied in critically ill patients having NCS using cEEG monitoring as a marker for ESz. Data obtained from this study has the potential to change the current practice of treating acute seizures in critically ill patients.

IL23

TITLE: COMPARISON OF ADD-ON LEVETIRACETAM VERSUS PLACEBO IN A PREHOSPITAL RANDOMIZED TRIAL IN CONVULSIVE STATUS EPILEPTICUS

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Text:

Generalized convulsive status epilepticus (GCSE) is associated with high level of morbidity and mortality. Improvements on the therapeutic management of the patients with GCSE are needed. Several clinical and experimental data have suggested that the earliest is the drug administration, the highest is the percentage of controlled GCSE (Lowenstein, 2006, Kapur and Macdonald, 1997, Bleck, 2006). But, only few studies have been performed before the admission of the patients at the hospital (Alldredge et al., 2001). Other data made the hypothesis that it would more efficient to associate two drugs, acting on different pathways in order to interrupt the status (Wasterlain, 2006).

We are conducting a prehospital, randomized, double blind, placebo-controlled, phase III clinical trial, evaluating the efficiency of intravenous levetiracetam in association with clonazepam versus clonazepam alone for GCSE (ClinicalTrials.gov identifier: NCT01150331). This trial is managed by prehospital physicians within emergency mobile units (SAMU).

Adult patients with GCSE, lasting more than 5 minutes or showing generalized convulsions without recovery of consciousness between seizures, confirmed by prehospi-

tal physicians, are included in the study. Post-anoxic and subtle status are excluded, together with status related to a pathological condition requiring an immediate surgery. Patients who do not benefit from the French medical insurance and women with possible pregnancy are not included. The trial is conducted in Paris, France and surrounding departments.

The therapeutic arm consists of the initial co-injection of 1 mg clonazepam and 2500 mg levetiracetam in 5 minutes. The control arm consists of the injection of 1 mg clonazepam and the placebo in 5 minutes. A second injection of clonazepam can be performed after 5 minutes if the status persists.

The primary outcome measure is the percentage of patients that stop to convulse in the 15 minutes following the initial injections.

Secondary outcome measures include i) the duration between the first injection and the interruption of the convulsion, ii) the duration between the first injection and the presence of signs of awakening, iii) duration of hospitalization, iv) percentage of patient receiving the second injection of clonazepam after 5 min. Other secondary outcome measures are indicated at ClinicalTrials.gov.

Emergency medical consents are obtained from family member, if they are present. In addition, an informed consent for continued participation is obtained from the patients, when they become awake.

The status of the study as of January 2013, consists in 191 patients included. Recruitment was stopped at the end of November 2012. The preliminary analysis of the pre-hospital phase did not show any significant difference between the two groups, as a function of the primary outcome parameter (percentage of patients that stop to convulse in the 15 minutes following the initial injections). The monitoring is still ongoing for the hospital phase and the secondary outcome measures.

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IL24

TITLE: SGE-102 – A NOVEL THERAPY FOR REFRACTORY STATUS EPILEPTICUS

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Text:

Status epilepticus (SE) is acknowledged as a neurological emergency with significant morbidity and mortality; the prognosis of the subgroup of patients who are refractory to first and second line therapies is particularly grim. The mortality rate among such patients is estimated to be about 35% and, at least 1/3 of the patients who recover, do so with significant neurological morbidity^{1,2,3,4}.

There is, therefore, a dire need for an effective treatment for patients in "refractory" SE (RSE). There are established therapies for "early" status epilepticus (benzodiazepines) and for "established" SE (fos-phenytoin, valproic acid, etc) that have been approved for marketing by regulatory

agencies in several countries. There are, however, no approved treatments for patients in RSE. The commonly used medications for patients whose seizures have been refractory to first and second line agents include midazolam, propofol, pentobarbital but all of these medications are used "off-label" and none of them has proven efficacy in SE. The use of these agents to treat patients in refractory status epilepticus has been the subject of several retrospective reviews^{5,6,7,8}; there has been, however, only one attempt at a prospective, randomized, double-blind trial aimed at evaluating the comparative efficacy and side-effect profile of two of these agents. (This trial did not complete because of enrolment issues)⁹.

SGE-102 for the treatment of Refractory Status Epilepticus:

To address the need for a proven treatment for RSE, a novel compound, SGE-102, based on allopregnanolone is being developed. The rationale for this development lays in the fact that allopregnanolone, a neurosteroid, allosterically modulates both synaptic and extra-synaptic GABA_A receptors. As seizures become prolonged benzodiazepine-sensitive GABA_A receptors, which are only present in synapses, become internalized and functionally inactive¹⁰. Extra-synaptic receptors are not internalized as seizures continue and therefore are a target through which allopregnanolone might treat SE, even when benzodiazepines have become ineffective¹¹.

Allopregnanolone has been shown to be effective in pre-clinical models of seizures and status epilepticus. This includes the enhancement of GABA-evoked chloride currents in cultured hippocampal neurons¹², the protection against pilocarpine or kainate induced limbic seizures and SE, with higher protective index values than clonazepam¹³, protection against bicuculline or picrotoxin induced seizures¹⁴, the lack of tolerance to pentylenetetrazol (PTZ) induced seizures in mice¹⁵, and a complete suppression of generalized amygdala-kindled convulsions¹⁶. A rat model of SE induced by kainate has shown that allopregnanolone (30 mg/kg, ip) eliminated SE whether administered at 10 minutes or at 70 minutes following chemoconvulsant administration, whereas diazepam (50 mg/kg, ip) was only effective at 10 minutes¹⁷.

Phase 2 Clinical Trial of SGE-102 for RSE:

In that there has never been a successfully completed clinical study to prove the efficacy of a therapy for RSE, a novel trial design is presented. The design is a double-blind, placebo-controlled, add-on trial in adult patients in RSE for < 24 hours, i.e., those patients who have failed to respond to first and second-line treatments and are being considered for drug-induced suppression of seizure activity/coma. In this trial, at the point when the physician decides to induce suppression of seizure activity and clinical coma in a patient who has not responded to first and second line medications, the patient will be assigned in a randomized fashion, to SGE-102 + midazolam IV or placebo + midazolam IV. This study will also be done in selected centers where cEEG can be performed and at which there is experience in treating RSE. Except for the treatment with study drug (placebo or SGE-102) + midazolam IV, all subjects will receive the standard of care, as per the center's protocol, for adults in RSE. All patients will be intubated.

After starting treatment with midazolam + study drug, the patient will be progressively weaned off midazolam IV. The patient will remain, however, on study drug, unless rescue medication is required. If no rescue medication is required and the patient remains seizure free, the study drug will be tapered and discontinued over 24 hours. If while on midazolam, hypotension (systolic BP < 90 mm Hg) occurs, the midazolam infusion will be suspended or reduced by half and the patient will be treated clinically as appropriate (e.g., vasopressors). If seizure activity resumes at any time during or after the weaning of midazolam, the patient will be treated as medically appropriate in the view of the investigator (including possibly restarting the midazolam IV at the same dose as before, or administration of another general anesthetic).

The primary efficacy assessment will be the determination of successful control of the patients' SE. Successful control will be defined by criteria such as the following: the patient is alive; there was no need, due to recurrence of seizures, to re-titrate midazolam IV or to use another general anesthetic from one hour after starting study drug + midazolam until the end of weaning from study drug. In addition, an assessment will be made of "post-treatment seizures" --- any seizures occurring within 48 hours after initially discontinuing study drug. Also, the functional out-

come of the patient one month after the onset of therapy will be reported

Safety will be addressed through an assessment of the incidence and severity of treatment emergent adverse events and clinically important changes in safety assessments (including vital signs, clinical laboratory tests, electrocardiographic monitoring, electroencephalographic monitoring, physical and neurological exams). All patients will be in NICUs where constant monitoring for AEs will take place. The sample size was derived based on assumptions derived from retrospective and observation studies on the success rate of midazolam IV in treating RSE. The studies used to derive this efficacy assumption used similar efficacy endpoints to the ones that will be used in his protocol. The sample size will be derived to have 90% power to show a difference between the SGE-102 group and the placebo group with an alpha level of 0.05.

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IL25

TITLE: VALNOCTAMIDE AND SEC-BUTYL-PROPYLACETAMIDE (SPD) FOR ACUTE SEIZURES AND STATUS EPILEPTICUS

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Abstract:

sec-Butyl-propylacetamide (SPD) is a one-carbon homologue of valnoctamide (VCD), a chiral constitutional isomer of valproic acid's (VPA) corresponding amide valpromide. VCD has a potential in epilepsy including status epilepticus (SE) and neuropathic pain, and is currently being developed for the treatment of bipolar disorder. Both VCD and SPD possess two stereogenic carbons in their chemical structure. SPD possess a unique and broad-spectrum antiseizure profile superior to that of VPA and better than that of VCD. In addition SPD blocked behavioral- and electrographic-SE induced by pilocarpine and soman (organophosphate nerve gas) and afforded in vivo neuroprotection that was associated with cognitive sparing. VCD has similar activity as SPD in the pilocarpine-induced-SE although at higher doses. The activity of SPD and VCD against SE is superior

to that of diazepam in terms of rapid onset, potency and ability to block SE when given 20 to 60 min after seizure onset. When administered 20 and 40min after SE onset, SPD (100-174mg/kg) produced long-lasting efficacy (e.g., 4-8hr) against soman-induced convulsive- and electrographic-SE in both rats and guinea pigs. SPD activity in the pilocarpine- and soman-induced SE models when administered 20 to 60 min after seizure onset differentiates SPD from benzodiazepines and all other AEDs.

Text:

Introduction

Valnoctamide (VCD) is a CNS-active chiral constitutional isomer of valpromide, the corresponding amide of valproic acid (VPA) that exhibits stereoselective pharmacokinetics (PK) in humans and animals (Baler et al., 1997; Baler and Yagen, 2007; Baler, 2012). sec-Butyl-propylacetamide (SPD) is a one-carbon homologue of VCD (White et al., 2012). Both VCD and SPD possess two chiral centers in their chemical structure. VCD (racemate) was commercially available as an anxiolytic drug (Nirvanil®) in several European countries from 1964 until as recently as 2005 (Baler and Yagen, 2007; Baler and White, 2010). VCD is now being developed for the treatment of patients with bipolar disorder and also has a potential in epilepsy and neuropathic pain (Bersudsky et al., 2010; Baler et al., 2013).

Anticonvulsant activity

VCD [racemate and/or two of its individual stereoisomers: (2R,3S)-VCD and (2S,3S)-VCD] demonstrated activity in various anticonvulsant models in mice (MES, scMet and 6Hz) and rats (MES and scMet) (Isoherranen, 2003; Baler & Yagen, 2007; Kaufmann et al., 2010). In all these anticonvulsant tests, VCD (racemate or individual stereoisomers) was 3-16 times more potent than VPA. The rat (po) MES-ED₅₀ values were: 29mg/kg (racemic-VCD), 34 mg/kg [(2R,3S)-VCD] and 64 mg/kg [(2S,3S)-VCD], and the rat-scMet- ED₅₀ values were: 54mg/kg (racemic-VCD), 11 mg/kg [(2R,3S)-VCD] and 33 mg/kg [(2S,3S)-VCD] (Baler et al., 2010 and 2013; Kaufmann et al., 2009 & 2010).

SPD's wide anticonvulsant activity (compared to VCD and VPA) in various rodent epilepsy models, including: maximal electroshock (MES), 6Hz psychomotor, subcutaneous metrazol, picrotoxin, bicuculline, audiogenic and corneal and hippocampal kindled seizures are presented in Table 1

(White et al., 2012).

Activity in benzodiazepine-resistant status epilepticus (SE)

Benzodiazepines such as diazepam are generally considered first-line therapy. Traditional antiepileptic drugs (AEDs) including phenytoin and VPA are second-line therapy for refractory SE (White et al., 2012). The anesthetics propofol and pentobarbital provide a third-line of therapy. First- and second-line therapies often do not suppress electrographic SE (ESE), and third-line therapies cannot be administered in the field (Pouliot et al, 2013). Therefore, a pressing need exists for novel AEDs to treat refractory SE.

The use of nerve agents for experimentation is highly restricted and limited to specific research sites, and nerve agents cause diverse systemic effects that can confound quantitative analyses of drug actions on repetitive seizures and ESE (McDonough et al., 2000). A widely used approach involves a single-dose i.p. treatment with pilocarpine, preceded by lithium. Accordingly, electrographic activity after lithium-pilocarpine treatment has thus been used to model the severe ESE that can result from nerve-agent exposure (Lehmkuhle et al., 2009; Pouliot et al., 2013). Because it is well-established that non-convulsive SE can persist after aggressive pharmacological treatment, prolonged and continuous EEG recording has become increasingly important in the diagnosis of ESE (Bautista et al., 2007). The need to analyze the effects of potential therapeutic agents on ESE led to the development of an algorithm to quantify ESE activity (Lehmkuhle et al., 2009).

SPD was evaluated for its ability to block benzodiazepine-resistant status epilepticus (SE) induced by pilocarpine (rats) and soman (rats and guinea pigs) following i.p. administration. SPD was tested for its ability to block excitotoxic cell death induced by the glutamate agonists N-methyl-D-Aspartate (NMDA) and kainic acid (KA) using organotypic hippocampal slices and SE-induced hippocampal cell death using FluoroJade B staining. The cognitive function of SPD-treated rats that were protected against pilocarpine-induced convulsive SE was examined 10-14 days post SE using the Morris water maze (White et al., 2012).

SPD was highly effective and displayed a wide protective index ($PI = TD_{50}/ED_{50}$) in the standardized seizure and epi-

lepsy models employed (Table 1). The wide PI values of SPD demonstrate that it is effective at doses well below those that produce behavioral impairment. Unlike VCD, SPD also displayed anticonvulsant activity in the behavioral rat pilocarpine model of SE when administered 30 min after the induction of SE in rats. SPD-ED₅₀ against convulsive SE in this model was 84mg/kg while VCD (80mg/kg) and VPA (300mg/kg) were inactive when given 30 min after SE onset (White et al., 2012). SPD was not neuroprotective in the organotypic hippocampal slice preparation; however, it did display hippocampal neuroprotection in both SE models and cognitive sparing in the Morris water maze test which was associated with its antiseizure effect against pilocarpine-induced SE. SPD (130mg/kg) strongly suppressed electrographic status epilepticus (ESE) when given 30 minutes after seizure onset, but not at 60 min. However higher SPD dose (180 mg/kg) profoundly suppressed ECE similar to propofol (100 mg/kg) and pentobarbital (30 mg/kg). VCD (180 mg/kg) was also efficacious in suppressing ESE 30 min after seizure onset (Pouliot et al., 2013).

When administered 20 and 40min after SE onset, SPD (100-174mg/kg) produced long-lasting efficacy (e.g., 4-8hr) against soman-induced convulsive and electrographic SE in both rats and guinea pigs. When SPD dissolved in multisol (propylene glycol: alcohol and water for injection 5:1:4) was administered 20 minutes after soman-induced SE in rats its ED₅₀ value was 71 mg/kg and the seizure termination latency was 6.8 min. SPD-ED₅₀ values in guinea pigs were 67mg/kg and 92mg/kg when administered at SE onset or 40min after SE onset, respectively (White et al., 2012).

Pharmacokinetics (PK)-pharmacodynamic (PD) correlation

A stereoselective pharmacokinetic (PK) analysis of VCD was previously described and is summarized in the EILAT X conference manuscript. (Baler et al., 2010). SPD PK was studied following i.p. administration (60 mg/kg) to rats of racemic-SPD. SPD had the following PK parameters: clearance (CL) 0.3 L/h that was mainly metabolic as only 0.1% of SPD dose or CL was excreted unchanged in the urine. In rats SPD displayed a 7-fold higher CL than VCD and due to its higher lipophilicity SPD volume of distribution (V) was 3-times more than that of VCD (White et al., 2012). As a consequence of these opposite trends in

CL and V, SPD half-life was similar to that of VCD. The dose was chosen as the intermediate SPD dose among various ED₅₀ values.

The relationship between SPD PK profile and its efficacy against soman-induced SE (pharmacodynamics-PD) was evaluated following racemic-SPD (60mg/kg, i.p.) administration in the soman SE rat model. A PK-PD correlation showed that SPD effective plasma levels in the soman-induced SE model ranged between 8-40 mg/L (20 min post seizure onset) and 12-50 mg/L (40 min post seizure onset). The time to peak effect (PD-t_{max}) occurred after the PK-t_{max} and may indicate slow distribution of SPD to the extra-plasmatic active site responsible for SPD activity. This slower distribution to the active site may contribute to the fact that SPD effect (expressed as responders' rate) declined significantly slower than SPD plasma levels and in few rats (at the 20min post-seizure onset group) lasted for 24h.

Ongoing and planned studies

Although VPA is the most prescribed AED, its clinical use is restricted in women of child-bearing age and in children due to its teratogenicity and hepatotoxicity, respectively (Baler and Yagen, 2007). Recently, a successful double-blind controlled Phase IIa clinical trial with VCD racemate in patients with mania funded by the Stanley Medical Research Institute (SMRI) was completed (Bersudsky et al., 2010; Baler et al., 2010). This study showed that VCD could be an important substitute to VPA in women of child-bearing age with bipolar disorder.

The development of VCD and its introduction as a new non-teratogenic and potentially non-hepatotoxic new CNS agent that is more potent than VPA, may offer a suitable solution for these clinical needs and for the treatment of therapy-resistant patients with bipolar disorder, epilepsy and neuropathic pain (Baler & White, 2010). Following the successful Phase IIa clinical trial, VCD is currently undergoing a 3-week (SMRI-funded) Phase IIb, randomized, double-blind, placebo- and risperidone-controlled, multicenter study of 300 patients with bipolar manic episodes. The study is a 3-arm monotherapy parallel group trial: a) placebo (n=120), VCD (n=120; 1500mg/day) risperidone (n=60; up to 6mg/day). The study's major objective is to evaluate the efficacy of VCD compared to placebo in patients with acute manic or mixed episodes. The role of risperidone in the

trial is as an active control to ascertain the trial’s validity (Bialer et al., 2013). Since SPD and VCD are chiral compounds with two stereogenic centers there are currently ongoing studies to comparatively evaluate the pharmacokinetics and anticonvulsant activity including pilocarpine- and soman-induced SE of each of the four individual stereoisomers of SPD and VCD.

Conclusions

The results demonstrate that SPD and VCD are a broad-spectrum antiseizure compounds that block SE induced by pilocarpine and soman. SPD affords in vivo neuroprotection that is associated with cognitive sparing. The activity of SPD and VCD against SE is superior to diazepam in terms of rapid onset, potency and its effect on animal mortality and functional improvement. SPD activity at 30 and 60 min after seizure onset in the pilocarpine-induced SE and at 20 and 40 min after seizure onset in the soman-induced SE models differentiates SPD from benzodiazepines and all current AEDs. The fact that SPD’s one-carbon homologue VCD is currently phase IIb shows that SPD has a potential beyond its parenteral anti-nerve gas & anti-SE activity for benzodiazepine-resistant SE. Acknowledgments:The authors thank Dr. Tracy Chen, Dr. Jeff Jiang and Mr. James P. Stables of the NIH–NINDS-Anticonvulsant Screening Program (ASP) for testing the compounds in their anticonvulsant program. This work is abstracted from the PhD thesis of Mr. Tawfeeq Shekh-Ahmad in a partial fulfillment for the requirements of a PhD degree at The Hebrew University of Jerusalem.

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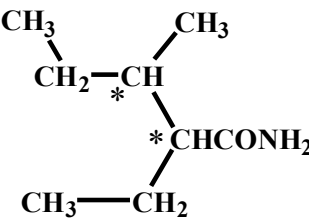
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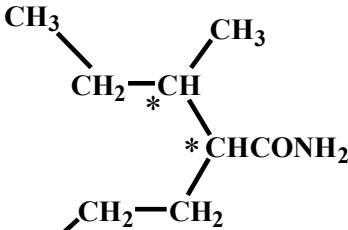
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Anticonvulsant test	SPD-ED ₅₀ (95%CI) (mg/kg)	VCD-ED ₅₀ (95%CI) (mg/kg)	VPA-ED ₅₀ (mg/kg)
Frings Audiogenic Seizures	20 (18-22)	-	155 (110-216)
Maximal electroshock seizure (mice-MES)	71 (55-90)	58 (41-71)	263 (237-282)
Maximal electroshock seizure (rats- MES)	ip: 20 (15-27) po:29 (1-53)	po:29 (19-38)	po:484 (324-677)
Metrazol-induced seizure (mice-scMet)	62 (47-71)	32 (22-45)	220 (177-268)
Metrazol-induced seizure (rats-scMet)	18 (13-25)	po:54 (46-63)	po:646 (466-869)
Picrotoxin-induced seizure (mice-Pic)	17 (9-28)	-	270 (186-356)
Bicuculine-induced seizure (mice-Bic)	94 (87-103)	-	589 (470-765)
Pilocarpine-induced status epilepticus (SE) at 0 min post SE onset	8/8 protected at 65 mg/kg	40 (30-65)	366 (23-575)
Pilocarpine-induced status epilepticus (SE) at 30 min post SE onset	84 (62-103)	0/8 at 80 mg/kg	0/8 at 300 mg/kg
Hippocampal kindled rats	19 (13-28)	~40	-
6 Hz-32mA (mice)	27 (24-30)	37 (26-50)	126 (95-152)
6Hz -44mA (mice)	45 (40-49)	67 (61-72)	310 (258-335)
Mice-Neurotoxicity (TD ₅₀)	88 (81-95)	81 (72-87)	398 (356-445)
Rat-Neurotoxicity (TD ₅₀)	ip: 49 (43-55) po: 131 (94-175)	po:58 (47-66)	po:784 (503-1176)

-^a Not tested
¹Taken form White et al., 2002 and 2012 and Isoherranen et al., 2003.



Valnoctamide (VCD)



sec-Butyl-propylacetamide (SPD)

Figure 1. Chemical structures of valnoctamide (VCD) and sec-butyl-propylacetamide (SPD). Asterisks denote chiral (stereogenic) centers.

TITLE: STIRIPENTOL IN REFRACTORY STATUS EPILEPTICUS

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Abstract:

Benzodiazepines (BZDs), which enhance GABA_A receptor mediated inhibition, are the first-line therapy for treatment of status epilepticus (SE). However, pharmacoresistance to BZDs develops rapidly after SE initiation. This is due to an activity-dependent internalization of BZD-sensitive GABA_A receptors during SE. Stiripentol (STP) is a positive allosteric modulator of GABA_A receptors with a unique subunit selectivity profile. We report that in a rodent model of SE STP terminates behavioral seizures and remains effective during prolonged SE when seizures have become BZD-resistant. In dentate granule cells STP potentiates GABAergic IPSCs as well as tonic GABAergic current. This potentiation persists during prolonged SE, while potentiation of GABAergic inhibition by BZDs is lost. We suggest that STP, either alone or as add-on therapy may prove useful in treating prolonged and BZD-resistant seizures.

Text:

Status epilepticus (SE) is a neurological emergency, characterized by prolonged, self-sustaining seizure activity, and is associated with high morbidity and mortality. SE is more prevalent in younger subjects than in adults, with nearly 50% of cases occurring in children less than 2 years of age. Benzodiazepines (BZDs) are considered the first-line therapy for the treatment of SE. BZDs are positive allosteric modulators of the GABA_A receptor and suppress seizures by enhancing GABA_A receptor mediated inhibition. Unfortunately, clinical experience reveals that SE in at least 35% of patients is refractory to these drugs (Mayer et al., 2002). Benzodiazepine pharmacoresistance can be

attributed to a variety of factors, including seizure etiology. Both clinical and animal studies have shown that the likelihood of a patient responding to benzodiazepines decreases as the duration of SE increases. Pharmacoresistance to BZDs develops rapidly after the initiation of SE due to activity-dependent changes in the subunit composition of the GABA_A receptor. The ability of BZDs to potentiate current at GABA_A receptors requires that these receptors contain $\gamma 2$ -subunits (Mayer et al., 2002). However, following the onset of SE, BZD-sensitive $\gamma 2$ -containing GABA_A receptors are rapidly internalized (Naylor et al., 2005; Goodkin et al., 2008), thus significantly reducing the efficacy of BZDs. In contrast, other BZD-insensitive GABA_A receptors, such as those containing $\alpha 4$ and δ subunits, remain functional on the membrane surface (Goodkin et al., 2008). GABA_A receptors containing γ subunits are important in mediating tonic inhibition. These observations suggest that agents that potentiate $\gamma 2$ -lacking GABA_A receptors may prove beneficial in the treatment of benzodiazepine-resistant SE by potentiating synaptic or tonic inhibition.

Stiripentol (STP, Diacomit) is an anticonvulsant drug approved in Europe for treatment of Dravet syndrome, a severe form of epilepsy in infants. STP is typically co-administered with other antiepileptic drugs as it has been found to increase the efficacy of these drugs through a variety of mechanisms. However, recent studies have shown anticonvulsant effects of STP when it is administered alone. In animal models STP is anticonvulsant in pentylenetetrazol (Poisson, 1984), electrical stimulation (Poisson, 1984) and cocaine-induced seizure models (Gasior, 1999). STP has been proposed to terminate seizures in these models through enhancement of GABAergic inhibition (Poisson, 1984; Quilichini, 2006). Recent studies using recombinant receptors support this conclusion by demonstrating that STP is a positive allosteric modulator of GABA_A receptors containing any of the α , β , or γ -subunits (Fisher, 2009). STP most strongly potentiates receptors containing $\alpha 3$ or δ subunits, suggesting its ability to potentiate both phasic and tonic inhibition. The subunit selectivity of STP suggests that during prolonged SE, when BZD-sensitive GABA_A receptors have been internalized, STP could continue to potentiate GABAergic inhibition. Thus, STP may hold promise for the treatment of BZD-resistant SE. Furthermore, $\alpha 3$ subunit expression is highest in immature brain, suggesting that STP may be particularly effective in terminating

SE in children when SE is most prevalent.

The initial goals of this study were to determine whether STP is active in SE and whether its effects were greater in juvenile animals. Behavioral studies were performed on young (15 – 23 days old) and adult (61 – 63 days old) male Sprague-Dawley rats. SE was induced using the lithium-pilocarpine model. STP (10 – 1000 mg/kg) or diazepam (DZP; 0.3 – 100 mg/kg) was administered at the onset of stage 3 behavioral convulsions (brief SE) and seizures were scored 15 min later. STP and DZP each terminated brief SE in young and adult animals. DZP was equally effective in both age groups. In contrast, STP was significantly more effective in juvenile than adult animals. While STP acts at GABA_A receptors containing any α subunit, it has highest activity at $\alpha 3$ -containing GABA_A receptors (Fisher, 2009). Accordingly, the reduction in anticonvulsant potency of STP with maturation is likely explained by the developmental loss of $\alpha 3$ subunit expression.

To determine whether STP was effective in BZD-resistant SE we compared the ability of STP or DZP to terminate SE when administered at the onset of stage 3 behavioral convulsions (brief SE) or 45 min after the first stage 3 seizure (prolonged SE). As previously reported (Kapur and Macdonald, 1997), during prolonged SE seizures became pharmacoresistant to DZP. In young animals the ED₅₀ for DZP increased 14 fold when DZP was administered following prolonged SE. Similarly, in adult animals the DZP ED₅₀ increased 11 fold during prolonged SE. This decrease in the effectiveness of DZP is thought to be caused by the activity-dependent internalization of $\gamma 2$ -containing GABA_A receptors (Naylor et al., 2005; Goodkin et al., 2008). In contrast, STP was equally effective in terminating both brief and prolonged SE in young animals. STP retained effectiveness during prolonged SE in adult animals as well. We suggest that the ability of STP to remain effective during prolonged SE, when seizures have become resistant to BZDs, is due to the unique subunit selectivity profile of STP at GABA_A receptors.

To further examine the effect of STP on GABAergic inhibition, we characterized the effect of the drug on GABA_A receptor-mediated currents in dentate granule cells. As previously reported (Quilichini, 2006), STP prolonged the decay time of the GABA_A receptor-mediated IPSC. How-

ever, we found that IPSC prolongation was significantly greater in young animals (5-8 days old) than in animals from older age groups (20-26 days old or 59-65 days old). This age-dependence of IPSC potentiation by STP is consistent with the observed age-dependence of the anticonvulsant effect of the drug.

The ability of STP to retain anticonvulsant potency during prolonged SE could be explained by the continued ability of the drug to potentiate the IPSC during SE. To investigate this possibility we compared the effect of STP on IPSCs in dentate granule cells from naïve animals and from animals that had experienced 45 minutes of continuous seizure activity. STP potentiated the IPSC in granule cells from both groups of animals to a similar extent. In contrast, potentiation of the IPSC by DZP was significantly reduced in animals that had experienced prolonged seizure activity. These findings demonstrate that STP, but not DZP retains potency following prolonged SE and suggest that the continued ability of STP to potentiate the IPSC underlies its ability to remain effective during prolonged SE.

Tonic inhibition in the dentate gyrus is mediated by GABA_A receptors containing $\alpha 4$ and δ subunits as well as those containing $\alpha 5$ and $\gamma 2$ subunits (Zhang et al., 2007). The ability of STP to act at receptors containing these subunits suggests that potentiation of tonic GABA currents may contribute to the anticonvulsant effect of STP. We compared the effect of STP on tonic GABA current in dentate granule cells in young (21-23 day old) naïve animals to that in animals that had experienced prolonged SE. STP significantly and similarly potentiated the tonic current in both groups of animals. The continued effectiveness of STP on tonic inhibition during prolonged SE was likely due to the persistence of δ -containing GABA_A receptors on the membrane surface (Goodkin et al., 2008). In contrast, DZP does not act at δ -containing receptors. However, DZP still potentiated the tonic GABA current in granule cells in naïve animals, possibly by acting on extrasynaptic $\alpha 5/\gamma 2$ -containing GABA_A receptors (Zhang et al., 2007). This potentiation by DZP was lost during prolonged SE, likely due to internalization of these $\gamma 2$ -containing receptors (Naylor et al., 2005; Goodkin et al., 2008).

STP can increase GABA release by acting presynaptically on inhibitory terminals (Quilichini et al., 2006). This ac-

tion could contribute to the effects of STP on IPSC decay and tonic inhibition as well as the anticonvulsant effect of the compound. In naïve animals we found that STP did not alter the amplitude of spontaneous miniature IPSCs (mIPSCs), but significantly increased the frequency and decay time of the events. These findings point to both pre- and postsynaptic actions of STP on GABAergic inhibition. The effects of STP on mIPSCs persisted during prolonged SE. In contrast, in naïve animals DZP significantly potentiated only the decay time of mIPSCs, without affecting mIPSC frequency. Thus, DZP acted entirely postsynaptically on GABA_A receptors. As predicted, during prolonged SE, the effect of DZP on mIPSC decay was significantly reduced. Thus, STP, but not DZP acts presynaptically to facilitate GABAergic inhibition and this effect remains during prolonged SE. The presynaptic effect of STP differentiates it from both barbiturates and BZDs, further demonstrating the unique pharmacological profile of this drug.

In summary, these findings suggest that at doses that yield therapeutically relevant concentrations, STP is anticonvulsant by potentiating GABAergic inhibition. The subunit selectivity profile of STP enables it to remain effective despite GABA_A receptor subunit changes during prolonged SE. The need for novel therapies for prolonged SE is underscored by clinical studies showing that the majority of patients undergoing SE do not receive treatment within 30 min of seizure onset (Pellock et al., 2004). The increased duration of these seizures decreases their likelihood of being successfully treated with BDZs. The present study points to the potential utility of STP, either alone or as add-on therapy for treatment of prolonged and BZD-resistant seizures.

Acknowledgements:

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IL27

TITLE: NEUROACTIVE STEROIDS FOR TREATMENT OF STATUS EPILEPTICUS

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Abstract:

Treatment of status epilepticus (SE) involves benzodiazepine administration as a first line agent. Epidemiological studies demonstrate that about one third of SE patients are refractory to intravenous or intramuscular benzodia-

zepines. Mechanism of action for benzodiazepine involves the direct positive allosteric modulation of fast-spiking (phasic) GABA_A receptor. Phasic GABA_A receptors are primarily localized to the synaptic compartment, and have been shown to be rapidly internalized with prolonged seizure, ultimately becoming functionally inactive. Neuroactive steroids, such as allopregnanolone, are endogenous molecules synthesized in the brain that can directly allosterically modulate GABA_A receptors without functionally interacting with classical nuclear hormone receptors. Pharmacologically, neuroactive steroids potentiate both synaptic (phasic) and extra-synaptic (tonic) GABA_A receptors providing them a differential profile that allows them to modulate excitatory drive distinct from benzodiazepines. Importantly, extra-synaptic GABA_A receptors do not show internalization and desensitization during continuous seizure in SE models. Here we describe intravenous allopregnanolone as a powerful anti-convulsant agent that demonstrates substantial protection against seizure, as well as termination of electrographic seizure activity

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P01

New onset Refractory Status Epilepticus -NORSE (SE) and electrophysiological -treatment insights

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Introduction /Background:

Since the descriptions of Van Lierde I (2003) (De novo cryptogenic refractory multifocal febrile SE in the young adult) and Hoerth MT (2007)(Malignant SE syndrome) new insights emerge in clinical diagnostic assessment.

Methods: Descriptives of NMDA –Ab series (2008) considering delat rhythmic onset-pattern and Glutamic Acid Decarboxylase series (Kanter IC 2008)

Results: Immunomodulation with cyclophosphamide (Epilepsia 2008)as suggested empiric treatment and theta /delta activity would be general hillmarks in these series.

Conclusions:

Opinions of Rahul Rathakrishnan and Wilder-Smith (2009) enhance the discussion about pathogenic mechanisms and directions.

P02

Hyponatremia augments kainic-acid induced status epilepticus in the mouse: a model for dysmetabolic status epilepticus

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Status epilepticus (SE) is a dreaded neurological emergency. A reignited interest in SE research has resulted in a more adaptive use of treatment protocols,

and tailoring of treatment to different patient groups is increasing. More knowledge on the effect of different antiepileptic treatments in various forms of SE is therefore needed. We are interested in optimising treatment of SE under dysmetabolic conditions, such as hyponatremia, and have here evaluated whether SE induced by systemic kainic acid could be a suitable platform for such studies. The requirements for the model should be low mortality, high rate of success in inducing SE and an inter-animal variability sufficiently small to allow for readout. After mounting of a three-channel epidural EEG, acute hyponatremia was induced in female C57/B6 mice by intraperitoneal injection of dDAVP and water loading, which was followed 2 hours later by an injection of kainic acid (20 mg/kg). One hour after kainic acid, diazepam 20 mg/kg was administered and the mice monitored for an additional hour. During induction, hyponatremic mice (n = 7) displayed an increased frequency of epileptiform spikes on EEG and 4/7 hyponatremic mice displayed electrographic seizures, which was not seen in normal mice (n = 5). During the EEG-monitoring after kainic acid, hyponatremic mice had significantly longer time with electrographic seizure activity both in the hour after kainic acid treatment and the hour after diazepam treatment. We conclude that hyponatremia augments kainic acid-induced SE, and that this model might be valuable platform for studying treatment of SE in hyponatremia.

P03

GABAA Receptor Trafficking in Hippocampal Neurons during Status Epilepticus

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Introduction/Objectives: GABA_A receptors are the most important inhibitory receptors. They are assembled from various different subunits forming heteropentamers that contain a binding pocket for Benzodiazepines between their α and γ subunits. During prolonged seizures of Status Epilepticus (SE), GABA_A receptors have been shown to

undergo rapid subunit-specific modulation and could therefore play an important role in Pharmacoresistance. We performed a live-imaging study to investigate the trafficking properties and mechanisms underlying the inhibitory plasticity in an *in vitro* model of SE.

Materials/Methods: GABA_A receptor trafficking in hippocampal neurons was studied by live-imaging. Co-expression of super ecliptic phluorin (SEP) – tagged GABA_A receptors and a genetically encoded calcium indicator (redGECO) allowed investigation of the activity-dependent trafficking of surface GABA_A receptor subunits. Epileptic activity of hippocampal neurons was driven by addition of NMDA or perfusion with Mg²⁺-lacking aCSF.

Results: We report a rapid biphasic trafficking response of γ_2 subunit containing GABA_A receptors by perfusion with Mg²⁺-lacking aCSF. These findings indicate that GABA_A receptors are highly dynamic ion channels and undergo rapid modulation by induced repetitive bursting activity.

Conclusions: Whilst previous studies focus on the $\gamma_{2/3}$ / γ_2 subunit, here we report modulation of the γ_2 subunit containing receptors. Despite recent studies investigating the trafficking hypothesis of GABA_A receptors during Status Epilepticus the molecular mechanisms remain widely undetermined. This study shows GABA_A receptors are highly adaptive inhibitory ion channels that may play an important role in seizure-induced inhibitory plasticity.

P04

Effects of long-term treatment with losartan on behavioural disturbances in kainate model of temporal lobe epilepsy

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Background: The selective Angiotensin AT1 receptor antagonist losartan showed neuroprotective and anticonvulsant effect in acute seizure models. The aim of the present study was to analyze the effect of long term losartan treatment during epileptogenesis on diurnal rhythms of behavior in Wistar rats in kainate (KA) model of temporal lobe of epilepsy.

Methods: Status epilepticus (SE) was induced by repetitive KA injections (5 mg/kg/h, i.p.) until sustained convulsive seizures of class III, IV or V (i.e. > 9 motor seizures per hour) were observed in rats for at least 3 hours. The development of chronic epileptic stage was confirmed by the presence of spontaneous motor seizures (SMS) detected by 24 h video monitoring for 4 months. The behavioural tests (open field and elevated plus maze) were executed in the end of losartan treatment (10 mg/kg/day, diluted in drinking water, 4 weeks).

Results: Long-term losartan treatment increased the latency for onset of the first SMS in rats. Only control rats treated with vehicle demonstrated diurnal locomotor activity rhythms. Diurnal rhythms in activity were abolished in losartan-treated rats (control and epileptic). Losartan treatment potentiated the enhancement of locomotion and alleviated the low anxiety level in epileptic rats. Losartan resumed the diurnal variations in anxiety level in epileptic rats.

Conclusions: Taken together, our results suggest that long-term treatment with losartan during epileptogenesis may have potential to prevent some of deleterious consequences accompanying chronic epileptic stage in a phase-dependent mode.

P05

Effects of long-term treatment with melatonin on epileptogenesis, neuronal damage and behavioral changes in kainate model of epilepsy in SHR

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Background: Melatonin is a potent antioxidant with anticonvulsant activities. In the present study, we examined the effects of long term treatment with melatonin during epileptogenesis on the consequences of a kainate (KA)-induced temporal lobe epilepsy in spontaneously hypertensive rats (SHR).

Methods: Status epilepticus (SE) was induced by repetitive KA injections (5 mg/kg/h, i.p.) until sustained motor seizures (i.e. > 9 per hour) were observed in rats for at least 3 hours. The development of chronic epileptic stage was confirmed by the presence of spontaneous recurrent seizures (SRS) detected by 24 h video monitoring. The behavioural tests (open field and elevated plus maze) were executed one month after the end of melatonin treatment (10 mg/kg/day, diluted in drinking water, 8 weeks). The relative neuronal densities were quantified after Nissl staining. Monoamine levels were determined by HPLC.

Results: Melatonin did not change the latency in the appearance of SRS but decreased their frequency during the 5-months period of observation. SHRs exerted an increased locomotor and decreased exploratory activity in chronic phase of epilepsy. Melatonin was able to reverse these deleterious behavioral changes to the control levels. It exerted a protective effect on the cell loss in

the hippocampus (CA1and CA3) and piriform cortex and recovered the decreased hippocampal serotonin (5-HT) levels in epileptic rats.

Conclusions: Data showed that long-term melatonin treatment after SE was unable to suppress the development of epileptogenesis. However, it showed a potential to reduce some of the deleterious alterations developing during the chronic epileptic state.

P06

Heterozygous POLG mutations may predispose patients with Dravet syndrome for acute encephalopathy

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Background. Dravet syndrome is a well-recognized epileptic encephalopathy associated with heterozygous *SCN1A* mutations in most patients and with rare occurrence of acute encephalopathy of unknown etiology.

Methods. We studied 25 children with clinically diagnosed Dravet syndrome. Clinical data, including information on episodes of status epilepticus, were collected from hospital charts. *SCN1A* and *POLG* were screened for mutations by sequencing.

Results. One or more episodes of convulsive status had occurred in 22 patients (88%), associated with acute encephalopathy in three (14%). In one patient with a missense *SCN1A* mutation and normal *POLG*, febrile status at 19 months was associated with extensive bilateral brain oedema and severe regression of all skills. The second patient with a nonsense mutation in *SCN1A*

and a heterozygous p.Trp748Ser mutation in *POLG* had a 12-hour status episode with a focal onset at 2.2 years, associated with severe neurological regression and hyperintensity of the left frontal lobe on MRI. Almost complete recovery of function and resolution of MRI abnormalities occurred within six months. The third patient had a prolonged seizure at 6.5 months with left-sided tonic-clonic semiology, followed by new left-sided hemiparesis lasting for six months. She had a deletion-insertion mutation in *SCN1A* and a heterozygous p.Gly517Val variant in *POLG*. Of the 22 patients with uncomplicated status, 19 (86%) had mutations in *SCN1A* and none in *POLG*.

Conclusion. Rare heterozygous *POLG* variants may increase susceptibility for acute encephalopathy. A possible mechanism could be a compromise in cortical metabolism during the high-energy demands associated with status epilepticus.

P07

Pretreatment with NMDA antagonist dizocilpine abolishes orphenadrine-induced convulsive status epilepticus in rats

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Background

Recently, we described a new model of generalized convulsive SE induced with orphenadrine (ORPH) in rats with interesting characteristics (Rejdak et al., 2011). The current study was aimed to assess the efficacy of new generation antiepileptic drugs (AEDs) and some of the experimental agents in suppressing ORPH-evoked seizures in rats.

Methods

ORPH was administered intraperitoneally (i.p.) in the dose of 80 mg/kg in male Wistar rats. The latency to first seizure,

the number of seizure episodes and the duration of overt SE as well as the incidence of deaths was scored with simultaneous electroencephalographic (EEG) recordings. Subsequently, the effects of the pretreatment with selected new generation AEDs and experimental drugs on ORPH-evoked seizure incidence were studied.

Results

ORPH induced seizures in 100% of animals at a dose of 80mg/kg, associated with low mortality and no drug-related neurotoxicity. Among new generation AEDs: felbamate, levetiracetam, topiramate, lamotrigine and progabide did not affect the seizure incidence. Among the experimental drugs, dizocilpine, the highly selective, non-competitive *N*-methyl-D-aspartate (NMDA) antagonist, dose-dependently affected the occurrence of the SE ($p < 0.001$). However, CGP-39551 competitive NMDA antagonist, showed no effect.

Conclusions

Based on the above findings one may speculate that NMDA activation is partly involved in proconvulsant activity of orphenadrine.

P08

Nrf2 defense pathway: experimental evidence for its protective role in epilepsy

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Background: Epigenetic mechanisms involved in transcriptional regulation of multiple molecular pathways appear as potentially attractive therapeutic interventions for epilepsy, since single target therapies are unlikely to provide both anticonvulsant and disease modifying effects.

Methods: A selection of epilepsy-related gene expression datasets were retrieved using NextBio® software and imported to Ingenuity Pathway Analysis® for transcription factor enrichment analysis. Nuclear factor erythroid

2-related factor 2 (Nrf2) was identified as a candidate for confirmation of mRNA expression in hippocampal tissue from patients with temporal lobe epilepsy and in mice following pilocarpine-induced status epilepticus (SE). Human Nrf2 was overexpressed via an adeno-associated virus (AAV) vector after the onset of spontaneous recurrent seizures (SRS) in the animals. Animals were continuously monitored over 5 weeks following Nrf2 transgene delivery to assess SRS. Quantitative immunohistochemistry using neuronal (NeuN), astrocytic (GFAP) and microglial (Iba-1) markers was performed at the end of the monitoring period.

Results: A significant increase in Nrf2 mRNA expression was observed in human epileptic hippocampal tissue. Nrf2 expression levels increased progressively in mice, reaching a peak at 72 h post SE and then declined. Similar expression patterns were observed for three genes regulated by Nrf2: HO-1, NQO1 and mGST. Remarkably, mice injected with AAV Nrf2 displayed significantly fewer SRS with profound reduction in microglia activation. Hippocampal neurons were preserved, while the number of astrocytes was not altered.

Conclusions: The present results extend the potential of Nrf2-based therapies to epilepsy and add to the rapidly accumulating evidence from other neurodegenerative and inflammatory disease models.

P09

Early deficits in social behavior and cortical rhythms in pilocarpine-induced mouse model of temporal lobe epilepsy

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Background: Although social deficits have been a major concern in epilepsy treatment, the relationship between social behavioral pathogenesis and the time course of epileptogenesis is not well defined. To address this, we investigated social behavioral alterations and cortical

rhythms during the latent period after status epilepticus (SE) and the subsequent chronic period characterized by spontaneous recurrent seizures (SRSs) in a mouse model of temporal lobe epilepsy (TLE):

Methods: According to SRS measurement by video-electroencephalographic (EEG) recordings, mice from days 5 to 7 and days 30 to 40 after pilocarpine-induced SE were used as latent-period epileptic mice and chronic-period epileptic mice, respectively. Mice performed tasks involving sociability/social novelty preference, social interaction, social fear learning, and aggression.

Results: Severe social impairments appeared in latent-period mice and were nearly comparable to those of chronic-period mice. We also found that both the latent- and chronic-period mice showed similar aberrant neural activities (enhanced delta-band activity and reduced alpha- and gamma-band activity).

Conclusion: Our results indicate that social deficits and abnormal neural activities appear at an earlier stage in epileptogenesis regardless of SRS occurrence.

P10

Synergistic effects of perampanel combined with diazepam in the lithium-pilocarpine rat model of status epilepticus

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Background: Perampanel, a structurally novel, potent, orally active AMPA receptor antagonist, was recently approved for adjunctive treatment of partial-onset seizures. In experimental models of status epilepticus (SE), the ability of agents (including other AMPA receptor antagonists) to terminate seizures typically declines as the duration of SE increases. Perampanel has been shown to terminate established, diazepam-resistant status epilepticus in the lithium-pilocarpine rat model of SE. Here, we examined pharmacodynamic interactions between perampanel and diazepam in this model.

Methods: Male Sprague Dawley rats weighing 250–450 g were implanted with an electroencephalography (EEG) electrode on the primary somatosensory cortex, and after at least 1 week recovery, SE was induced with 3 mEq/kg of lithium chloride, 5 mg/kg scopolamine methyl bromide and 30 mg/kg of pilocarpine. Thirty minutes after seizure initiation, perampanel alone, diazepam alone, or the combination, was administered intravenously.

Results: Perampanel at 1 mg/kg failed to terminate EEG seizures, and 5 mg/kg perampanel terminated seizures in a third of rats. Diazepam alone at 5 mg/kg and 20 mg/kg failed to terminate electrographic SE seizures. Combination of perampanel (1 mg/kg) and diazepam (5 mg/kg), doses that were individually ineffective, terminated seizures in all treated rats.

Conclusions: After 30 minutes of SE, at which point it is typically considered to be self-sustaining and resistant, seizures were terminated by combination treatment with perampanel and diazepam at doses that were ineffective alone. Thus, perampanel shows synergistic pharmacodynamic interaction with diazepam in diazepam-resistant and established status epilepticus in the rat.

P11

Perampanel terminates diazepam-resistant status epilepticus in a lithium-pilocarpine rat model

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Background: Perampanel, a structurally novel, potent, orally active AMPA receptor antagonist, was recently approved for adjunctive treatment of partial-onset seizures. In experimental models of status epilepticus (SE), the ability of agents (including other AMPA receptor antagonists) to terminate seizures typically declines as the duration of SE increases. Here, we explored the ability of perampanel and of diazepam to terminate seizures in the lithium-pilocarpine model of status epilepticus.

Methods: Male Sprague Dawley rats were implanted with

an electroencephalography (EEG) electrode on the primary somatosensory cortex and after at least 1 week recovery, SE was induced with 3 mEq/kg lithium chloride, 5 mg/kg scopolamine methyl bromide, and 30 mg/kg pilocarpine. Drugs (perampanel or diazepam) were administered intravenously 10 or 30 minutes after seizure initiation and EEGs evaluated for 60 minutes.

Results: Diazepam (20 mg/kg) terminated seizures when administered 10 minutes after seizure initiation in all animals, but failed to terminate seizures in any animals when administered 30 minutes after seizure initiation. Perampanel, administered 30 minutes after seizure initiation, terminated seizures in one-third of animals at 5 mg/kg and in all animals at 8 mg/kg. At this dose (8 mg/kg), perampanel terminated electrographic SE seizures within 1–5 minutes, with occasional spikes thereafter, and all animals were spike-free at 60 minutes after dosing.

Conclusions: Both perampanel and diazepam were able to terminate SE seizures, but only perampanel terminated seizures in animals with established SE (30 minutes duration), a point at which it is usually considered to be self-sustaining.

P12

Dysplasias of different genesis switch the brain between tonic or clonic seizure reactivity

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Background: Brain dysplasias of different genesis determine variations in susceptibility to seizures depending on the neurochemical specificity of pharmacological agents used to evoke seizures. To verify a considerable discrepancy between the data obtained using different pharmacological models, neurochemically neutral electroshocks were applied here.

Methods: Brain dysplasias of different degrees were produced by exposure of pregnant Wistar rats to single 1.0 Gy dose of gamma rays on gestation days 13, 15, 17 or 19. From the postnatal day 60, their male offsprings (E13s, E15s, E17s and E19s, respectively) were subjected to 21 daily electroshocks to evoke seizures.

Results: Profiles of tonic and clonic reactivity to electroshocks significantly differed from those observed following pilocarpine or kainic acid administration. E17s showed minimal intensity of tonic but maximal of clonic responses. On the contrary, very high tonic and low clonic reactivity was observed in E13s and E15s. Significant correlations were also shown between a broad continuum of anatomical features of dysplastic brains (for example the size of periventricular heterotopias or of the neocortex) and the frequency of maximal tonic and clonic seizures.

Conclusions: Opposite correlations between frequencies of tonic or clonic seizures and sizes of selected brain regions suggest differences in anatomical substrates for the two types of reactivity.

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P13

Modern spectroscopic methods in the analysis of the biochemical basis of neurodegenerative changes in the epileptic rat brain

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Background: Temporal lobe epilepsy (TLE) is the most frequent type of epilepsy in adults. Of the animal models developed to investigate the pathogenesis of TLE, one with pilocarpine-induced seizures is the most often used. The purpose of the following study was to show how the modern spectroscopic techniques based on the unique features of synchrotron radiation can support the research under pathogenesis and progress of epilepsy in the pilocarpine model of TLE.

Methods: Two experimental methods were used to study biochemical changes of hippocampal formations from animals experiencing pilocarpine-induced seizures. These were: X-ray fluorescence microscopy and Fourier-transform infrared microspectroscopy. The first method was used for the topographic and quantitative analysis of selected elements, whilst the second one for investigation of anomalies in distributions of main biomolecules as well as their structural changes. The measurements were carried out at HASYLAB beamline L, ANKA beamline FLUO and SOLEIL beamline SMIS. The used measurement setups and conditions allowed us to carry out the research with the spatial resolutions at the level of single cells.

Results and conclusions: The obtained results confirmed the great usefulness of synchrotron based experimental methods in the research of epileptogenesis and showed that excitotoxicity, mossy fibers sprouting and decreased enzymatic activity of creatine kinase may be the processes responsible for seizure-induced neurodegenerative changes of hippocampal formation and spontaneous recurrent seizures in the chronic phase of pilocarpine model.

Acknowledgements: The studies were supported by the Polish Ministry of Science and Higher Education and Polish National Science Centre grant 2921/B/T02/2011/40.

P14

Cortical postictal refractoriness after status epilepticus in immature rats

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Status epilepticus (SE) induced in 12-day-old rats affects excitability of cerebral cortex measured by duration of epileptic afterdischarges (ADs) – they are shorter in experimental than in control animals 3 days after SE but 6 days after SE the situation is reversed (Tsenov et al. 2007). To analyze if mechanisms arresting seizures are responsible for these changes we started to study postictal refractoriness.

Lithium—pilocarpine SE was elicited in 12-day-old (P12) rats, convulsions were

interrupted after 2 h by paraldehyde. Cortical electrodes were implanted 3, 6, 9, and 13

days after SE. Low-frequency stimulation of sensorimotor cortex with suprathreshold intensity was repeated four times with intervals 1, 10 and again 1 min. Duration of the first and second ADs was compared in both 1-min-intervals and of the first and third ADs (i.e. 11-min interval).

Three days after SE potentiation of the second ADs with 1-min intervals; this prolongation was not marked in control rats. Only relative refractoriness was observed in both experimental and control animals at longer postSE intervals. The longer interstimulation interval resulted in potentiation of the ADs in 21-day-old experimental rats (i.e. 9 days after SE) but not in younger or older animals.

To conclude, we found only transient changes of cortical postictal refractoriness after SE induced in immature rats. Tsenov G, Kubová H, Mareš P: *Epilepsy Res.* 78:178-185, 2008.

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Therapy

P15

First report of successful treatment of refractory tonic status epilepticus with rufinamide

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Introduction: Rufinamide (RUF) is used as an adjunctive antiepileptic agent in Lennox-Gastaut syndrome (LGS), but we are not aware of any published experience in Status.

Method: Clinical case study.

Results: A 24-year-old man with mild autistic spectrum disorder and learning disability presented with a recurrence of tonic seizures, having been seizure free since and off medication since the age of 10. Within days of recurrence, with no identified precipitant, the seizures rapidly escalated until they were occurring every 1-2 minutes, >95% of the time. Benzodiazepines, phenobarbitone and levetiracetam had no impact. Valproate was partially successful at high doses, but led to a hyperammonaemic encephalopathy. Burst suppression was eventually achieved only with a combination of ketamine, propofol and barbiturate with hypothermia. Subsequent trials with high doses of lacosamide, phenobarbitone, further benzodiazepines and topiramate were of no benefit, with seizure recurrence on multiple attempts at withdrawal over a 6 week period. As the electro-clinical picture had features reminiscent of LGS, RUF was rapidly titrated up to a total dose of 3g/day over 5 days. His seizures abated completely for several days despite withdrawal of all sedation, with no apparent adverse effects. Intermittent seizures and self-limiting clusters subsequently recurred, but have further improved on RUF at 4.4g/day, the ketogenic diet and a combination of Valproate and

later Carbamazepine. He was discharged home without any neurological sequelae, though is not yet seizure free.

Conclusion: RUF can be an effective adjunct in the treatment of tonic status epilepticus, and despite rapid escalation was well tolerated.

P16

Benzodiazepine over-dosage in status epilepticus treatment: assessment of intubation need and hospitalization length

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Introduction/Objectives: Respiratory depression is a known dose-dependent complication of benzodiazepines (BDZ), which represent the widely recognized 1st-line status epilepticus (SE) treatment. BDZ overdose could thus be associated with higher morbidity and mortality in this setting.

Methods: Incident SE episodes were identified from a prospective registry (2009-2012), excluding spontaneous remitting SE and cerebral anoxia. The "standard-BDZ-dose" group was compared to the "exceeding-BDZ" group (>30% of the recommended dose), in terms of likelihood to receive oro-tracheal intubation, morbidity (return to baseline versus new handicap) and mortality. Hospitalization length was assessed for subjects receiving oro-tracheal intubation for airway protection versus 26 matched subjects not admitted to ICU.

Results: Among 202 patients, we identified 29 "excessive-BDZ-dose" subjects versus 173 "standard-BDZ-dose". While intubation for refractory SE treatment was equally performed in 10% in each group, 45% of the over-treated patients received oro-tracheal intubation for airways protection, but only 8% in the standard-dose group (p<0.001)). Both groups presented similar clinical outcomes: about 50% returned to baseline, less than 40% acquired a new handicap and 10% died. Oro-tracheal

intubation due to airway protection was associated to significantly longer time in hospital (about 2 weeks instead of 1 week).

Conclusions: This cohort study suggests that the administration of excessive BDZ doses as 1st line SE treatment is not associated to worse outcome (strengthening the prognostic role of etiology and age), but BDZ is related to higher risk for respiratory depression, intubation, and significantly longer hospitalization, potentially exposing patients to unneeded complications and costs.

P17

Intravenous Levetiracetam in Status Epilepticus

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The clinical data of intravenous levetiracetam treatment in status epilepticus is limited. We retrospectively reviewed clinical data of patients who diagnosed as status epilepticus, aged over 15 years, and received intravenous levetiracetam. The study was done at Srinagarind hospital, Khon Kaen University, Thailand. The study period was between August 2010 and June 2012. There were 34 prescriptions of intravenous levetiracetam treatment for patients with status epilepticus. Approximately half of patients were male (18 patients) and the mean age was 58.35 (range 15-91 years). All patients had at least one co-morbidity conditions (Table 2). The four most common causes or precipitating factors of SE were electrolyte abnormalities or hypoglycemia with sepsis (14 times), renal dysfunction (12 times), encephalopathy (11 times), and hepatic dysfunction (6 times), respectively. The seizure control rate was 61.8% or 21 patients. There were 14 patients (41.2%) who were alive and had improvement at the time of discharge. Compared to those with worse outcome, there was no statistical difference in age, gender, type of SE, renal dysfunction, or second-line treatment except numbers of co-morbidity conditions. The worse

outcome group had significantly higher numbers of co-morbidity conditions (p value 0.036). In conclusion, intravenous levetiracetam may be a good option for SE treatment. Having numbers of co-morbidity conditions more than 3 was leading to worse outcomes.

P18

Long Term Immunosuppressive Treatment in a Patient with Recurrent Refractory Status Epilepticus

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Introduction

Increasingly, more patients with refractory status epilepticus (SE) are being treated with immunotherapy with steroids, intravenous immunoglobulins (IVIG) or plasma exchange, even in absence of any evident immunological cause. There are many cryptogenic cases between refractory SE. Some of them may have an immunological etiology despite of the antibodies have not been identified yet.

The aim of the study is to present a patient with relapsing and refractory SE treated acutely with corticoids and immunoglobulins with complete but not maintained improvement. Therefore she had been treated with long term immunosuppressive treatment to prevent relapses.

Methods

Sixty-nine years old woman without personal and pathological antecedents whom suffered 4 refractory aphasic SE in 3 years with clear suspicion of immunological etiology (inflammatory involvement of the limbic area in first MRI was observed and after several months

an hippocampal atrophy was found in a control MRI). Although all neuronal antibodies (antineuropil: antiNMDA, antiGABA, antiAMPA, antiLGI1, antiCASPR2, antiGAD) and onconeural antibodies (Anti-Tr, Ma2, Ma1, AnFi, CV2, AntiRi, AntiYo, AntiHu) were both negative in serum and CSF.

Results

The 4 SE did not respond either to antiepileptic treatment (PHT, VPA, LEV and LCM) or pharmacologic anesthesia, however, a dramatic response to corticoids and IVIG was observed every time. After adding Azathioprine the patient did not suffered more relapses.

Conclusions

Indications and duration of immunotherapy in patients with relapsing limbic encephalitis had to be established.

P19

Efficacy of intravenous lacosamide as add-on treatment in refractory status epilepticus

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Background: Refractory status epilepticus is life threatening condition and appropriate treatment given in time is important. IV Lacosamide showed to have some effects in refractory status epilepticus in previous studies.

Methodes: All patients with convulsive status epilepticus (CSE) and non convulsive status epilepticus (NSE) treated with IV Lacosamide (LCM) in our institution in period October 2011 and December 2012 were retrospectively indentified.

Results: Nine patients, 4 men and 5 women, were indentified. Six patients had NSE and three CSE. Patient's average age was 64(45-76) years old. The IV Lacosamide was give as bolus of 400 mg for all patients. Lacosamide was used in average as a 3(2-5) in NSE and in average as a 7 drug (6-7) in patients with CSE. Lacosamide was given in

average after 1 dag (0-3) after onset of NSE and in overage after 7 (5-9) days after onset of CSE. Six patients (2 with CSE and 4 with NSE) had positive effect of Lacosamide treatment with discontinuation of status epilepticus. Three patients (2CSE and 1 NSE), whom had acute brain lesions as reason for acute status epilepticus, died later on. One patient experienced worsening of her EEG changers after treatment with LCM and required further treatment.

Conclusions: In our small series IV LCM were effective in 67 % cases for treatment of refractory CSE and NSE status epilepticus even if it was give late in course of treatment. Larger studies are needed to confirm our findings.

P20

A Miniature Anesthetic Vaporizer for Status Epilepticus (STONY'S Vapo-Ject)

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Background: Isoflurane/Sevoflurane is widely used as anesthetic agent for its easy control of gas concentration. Isoflurane is also well known as a powerful anti convulsive drug which can stop seizure much faster than current intravenous or rectal medications during Status Epilepticus(S.E). It is essential to stop seizure as fast as possible to protect the brain function from neuronal injuries. Isoflurane is useful, however, necessity of anesthesia machine makes it difficult to apply for the first line treatment of S.E. Our aim is to develop new anesthesia vaporization system which can be used without technical skills, and evaluate the applicability of the system for the treatment of S.E.

Method: We developed a miniature inhalational anesthesia attachment combined with 10 milliliters injector (STONY'S Vapo-Ject). VEO multigas monitor was used to measure concentration every 100 milliseconds for 15 minutes.

Result: In most cases, the increase of concentration of anesthetic agent in the closed circuit was rapid and then declined gradually. After the initial therapeutic increase ET

of Isoflurane to 1% within 15 seconds, moderate increase was kept in 2 minutes. Exhaled gas was removing 99.9% by attached filter in 15 minutes.

Conclusion: Isoflurane was immediately rose to the therapeutic range, even faster than original method. Our APL valve worked as automatic ventilation to control pulmonary concentration and exhaled gas was cleaned by attached filter. This study indicates that VapoJect is applicable to be clinical use and to treat S.E. with Isoflurane as soon as possible to protect the brain function.

P21

Refractory status epilepticus treated successfully with trigeminal nerve stimulation

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Background: Refractory status epilepticus (RSE) accounts for up to 44% of status epilepticus (SE) and is associated with high mortality. External trigeminal nerve stimulation (eTNS) is a newly approved therapy for epilepsy in the EU; however the use of eTNS in the treatment of SE has not been explored.

Methods: Case-report and literature review.

Results: A 32 year-old male with severe drug resistant epilepsy was admitted for complex partial SE. Electroencephalography (EEG) revealed nearly continuous epileptiform discharges over the left frontal region with impairment of awareness. His seizures were refractory to lorazepam, carbamazepine, phenobarbital, levetiracetam, and IV midazolam, necessitating intubation and continuous pentobarbital infusion. Although a burst suppression pattern was achieved with pentobarbital, clinical/electrographic seizures returned when tapered. A trial of eTNS was pursued. TNS was provided at 15 seconds on/15 seconds off at 120 Hz. Four days following eTNS, the pentobarbital infusion was successfully weaned, and the EEG revealed no further clinical/electrographic seizures. His

mental status improved, with return of the ability to follow some commands. Following tracheostomy, he was discharged to a respiratory care facility with moderate disability.

Conclusions: Preclinical studies indicate that eTNS has an antiepileptic effect, and clinical trials in DRE demonstrate that eTNS is safe and effective. This is the first report that eTNS may be useful as an adjunctive treatment in RSE. Given the non-invasive nature of eTNS and its ability to be used in the emergency room and intensive care unit, eTNS should be investigated as an adjunctive treatment for RSE.

P22

Intravenous lacosamide for refractory seizure clusters and status epilepticus: comparison between 2 loading doses: 200 and 400 mg

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Background

The treatment of status epilepticus remains largely empirical. Lacosamide (LCM) is a new AED available in intravenous (IV) form. We report our experience with IV LCM, comparing 2 initial doses, 200 and 400 mg.

Methods

We reviewed the charts of all patients who received IV LCM for status epilepticus or seizure clusters between October 2010 and December 2012. The first patients received an initial IV load of 200 mg of LCM (group 1). Due to poor results with this dosage, we increased the loading dose to 400 mg (group 2). Seizure cessation after LCM, seizure cessation after another AED treatment, and mortality were studied.

Results

Group 1 included 11 patients. Six patients were in non convulsive status epilepticus (NCSE), 3 were in post

convulsive NCSE, and 2 had seizure clusters. Intravenous LCM was the last drug added in 2 patients (18%). Six patients needed further AEDs to stop seizing; in 1 patient, seizure cluster worsened and 2 patients died uncontrolled. Group 2 included 14 patients. Ten patients were in NCSE, 2 were in post convulsive NCSE, 1 was in convulsive status epilepticus and 1 had seizure cluster. LCM was the last drug added in 7 patients (50%). Two patients needed another AED treatment to stop seizing, and 5 patients died uncontrolled.

No serious adverse event occurred.

Conclusion

In this small retrospective study, an initial dose of 400 mg of IV LCM seemed to be superior to 200 mg, stopping status in 50% of the cases.

P23

Open loop chronic electrical stimulation (ChES) of epileptic foci localized in primary and supplementary motor cortices with nonlesional MRI

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Introduction/Objective: The treatment of refractory motor seizures constitutes a challenge. These patients are referred to epilepsy surgery, but resection of the focus can be difficult when primary motor or movement-planning areas are involved. If MRI is non-lesional, the problem is more complicated. (Asztely 2007, Jeha 2008), bringing high risk of sequelae or seizure relapse. ChES has been used with good results in the control of generalized seizures (Velasco 2005 and 2006) and mesial temporal ones (Kerrigan 2004, Velasco 2007, Boon 2007). Elsevich (2006) published a case report with ChES of epileptic foci in motor cortex. Fountas (2006) has performed closed-loop stimulation with good results. We aspire to determine if open-loop ChES decreases motor seizures without disturbing motor function.

Participants/Method: Research and Ethics Committees authorized this study. We included three patients with SMA foci and four with primary motor areas foci. All had non-lesional MRI. We performed phase I and II studies to localize the epileptic foci and the involved functional area (18). Once localized, we substituted the diagnostic electrodes for a permanent ChES electrode. Follow-up period was for one year. Seizure diaries, EEGs and neuropsychological batteries every 6 months were reviewed.

Results: There was a seizure reduction above 85% (85-95%) in all patients. There was no neurologic dysfunction. Only one patient was dropped out due to system rejection, as reported by Oh 2002).

Conclusion: The ChES of epileptic foci in motor cortices is a surgical option to control refractory seizures.

P24

Possible effect of perampanel on focal status epilepticus after generalized tonic-clonic status epilepticus.

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Background: Since in refractory status epilepticus (SE) additional AMPA receptors are built up, perampanel, an AMPA-receptor antagonist, may be effective in this condition.

Methods: A case where perampanel was the last AED introduced in the treatment of a focal SE before its termination is presented.

Results: A woman aged 81 years with symptomatic epilepsy after a stroke was found in the early morning with generalized tonic-clonic SE in her nursing home. Her regular medication was levetiracetam 500 mg and valproate 1800 mg. The SE was terminated with 2 mg Clonazepam i.v. by the emergency doctor. But myoclonic jerks of the left arm and the left side of the face persisted. After cumulative doses of levetiracetam 2750 mg, valproate 600 mg,

lorazepam 1.5 mg, acetazolamide 250 mg and lacosamid 100 mg perampanel 2 mg was introduced into the therapy. Another 2 mg clonazepam and 1000 mg levetiracetam were given on the same day to terminate the jerks for a few hours. The treatment regime scheduled for the next day was levetiracetam 4000 mg, valproate 1800 mg, lacosamid 200 mg. Additionally 2 mg perampanel were given in the morning. In the afternoon another 2 mg clonazepam were needed to suppress the jerks. Afterwards another 2 mg perampanel were given and the daily dose of perampanel was increased to 2 mg twice a day. After this no further spontaneous myoclonic jerks were seen.

Conclusions: Perampanel may be a treatment option in refractory focal SE. Perhaps a loading dose would increase its efficacy.

P25

Analysis of efficiency and safety of topiramate depending on patient's age and forms of epilepsy

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Introduction/Objectives: The aim of the study was analysis of efficiency and safety of topiramate at children and adult epileptic population depending on patient's age and forms of epilepsy.

Materials/Methods: 722 epileptic patients receiving topiramate (male = 374, female = 348) of the age from 3 month till 57 years are observed in dynamics with video-EEG control at the period 2002-2012.

Results: Topiramate was effective at 64,4% of patients (n=465), and among the patient at monotherapy effectiveness (72,2%, at 127 from 176 patients) was higher than in combined therapy (61,9% at 338 of 546 patients). Low efficiency was seen at 27,4% (n=198) patients. The aggravation effect has been noted at 8,2% (n=59) of patients. Drug compliance (for >1 year) was 60,7% (n=438). High efficiency in group <1 year (n=58)

was 55,2% (n=32), low 34,5% (n=20), aggravation 10,3% (n=6); in group 1-3 years (n=201) high efficiency 54,8% (n=110), low 31,8% (n=64), aggravation 13,4% (n=27); in pediatric population >3 years (n=385) high efficiency 67,3% (n=259), low effect in 26,2% (n=101), and 6,5% aggravation (n=25), in adult population >18 years (n=78) the efficiency was 82,1% (n=64), low effect 16,6% (n=13) and aggravation in 1,3% (n=1).

Conclusions: Topiramate is highly effective drug in therapy of idiopathic generalized epilepsies without absences and in symptomatic/cryptogenic focal forms of epilepsy. Topiramate also could be useful additional drug in therapy of epileptic encephalopathies. With increasing of patients age the efficiency of topiramate raises, while aggravation risks decrease.

P26

Perampanel in post-hypoxic myoclonus

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Background: Patients who survive a cardiac arrest may suffer from post-hypoxic myoclonus (PHM). Antimyoclonic treatment can be difficult with little evidence available from clinical studies, but empirical data supports the use of GABA agonists and antiepileptic drugs, such as valproat, piracetam or levetiracetam. However, experimental data in rodent models of PHM suggest that activation of glutamate receptors may mediate post-hypoxic myoclonus and glutamate receptor antagonists can decrease myoclonus episodes.

Methods: We report the case of a 36 year old man, who was admitted to our department two months after suffering a near-drowning accident in the north sea with cardiac arrest and lay reanimation. The patient had initially been treated on an ICU in a regional hospital, including therapeutical hypothermia, mechanical ventilation and deep sedation with propofol and thiopental. Cessation of sedation resulted in persistent generalised myoclonus,

that proved to be refractory to valproat and phenytoin. Levetiracetam (8 g) and clonazepam (12 mg) had moderate effects on myoclonus, but the patient remained in a minimal conscious state.

Results: We initiated a therapy with perampanel via nasogastric tube, starting with 2 mg/day increased by 2 mg every 3 days until a dose of 12 mg/day. Within the next 8 weeks myoclonus significantly diminish and clonazepam doses could be partly reduced. No adverse effects could be observed clinically or in laboratory testings, however the patient further remained in a minimal conscious state.

Conclusions: Post-hypoxic myoclonus is often difficult to treat, but benzodiazepines and levetiracetam can be beneficial. Our experience with perampanel supports results obtained in animal models that glutamate receptor antagonists can alleviate myoclonus. Further studies are necessary to confirm this observation.

P27

The Value of Pharmacological EEG Reactivity to Benzodiazepines in Post-Cardiac Arrest Patients

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Background: About 80% of cardiac arrests occur at home, for which the rate of death is at least 90%. When patients are comatose after resuscitation (a state commonly referred to as anoxic-ischemic encephalopathy), there is a spectrum of outcomes, ranging from brain death to good recovery. Seizure activity (especially nonconvulsive status epilepticus) is common in patients with anoxic-ischemic encephalopathy and may contribute to brain damage and prolonged coma. (N Engl J Med 2009;361:605-11. 2009 Massachusetts Medical Society). Status Epilepticus is common after cardiopulmonary resuscitation (CPR). The pathophysiological mechanisms occurring during an episode of Status Epilepticus have been well described in animal studies which serve as a rationale to begin Status

Epilepticus treatment with benzodiazepines (Edward B Bromfield, Andrea O Rossetti).

Aim: A retrospective review of Video EEGs. To test the predictive value of pharmacological reactivity of the EEG performed on patients who survived and out-of-hospital cardiac arrest, and remained comatose. All of these patients were referred to exclude non-convulsive status epilepticus.

Method: The EEG was used to monitor and assess the background reactivity. These patients were given a bolus of benzodiazepines if GPEDs or ictal seizure patterns were present. The EEG reactivity is analysed following administration of benzodiazepines, and can be defined as follows: **'the change in the EEG activity leading to attenuation of epileptiform discharges or full abolition of the discharges'**. Of the 33 patients referred only 7 were found to have been given a bolus of benzodiazepines **during** the EEG recording. Of these 7 patients, 6 of them showed EEG reactivity to benzodiazepines, and 1 showed no reactivity.

Conclusion: Of the 6 patients who showed reactivity with benzodiazepines, 5 died and 1 survived in a persistent vegetative state (PSV). The single unreactive patient also survived in a persistent vegetative state.

P28

Results of a randomized controlled trial of lorazepam versus diazepam for pediatric status epilepticus.

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Background: Some studies suggest that lorazepam might be superior to diazepam for status epilepticus (SE). We performed this study to compare the two drugs for efficacy and safety in treating children with SE to seek FDA-approval for lorazepam for this indication.

Methods: We performed a double blind, randomized trial at 12 sites using the infrastructure of the Pediatric Emergency Care Applied Research Network (PECARN). Children 3 months to 17 years of age with generalized convulsive SE were randomized to receive either 0.1 mg/kg lorazepam (max 4 mg) or diazepam 0.2 mg/kg (max 8 mg) by slow IV push. Half this dose was repeated at 5 minutes, if needed. The primary efficacy outcome was cessation of SE by 10 minutes with no recurrence by 30 minutes. The primary safety outcome was the need for assisted ventilation. Patients were enrolled under the Exception from Informed Consent for Emergency Research. The investigators are blinded to the medication names pending final analyses.

Results: 275 children were enrolled. There were no differences in either efficacy (Drug A 74% versus Drug B 71%) or safety (Drug A 16% versus Drug B 17.6%). With the exception of sedation (Drug A 50%, Drug B 66.9%), all secondary efficacy and safety outcomes were similar.

Conclusions: Lorazepam and diazepam show similar efficacy and safety in treating pediatric status epilepticus. Logistical considerations, such as the need for refrigeration, drug availability, and duration of effect, should guide the choice of benzodiazepine for first-line treatment of pediatric status.

P29

Successful Allopregnanolone Treatment of New Onset Refractory Status Epilepticus (NORSE) Syndrome: First in Man Experience

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Background: Treatment of status epilepticus is frequently associated with progressive diffuse cortical hyperexcitability believed to result from synaptic GABA receptor internalization and desensitization. Allopregnanolone is a neurosteroid which both activates and modulates synaptic and extrasynaptic GABA receptors.

Methods: We describe a 23 year - old man with New Onset Refractory Status Epilepticus (NORSE) Syndrome with myoclonic status epilepticus and striking stimulus sensitivity.

Results: The patient was treated with 21 discrete anticonvulsants including pentobarbital to achieve burst suppression for over 90 days and underwent 8 unsuccessful attempts at lifting the burst-suppression with varying background anticonvulsants in place. On the 9th attempt he was successfully weaned from pentobarbital during continuous infusion of allopregnanolone. Serum levels of allopregnanolone were maintained at 150 ng/l over a 5 day period beginning 24 h prior to taper and discontinuation of pentobarbital. The patient has continued to recover and is currently seizure free.

Conclusions: To our knowledge, this is the first reported use of IV allopregnanolone in humans.

P30

Ketamine in refractory status epilepticus - A retrospective study on 16 patients

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Objectives: Refractory status epilepticus (RSE) is defined as a status epilepticus (SE) not responding to first- and second-line antiepileptic drug (AED) therapies. Ketamine is a noncompetitive NMDA receptor antagonist. Few cases and retrospective studies on Ketamine use in SE exist. We aimed to evaluate Ketamine efficacy in RSE.

Methods: We retrospectively analysed data of all patients with SE (n=84) treated in our neurological intensive care unit from January 2012 (n=70) to February 2013 (n=14). We analysed aetiology, duration and type of SE, daily dose of Ketamine, co-therapeutic agents, treatment response and disposition.

Results: In 16 /84 patients (median age 68.5 years; range 50-80) with SE, Ketamine in combination with Midazolam was used. In all 16 patients, initial treatment with standard AED failed. RSE causes: 6/16 post-anoxic, 3/16 systemic infection, 3/16 stroke/intracerebral haemorrhage, 2/16 unknown, 2/16 pre-existing epilepsy with low AED level. RSE types: 2/16 myoclonic SE, 4/16 convulsive SE, 10/16 nonconvulsive SE. Median delay of Ketamine initiation was 4th day of SE (range 1-18); In 4/16 patients Ketamine was started with a bolus of 200 mg, followed by continuous infusion; Remaining 12 patients received continuous infusion. Median maximum dose of Ketamine was 175 mg/hour (range 100-300). RSE was successfully terminated in 10/16 patients, however 11/16 patients died either due to RSE (6/11) or their main disease despite terminated SE (5/11).

Conclusions: Ketamine may be effective in later stages of SE when adequate first and second line treatments fail, but overall outcome remains poor with a 70% in hospital mortality.

Clinical Epileptology

P31

A case report of a new onset refractory status epilepticus (NORSE)

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Introduction: Status epilepticus is one of the most severe and most common neurological emergencies today. Here, we report a case of a 25 year-old previously healthy woman who was admitted to our university hospital with a generalized tonic-clonic status epilepticus and who died 10 days after admission.

Methods: After the standard therapy for status epilepticus including general anaesthesia, we administered several antiepileptic drugs (AED) among others retigabine, a new AED together with several GABAergic or NMDAergic anaesthetics like Propofol or Ketamine. Despite thorough investigation (cranial magnetic resonance imaging (cMRI), several blood and cerebral spinal fluid (CSF) screenings and tumor scans, including abdominal CT) an underlying etiology could not be detected. Pathological findings e.g. cortical diffusion weighted imaging changes were due to the status epilepticus.

Conclusion: This case seems to be a new onset refractory status epilepticus (NORSE), which is a very rare described sub-entity of status epilepticus occurring mostly in young women (> 80%) with devastating outcome. The underlying etiology of NORSE remains elusive. Several etiologies are discussed in the literature: an immunosystem-mediated etiology is suspected to play an important part in NORSE or a receptor antibody encephalitis could be another underlying etiology. To further characterize this new entity larger case series are needed.

Key Words: Epilepsy, New Onset Refractory Status Epilepticus (NORSE), Cryptogenic Encephalitis, Malignant Status epilepticus, FIRES

P32

EpiNet to collect clinical information on Status Epilepticus

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Background: The EpiNet project has been established to facilitate investigator-initiated clinical research in epilepsy. It was recognised at the outset that the platform could be used to undertake research in status epilepticus, as well as other aspects of the management of epilepsy.

The EpiNet database is accessed via a secure website which is password-protected. Information is encrypted before transmission. This international database stores information about patients with epilepsy according to a number of different fields, including: seizure types, electroclinical syndromes, aetiology, investigations, drug history, and other illnesses.

A pilot study was performed in 2011, during which investigators from 15 countries assessed the platform.

As well as facilitating research, EpiNet also provides each user with their own personal database, and a clinically useful record for each patient.

Methods: At the end of 2012, a questionnaire was sent, to all investigators who have used the EpiNet platform, and others who have expressed interest in it. Opinions were sought as to how the platform could be improved, and what extra data should be collected.

Results: Eighty responses were received by Dec 30 2012. 72% of respondents want EpiNet to collect information on status epilepticus. 75% of respondents considered that this is either very important or fairly important.

Conclusions: EpiNet will collect information on episodes

of status epilepticus in 2013. Information will be collected in prospective registries. The EpiNet platform will facilitate clinical trials in status epilepticus.

EpiNet requires a classification system that is widely accepted to collect information on Status Epilepticus.

P33

Status epilepticus as presenting manifestation of hemorrhagic shock and encephalopathy syndrome

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Background: Hemorrhagic shock and encephalopathy syndrome (HSES) is a rare disorder in infancy with high mortality and morbidity. The main features of HSES are: diarrhea, shock, disseminated intravascular coagulation, multi-systemic damages, Reye-like syndrome, anemia, thrombocytopenia and encephalopathy including seizures.

Methods: We are presenting two month-old infant with refractory status epilepticus (SE) as presenting manifestation of HSES.

Results: Presented infant fulfilled all criteria for HSES diagnosis. Refractory generalized status epilepticus was initial and most prominent presentation, followed by other seizure types such as complex focal seizures and carbamazepine-induced myoclonus. Since initial SE treatment by intravenous boluses of midazolam (0.2mg/kg) and phenobarbital (20mg/kg) failed, continuous intravenous infusion of midazolam started with increasing dosage according to clinical response, (0.07 to 0.2mg/kg/h) for eight days. After SE cessation, the infant continued to suffer everyday complex focal seizures and the episodes of irritability. By clonazepam and valproate introduction, irritability stopped, but seizures were still very frequent. Serial EEG showed depressed background activity and multifocal epileptic discharges, while brain CT showed prominent cerebral edema followed by rapid progressive brain atrophy. Introduction of carbamazepine provoked

terrible myoclonus, so the drug was stopped. Long-lasting seizure control was achieved by topiramate in dosage of 5mg/kg,.

Conclusion: SE might be very refractory in HSES cases contributing to poor prognosis and very challengeable SE treatment.

P34

EEG findings in autoimmune limbic encephalitis

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Introduction: EEG is an important diagnostic test in autoimmune limbic encephalitis (LE), specificity of abnormality is however low. The aim of our study was to analyze EEG findings in our series of patients.

Methods: Overall, 33 routine EEG recordings in eleven patients with LE were analyzed. Diagnosis was based on clinical symptoms, MRI findings, autoantibody testing and cerebrospinal fluid results. In nine patients, autoantibodies commonly associated with LE were found in the serum (anti-Hu n=1; anti-Ma2 n=3; anti-Yo n=2 combined with anti-Ri in 1 case; anti-AMPA1, anti-LGI1 and anti-GAD all n=1). Two LE patients were seronegative.

Results: EEG was abnormal in all cases. Background slowing was found in four cases, always combined with another abnormality. Persistent slowing was noted in four patients. Intermittent slow activity was found in seven patients and was always bilateral, most commonly involving frontotemporal regions; symmetrically in three and with marked asymmetry in four. Focal interictal epileptiform discharges were found in five patients, always with frontotemporal predominance. Ictal pattern was recorded in two patients, in one of them subclinical. Non-convulsive status epilepticus was seen in one patient. Follow-up recordings were available in eight patients with abnormality persisting in most of them; only in two

patients the type of abnormality changed over time (focal epileptiform discharges to regional persistent slow).

Conclusions: Normal EEG is uncommon in patients with LE. The range of abnormalities is broad and non-specific in relation to certain LE subtypes. EEG abnormalities may evolve over time however in all our cases recording remained abnormal.

P35

Psychiatric symptoms as a result of the expanded status epilepticus

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Psychiatric state of 10 patients with verified epilepsy was analyzed in 4-8 hours after status epilepticus cupping. Duration status was 2 - 4 hours. In 2 patients status was presented complex partial seizures, at 6 - secondary generalized and 2 - the combination of complex partial and secondary generalized seizures. During the 3 months before status patients had not clinically significant cognitive and psychotic symptoms.

The 4 patients had psychotic symptoms which were shown crepuscular disorders of consciousness with excitation the emotional tension and aggression, as well as the fantastic hallucinations, affective intensity, phobic symptoms.

6 patients reported the presence of cognitive impairment, which were confirmed by in assessing scale MMSE (18 - 23 points). In this case, they observed affective stress Psychotic symptoms cupped using zuclopenthixol 30 – 50 mg a day and then applying a maintenance dose. For the treatment of cognitive impairment neuroprotectors were used with significant improvements in MMSE at 3 months. Conclusions. The result of the expanded status epilepticus may be development of psychotic and cognitive symptoms, which when early diagnostics cupped good. Character of cognitive and psychotic symptoms gives reason to study the presence of affective symptoms after expanded status epilepticus.

P36

Children with refractory convulsive status epilepticus admitted to intensive care in England and Wales: a two-year national epidemiological study

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AIMS: To obtain national epidemiological data on the prevalence, aetiology, management and outcome of refractory convulsive status epilepticus (RCSE) in children.

METHODS: Data were collected from eight paediatric intensive care units (PICUs) between 31/12/2007 and 31/12/2009 using a standard proforma, in collaboration with PICANet.

RESULTS: The study included 245 (male, 179) patients aged <1 to 16.5 years (mean 3.8, median 2.8 years). Causes included acute symptomatic (12.4%), remote symptomatic (18.4%), epilepsy-related (22.4%), progressive encephalopathy (5.3%) febrile (14.7%) and no cause (23.7%).

In the Emergency Department (ED), 219 patients (89%) received at least one benzodiazepine dose, 197 (80.4%) received phenytoin, 23 (9.3%) received phenobarbital. Subsequent anticonvulsants in ED included thiopentone (105 patients; 42.9%), midazolam (15; 6.12%), propofol (4; 1.63%). Only one third were treated according to Advanced Paediatric Life Support guidelines.

Average length of admission to PICU was 3.71 days (range 1-45, median 2), with an average of 3.19 days ventilated (range 1-31, median 2).

Nine patients died (3.7%). Twenty seven patients (11%) showed a new neurological deficit on discharge from

PICU, persisting in 10 (4%) at the 30 day follow-up.

CONCLUSIONS: Thiopentone was the most commonly used first-choice anticonvulsant to treat RCSE on admission to PICU. Mortality was low. Approximately 1 in 25 showed a new neurological deficit at 30 days following discharge from PICU. These data could help design a randomised controlled trial of the treatment of paediatric RCSE.

P37

Nonconvulsive seizures in the Intermediate Care Unit: A Retrospective Analysis of Periodic and Rhythmic Patterns and Mortality

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Objectives: 1) Review of routine electroencephalography (EEG) and descriptive data to assess the occurrence and features of nonconvulsive seizures (NCS) in critically ill patients. 2) Further detailed analysis, classification and comparison using the proposed ACNS Standardized ICU EEG Nomenclature (2012).

Methods: We retrospectively investigated routine EEG recordings of 268 patients who were referred to the Neuro Intermediate Care Unit (2nd Department of Neurology, Rosenhügel, Vienna) between October 2009 and August 2012.

Results: The incidence rate for NCS was 10.5% (28 patients), associated with a mortality rate of 25% (compared to 6.3% in the non-NCS group, $p=0.004$). 17 patients fulfilled criteria for periodic discharges (PD, Main Term 2 – ACNS Nomenclature). Compared to both other main terms (Rhythmic Delta Activity [6 patients] and

Spike-Wave [3 patients]) and electrographic seizures (2 patients) regarding mortality, PD were significantly higher associated with in-patient death ($p=0.014$). Regarding typical frequency (Modifier 3 – ACNS Nomenclature) all patterns above 1.5/s were not associated with death in our study. Only four patients had an immediate improvement in clinical state after antiepileptic drug administration. The most frequent etiologies in the NCS group were: preexisting epilepsy (53.6%), acute CNS disease (32,1%) and other acute disease (7,1%).

Conclusions: In the NCS group PD were the most common EEG pattern and exclusively associated with in-patient death. Among those who died three patients were comatose, two stuporous and two somnolent. RDA, SW and electrographic seizures seem to have better prognosis or treatment options.

P38

Seizure manifestation and EEG findings in three patients with anti-GABA-B receptor encephalitis

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Introduction: Recently anti-GABA-B receptor antibody has been proved to be related to a subset of autoimmune encephalitis. In previous studies, anti-GABA-B receptor encephalitis was shown to be a treatable disorder mainly characterized by seizures.

Methods: We report seizure manifestation and EEG findings in three patients with anti-GABA-B receptor encephalitis.

Results: 1. A 71-year-old woman with underlying small cell lung cancer presented with confusion and generalized tonic-clonic seizure (GTCS). EEG, Brain MRI and CSF studies were unremarkable and whole-body PET-CT showed no abnormal finding except known lung cancer. Indirect

immunofluorescence assays (Euroimmun AG, Germany) with patient's serum indicated positive results for anti-GABA-B receptor and anti-Hu antibodies. There was partial response to immunotherapy and anti-epileptic drug (AED).

2. A 62-year-old man complained of confusion and GTCS. Brain MRI was normal and diffuse slowing was seen on EEG. Indirect immunofluorescence assays confirmed anti-GABA-B receptor encephalitis. Whole-body PET-CT revealed lung cancer. He was partially improved after treatment.

3. A 64-year-old woman presented with abnormal behaviour. She had a history of breast cancer, which was in complete remission and her workup including blood, imaging and CSF studies was normal. Indirect immunofluorescence assays revealed the presence of autoantibodies against GABA-B receptor. Her EEG showed frequent left temporal spikes. She was significantly improved after initiating immunotherapy and AED.

Conclusions: We report three cases of anti-GABA-B receptor encephalitis and ascertained the association with lung cancer. Two patients presented with initial GTCS and the other with EEG abnormality, which supports the importance of seizure control in anti-GABA-B receptor encephalitis.

P39

Neonatal status epilepticus in patients of NICU. Diagnostics and prediction of outcome

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Background. Substantial part of the neonatal seizures are subclinical, including status epilepticus (SE).

Aim. To evaluate incidence of SE detection with aEEG in

newborns of different gestational age (GA) in NICU, to study its prognostic value.

Methods. 150 infants, birth weight 620-4940 g, GA 23-41 weeks, with moderate or severe perinatal brain damage were enrolled. Groups were formed depending on the GA: group I (n=26) 23-27 weeks, group II (n=56) 28-32 weeks, group III (n=38) 33-36 weeks, group IV (n=30) 37-41 weeks. aEEG-monitoring was provided. aEEG-patterns were scored according L.Hellström-Westas' classification, 2006. SE was defined as ongoing ictal activity at least 30 minutes' duration.

Results. SE was recorded in 32 children and its incidence was higher in mature patients, in group I 7,7% (n=2), in II - 12,5% (n=7), III - 23,7% (n=9), IV - 46,7% (n=14) newborns (Pearson χ^2 (df=3)=16,85, $p=0,001$). aEEG-pattern of SE was not accompanied with clinical seizure in 29% of cases (n=9). CNS functional state out of SE corresponded to continuous aEEG background pattern in 53,1% (n=17) of cases, discontinuous pattern in 21,9% (n=7). The presence of aEEG cyclic variability was observed in 65,6% children with SE (n=21), was absent in 31,3% (n=10), was uncertain at 3,1% (n=1). Mortality was associated with aEEG background (Pearson χ^2 (df=5)=52,8, $p=0.000$). No relationship was observed between mortality and confirmed SE.

Conclusion. Incidence of SE was significantly higher in neonates with GA ≥ 33 weeks. The predictive value had aEEG background. Identification of SE aEEG-pattern was not associated with mortality.

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P40

Nonconvulsive status epilepticus and coma: EEG role - Case Report

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Nonconvulsive status epilepticus and coma: EEG role - Case Report

Introduction/Objectives: If NCSE diagnosis is strongly supported by EEG, in comatose patients is impossible without it. Otherwise EEG in coma stages has risk of misinterpretation in order to periodic abnormalities and epileptiform discharges, but it's determinant for therapeutic strategy and prognosis.

Method-Results: 64 ys old woman with high grade frontal glioma treated only with chemio / radio-therapy and phenitoin 200 mg/day despite no seizures (apr.2012) Aug.,10,2012:first focal secondary generalized seizure (PHT: 2.3 ug), phenitoin was increased to 300 mg Oct 9,2012: convulsive status epilepticus (PHT 5.3 ug) stopped after 1250 mg Phenitoin iv; pt was discharged with lamotrigine 200 mg/day Nov.11,2012: refractory convulsive SE (60 mg DZP); versive seizures were stopped after phenitoin 1250 mg iv; coma; (PHT:19.9 ug); first brain CT EEG during coma was done to detect eventual epileptic activity; neurological examination showed an anisocoria (left>right) A second brain CT showed a frontal haematoma with mass effect. Neurosurgery evaluation excluded the evacuation of haematoma; Pt died the day after

Conclusions: Our case underlines EEG role after clinic resolution of seizures consenting us to reflect about following issues:

1. The electric seizures originated unexpetedly from right frontal regions showing us that coma would caused not only by diazepam 60 mg but also by NCSE

2. More aggressive treatment for NCSE?
3. Epileptic activity were located in the right frontal region (pt had left frontal glioma); this new data induced to repeat brain CT after 6 hour that was determinant for the prognosis.

P41

Long-term follow-up of patients with status epilepticus (SE): prognosis, recurrence and survival after one year.

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Objective: To establish the prognosis of SE patients after one year of follow-up.

Methods: We prospectively followed all patients included in our SE registration from June-2010 to June-2011. We collected data on type of SE, etiology, refractoriness, recurrence, subsequent emergence of seizures in previous non-epileptic patients, mortality and causes of death.

Results: We evaluated 61 patients with SE: 11(18%) convulsive, 16(26%) non-convulsive and 34(55%) with minimal motor symptoms. Regarding etiology: 32(52%) were considered acute symptomatic, 21(34%) remote symptomatic, 5(8%) cryptogenic and 3(5%) in the context of IGE. 26(42%) were considered refractory. At one year follow-up, the recurrence rate was 15%(9), seizures occurred in 16 of the previously non-epileptic patients, and the mortality rate was 34%(21): 15(71%) by SE itself or its cause, and 6(29%) for unrelated causes. Mortality was associated with male gender (p=0.032), etiology (cryptogenic and acute symptomatic,p=0.03), and a trend in longer SE (p=0.08). Patients with a longer

duration tended to develop subsequent epilepsy(p=0.08). In survivors, SE recurrence was higher in patients who developed epilepsy (p=0.019), and with longer SE (p = 0.08). A subsequent worse seizure control was clearly associated with longer status (p=0.026).

Conclusion: After one year follow-up mortality in SE comprises approximately one third of patients. We found a relationship with the cause and gender. and possibly with duration. SE duration seems to be a factor related with a subsequent development of epilepsy and a worse control of seizures.

P42

Autoimmune synaptic encephalitis with LGI1 and Caspr2 antibodies: seizure manifestation, EEG and other findings

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Introduction/Objectives: Autoimmune synaptic encephalitis (ASE), a rare condition comprising encephalitides associated with autoantibodies against structures of the neuronal synapse, usually accompanies seizure disorder. Leucine-rich, glioma inactivated 1 (LGI1) and Contactin-associated protein-like 2 (Caspr2) antibodies, formerly known as voltage-gated potassium channel antibody, were not identified until recently, hence case reports deals with them separately are small in number. To strengthen our understandings, we presented 6 cases with LGI1 and caspr2 antibodies herein.

Participants, Materials/Methods: Clinical analysis was conducted on patients with suspected ASE. Autoantibodies to NMDA, AMPA, GABA-B, LGI1, Caspr2 were checked by indirect immunofluorescence test (Euroimmun AG, Germany).

Results: There were 5 patients with LGI1 antibodies and

one with Caspr2 antibodies. All 6 patients presented with cognitive impairment and seizure, 4 of them developed non-convulsive status epilepticus (NCSE). 1 patient had prominent autonomic symptoms, such as orthostatic dizziness, urinary incontinence, and constipation. Electroencephalogram detected temporal spikes (3 cases) and sharp-and-slow wave complexes (1 case). Brain magnetic resonance imaging revealed medial temporal lesion in 3 patients, brainstem involvement in 1 patient. Fluorodeoxyglucose positron emission tomography identified medial temporal hypermetabolism in 4 patients. Only the patient with Caspr2 antibodies had pleocytosis on cerebrospinal fluid analysis. None of the patients showed malignancy and all showed symptomatic improvement after immunotherapy.

Conclusions: All 6 patients presented with seizure and 4 with NCSE. For anti-epileptic drug alone is not sufficient to control symptom, early diagnosis and immunotherapy is of importance. Antibodies associated with ASE are gradually clarified, which contributes to diagnosis.

P43

Clinical features and laboratory findings of 22 patients with anti-NMDA-receptor encephalitis in Korea

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Objectives: Anti-NMDA-receptor encephalitis is a recently described immune-mediated condition that commonly affects younger patients and presents with psychiatric symptoms. We aimed to analysis the initial clinical manifestation, seizure, EEG, and MRI findings of patients in whom NMDA-receptor antibodies were detected.

Methods: Between June 2005 and December 2012, we performed indirect immunofluorescence test (Euroimmun AG, Germany) on sera from 230 patients in Korea who are

suspected autoimmune neurologic disorder and reviewed medical records.

Results: Demographic information for the patients were slightly different compared to the previous reports; 50% were female and median age was 40.3 years. Initially, 10 patients (45.5%) showed psychiatric symptom, 5 (22.7%) seizure, 4 (18.2%) cerebellar dysfunction, and 2 (9.1%) decreased consciousness. During the first 3 weeks of symptom presentation, seizures were documented 14 of 22 patients (63.6%). 3 (21.4%) showed complex partial seizure, 7 (50%) generalized tonic clonic seizure, 4 (28.6%) nonconvulsive status epilepticus. EEG abnormal in 15 of 21 patients tested (71.4%). 12 patients (57.1%) had generalized or predominantly frontotemporal slow or disorganized activity without epileptiform discharges. Epileptiform discharge showed in 3 patients. Of 21 patients, 7 had increased signal on MRI fluid-attenuated inversion recovery or T2 sequences; 3 in medial temporal, 3 in cerebral cortex, and 1 in basal ganglia. 2 patients had transient contrast enhancement meninges. 13 of 21 patients (61.9%) had normal MRI.

Conclusions: In our patients with anti-NMDA-receptor encephalitis, overall clinical manifestations were similar with previous reports, but showed some differences. Additional analysis of association with response to immunotherapy will be performed.

P44

Long term clinical outcome and prognostic factor of herpes simplex encephalitis: seizure manifestation and EEG findings

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Objectives: To identify prognostic factors of 6 months clinical outcome including mainly initial seizure manifestation, EEG and MRI of the herpes simplex

encephalitis (HSE) patients diagnosed by cerebrospinal fluid (CSF) herpes simplex virus (HSV) DNA PCR.

Methods: This is retrospective study. Data were collected between 2000/01/01 and 2012/07/31 at the Seoul National University Hospital. MRI lesion volume were extracted from FLAIR and DWI MRI using a semiautomatic procedure based on in-house software developed as a plug-in for the Medical Image Processing, Analysis, and Visualization (MIPAV) package. EEG was classified by Synek classification and 6 month clinical outcome were graded by Glasgow outcome scale.

Results: We analyzed 29 HSE patients. HSE was associated with HSV type 1 in 22 patients and with HSV type 2 in 7 patients. 16 patients (55%) initially presented with seizure, 10 (35%) of them showed focal seizure, 4 (14%) generalized tonic clonic seizure, and 2 (7%) status epilepticus. Patients with poor outcome had significantly more frequent initial seizure ($p=0.009$, univariate analysis and $p=0.084$, multivariate analysis). Patients with favor outcome had significantly more favor EEG (Synek classification grade 1-2) grading ($p=0.004$). There was no relationship between 6 month clinical outcome and MRI volume analysis, acyclovir initiation delay, or initial mental status.

Conclusions: There was significant relation between poor clinical outcome and initial seizure manifestation and poor EEG grading in HSE patients. With a larger number of patients, additional analysis will be needed.

P45

Outcome in newborns with status epilepticus

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Background: In order to analyze the contribution of neonatal status epilepticus (NSE) on the outcome, we studied newborns with recurrent seizures compared to those with NSE.

Methods: A cohort of 154 newborns with Video-EEG confirmed neonatal seizures consecutively admitted to the University-Hospital of Parma between January 1999 and December 2012 were enrolled. Seventy-six were preterm and 78 were full-term newborns. NSE was defined as continuous seizure activity for at least 30 minutes or recurrent seizures lasting a total of 30 minutes without return to the baseline neurologic condition between seizures. Follow-up ranged from 10 months to 13 years. After univariate analysis, we applied a multiple logistic regression model to determine independent risk factors for adverse outcome.

Results: Forty-seven newborns had NSE (19 preterm and 28 full-term neonates), representing 13.2% of the children with favourable outcome (7/53) and 39.6% with adverse outcome (40/101). The majority (85.1%) of the subjects with NSE had an adverse outcome. Nine variables were related to adverse outcome with $p<.01$ [birth-weight, gestational-age, Apgar score at 1', 5', 10', neurological examination, NSE, EEG, cerebral ultrasound (US)]. Multivariate analysis revealed that US (OR: 3.669; 95% CI: 1.977 to 6.810; $p=.000$), neurological examination (OR: 2.611; 95% CI: 1.352 to 5.041; $p=.004$), NSE (OR: 5.618; 95% CI: 1.879 to 16.802; $p=.002$), and Apgar score at 5' (OR: 2.565; 95% CI: 1.320 to 4.982; $p=.005$) were independent predictors of outcome, with a PPV of 0.85 and a NPV of 0.77.

Conclusion: Newborns with status epilepticus are at high risk of adverse outcome.

P46

Independent external validation of the Status Epilepticus Severity Score (STESS)

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Background: Recently, a Status Epilepticus Severity Score (STESS) was developed to provide a methodology for predicting outcome, planning the level of monitoring needed and for guiding treatment. The aim was to confirm the external validity and transportability of the STESS prediction functions for outcome.

Methods: Four variables (history of seizures, age, seizure type, and level of consciousness) were determined for consecutive adult ICU patients at status epilepticus (SE) onset, in a tertiary academic medical care center in order to calculate STESS. The main outcome measure was the ability to accurately predict the outcome of SE by measures of discrimination and calibration. Discrimination was defined as the ability of STESS to separate survivors from non-survivors; calibration, as the measure of how closely predicted outcomes agree with the actual outcomes.

Results: Among 171 SE patients with a mean age of 64.1 years (± 16.3), mortality was 18%. The receiver operating characteristics (ROC) curve for prediction of death by STESS had an area under the curve (AUC) of 0.744 with an optimal cutoff point of ≥ 4 . Hosmer-Lemeshow statistics revealed good calibration of STESS (Hosmer-Lemeshow χ^2 goodness-of-fit test = 1.39; $p=0.845$).

Conclusions: This study is the first independent, external validation of the predictive accuracy of STESS and its transportability to ICU patients with SE. Measures of discrimination and calibration indicated that STESS performed reasonably well on our cohort of ICU patients with SE. However, the specific optimal cutoff point for survival versus death in our cohort was different than proposed.

P47

Baseline EEG Pattern on Continuous ICU EEG Monitoring and Incidence of Seizures

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Methods: CEEG monitoring reports from 243 adult patients were reviewed, assessing the baseline cEEG monitoring pattern in the first 20-30 minutes and the presence of seizures during the entire monitoring period. The baseline EEG patterns were classified into nine categories: seizures, periodic lateralized epileptiform discharges (PLEDs), generalized periodic epileptiform discharges (GPEDs), focal epileptiform discharges, burst suppression, focal slowing, diffuse slowing, triphasic waves and normal.

Results: Overall, 51 patients (21%) had NCS at any time during cEEG monitoring. Notably, 112 patients had diffuse slowing as the initial EEG pattern and none of these patients were noted to have seizures. Similarly, no patients with triphasic waves (n=3) developed seizures. Seizure rates were as follows: PLEDs (56%, n=9), burst suppression (50%, n=10), GPEDs (50%, n=2), normal (33%, n=3), focal epileptiform discharges (31%, n=35) and focal slowing (11%, n=46). Patients in the high-risk group (PLEDs, GPEDs, burst suppression and focal epileptiform discharges, n=56) were more likely to have seizures compared with the low risk group (diffuse slowing, focal slowing, triphasic waves and normal, n=164), odds ratio 16.9 (p < 0.0001).

Conclusions: Patients with diffuse slowing, focal slowing and triphasic waves seen on the baseline EEG recording are very unlikely to develop seizures on subsequent cEEG monitoring. This data can be used to decide how long to continue cEEG monitoring in patients based on their initial EEG findings.

P48

Seizure Burden Score: A Quantitative Description of Seizure Intensity in Continuous EEG Recordings

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Background: Electrographic seizures are common in continuous EEG (CEEG) recordings in critically ill patients. They can show a wide range of patterns, including differences in frequency of seizures (from isolated seizures to continuous seizure activity or status epilepticus), duration of individual seizures, and spatial extent of individual seizures. These various patterns likely have different clinical implications, some requiring aggressive management while others may not. While factors such as etiology of seizures, co-morbid conditions, functional status and level of consciousness play a role in guiding management of seizures, the actual pattern of seizure activity has implications for treatment as well.

Methods: Here we report on our initial attempt to develop a seizure burden score (SBS) based on ESz parameters that could be used to summarize features of CEEG in a clinically meaningful way. In this retrospective analysis of 41 critically ill patients who had ESz during CEEG, we calculated an SBS based on the total amount of ictal time/hour, a parameter reflecting spatial extent of the seizures, and the average duration of individual seizures.

Results/Conclusions: Various forms of this SBS were evaluated for their ability to differentiate between patients with a good outcome versus a poor outcome. We discuss future directions and considerations for optimizing the SBS to allow for its use, in combination with the clinical scenario, for clinical decision making, including prognosis and treatment.

P49

Antibody-Mediated Status Epilepticus: A Retrospective Multicenter Survey

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Background: In recent years, an increasing number of autoantibodies (AB) have been detected in the CSF and serum of patients with new onset epilepsy. Some of these patients develop convulsive or nonconvulsive status epilepticus (ABSE), necessitating intensive medical care and administration of multiple antiepileptic and immunomodulatory treatments of uncertain effectiveness.

Objectives: In this retrospective multicenter survey we aimed to determine the spectrum of gravity, the duration and the prognosis of the disorder. In addition, we sought to identify the antibodies associated with this condition, as well as determine whether there is a most effective treatment regime. **Methods:** 12 European Neurology University Clinics, with extensive experience in the treatment of SE patients, were sent a detailed questionnaire regarding symptoms and treatment of AB-SE patients. Seven centers responded positively, providing a total of 13 patients above the age of 16. **Results:** AB-SE affects mainly women (12/13, 92%) with a variable age at onset (17–69 years, median: 25 years). The duration of the disease is also variable (10 days to 12 years, median: 2 months). Only the 3 oldest patients died (55–69 years). Most patients were diagnosed with anti NMDAR encephalitis (8/13) and had oligoclonal bands in the CSF (9/13). No specific treatment regimen (antiepileptic, immunomodulatory) was found to be clearly superior. Most of the surviving 10 patients (77%) recovered completely or nearly so within 2 years of index poststatus.

Conclusion: AB-SE is a severe but potentially reversible condition.

Long duration does not seem to imply fatal outcome; however, age older than 50 years at time of onset appears to be a risk factor for death. There was no evidence for an optimal antiepileptic or immunomodulatory treatment. A prospective multicenter study is warranted in order to stratify the optimal treatment algorithm, determine clear risk factors of unfavorable outcome and long-term prognosis.

P50

Types of status epilepticus in infancy fixed by video-EEG

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Introduction/Objectives: The aim of the study was analyzing the types of SE in infants fixed by video-EEG.

Materials/Methods: At Department of Psychoneurology N2 of RCCH and Department of Neurology, Neurosurgery and Medical Genetic of RNRMU were analyzed 173 cases of infantile SE fixed by video-EEG monitoring for the period of 2005-2012.

Results: In the total of 173 cases of infantile SE were fixed the following types: SE of minor motor seizures in clusters – 25,4% (n=44), SE of infantile spasms in clusters (series >30 min) - 21,4% (n=37), SE of migrating multifocal seizures - 12,1% (n=21), focal motor SE - 7,5% (n=13), erratic myoclonus with suppression-burst pattern - 6,9% (n=12), clusters of bilateral myoclonies - 6,4% (n=11), non-convulsive SE of dialeptic and inhibitory seizures - 4,6% (n=8), hemiconvulsive - 4,0% (n=7), alternative hemiconvulsions - 2,3% (n=4), tonic-autonomic with occipito-posteriotemporal ictal patterns - 3,5% (n=6), tonic-automotor - 1,2% (n=2), secondary generalized tonic-clonic - 1,2% (n=2) and combine forms of SE such as combination of migrating multifocal SE, suppression burst pattern and diffuse polyspike-waves accompanied

by myoclonies - 2,9% (n=5) and one infant (0,6%) – combination of tonic-automotor-autonomic SE with occipito-temporal ictal pattern from right hemisphere and at the same time - clusters of tonic spasms with “lafa” patterns started from left centro-parietal regions.

Conclusions: SE in infancy is characterized high incidence of infantile spasms and minor motor seizures in clusters and migrating multifocal seizures in comparison with rare incidence of such common form of SE for elder children and adults as GTCS.

P51

Status epilepticus in patients with focal cortical dysplasia

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Background: Focal cortical dysplasia (FCD) is frequently associated with pharmacoresistant epilepsy. According to current classification of ILAE, FCD are divided into FCD I, FCD II and FCD III (FCD I combined with other lesions). We aimed to identify FCD spectrum in patients who had status epilepticus (SE) and compare clinical features of patients with FCD and SE (wSE) to those with FCD and without SE (w/oSE).

Methods: We identified 55 patients (24 women; median age 36 years, SD 17.6) with FCD and epilepsy in large adult and children epilepsy units. SE (no acute symptomatic cases) was defined as a seizure lasting over 10 minutes (for convulsive SE) or 30 minutes (for non-convulsive SE) or seizure series without function regain between seizures.

Results: In 5/55 (9%) of FCD patients (3 women; median age 13 years, SD 18.7) merely convulsive SE was observed. Four patients had FCD II and one patients - FCD III, no patient with FCD I in our cohort had SE. Patients wSE compared to those w/oSE were younger (13 years SD 19 vs. 36 years SD 17; p=0.036), had earlier seizure onset (1 year DS 0.9 vs. 15.5 years SD 14.6; p=0.003), commoner daily seizures (3/5 vs. 3/50; p=0.007), delayed milestones (3/5 vs. 6/50; p=0.027) and tendency for cognitive impairment (3/5 vs. 9/50; p=0.063). There was no difference between two groups with regard to other electro-clinical features.

Conclusions: Younger patients with FCD II with earlier seizure onset, frequent seizures and delayed milestones were more prone to develop SE.

P52

Cardiac Telemetry and Pulse Oxymetry Monitoring in Epilepsy Monitoring Units to Study Dysautonomia and the Risk of Sudden Unexplained Death in Epilepsy

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Background: Ictal bradycardia and asystole are rare but serious complications of seizures. It is hypothesized that they cause or contribute to sudden unexplained death in epilepsy (SUDEP). The objective of this study is to evaluate changes of heart rate and oxygen saturation during the ictal period.

Methods: In this ongoing prospective multicenter study (GUH & DSMC) we monitored heart rate (HR) and

oxygen saturation (O2) in patients undergoing video-EEG monitoring (9 patients, 6 female, mean age 45; mean events 2.22). The resting baseline values were recorded for wakefulness, and stage N2 sleep. Two different methods were used i.e., the HR and O2 values were either averaged in 20-second bins or recorded per-second.

Results: Using averaged values we found a significant increase from the baseline awake HR to ictal (74.6 vs. 98.3, p=0.020) and post-ictal HR (74.6 vs. 101.8, p=0.006). When comparing only pre-ictal, ictal, and post-ictal values, there was a significant increase from the pre-ictal to post-ictal HR (89 vs. 98.3, P=0.038). Using second by second recorded values, there was a significant drop from pre-ictal to post-ictal O2 levels (96.2% vs. 91.1%, P=0.003). There was a significant drop in O2 from pre-ictal to ictal period (96.4% vs. 95.41%, P=0.032), and from pre-ictal to post-ictal period (96.4% vs. 92.8%, P=0.003).

Conclusions: These findings indicate a significant increase in ictal HR compared to baseline and pre-ictal period, a significant drop in post-ictal O2 saturation compared to pre-ictal levels, and a significant difference in O2 between epileptic and non-epileptic seizures.

P53

Frequency of status epilepticus at woman's epilepsy

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The problem of reproductive health at woman's epilepsy united two important directions. Status epilepticus at women's epilepsy has the special importance.

Purpose: to study the frequency of the status epilepticus at women of reproductive age in groups mono - and polytherapy by antiepileptic drugs (AEDs).

Material and methods: 155 women were included in observational comparative study of the AEDs reproductive side effects. Inclusion criteria were the verified diagnosis of epilepsy. An exclusion -exception of the periods till 16

years and after 45 years. Data of epilepsy debut and current were studied with aim to identify the status epilepticus in the past. Patients were divided into 3 groups according AEDs therapy.

Results: 1 gr.- 70 patients receiving monotherapy (45%), 2gr. - 65 on polytherapy (42%), 3gr. - 20 without AEDs (13%). Middle age - 25 years. In 1 gr. the average duration of epilepsy made 10, in 2gr. - 12, in 3 gr. - 5 years. Statistically significant differences in epilepsy characteristic weren't observed. In the general cohort the status epilepticus was at 6 women (3, 5%). The status of generalized convulsive seizures was observed in all cases. Distribution in groups: 1 gr. - 1, 2gr. - 5, 3 gr. -no. Emergence periods: epilepsy onset - 1, pregnancy-1, change of AEDs therapy - 4. In 1gr. the status was observed after the delivery.

Conclusion: high frequency of status epilepticus observed at women of reproductive age with resistant epilepsy. Feature of woman's epilepsy was danger of the status epilepticus during pregnancy

P54

De-novo absence status epilepticus with azithromycin for respiratory tract infection

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Background: Confusional states are common, especially in elderly people suffering acute, febrile disease, possibly induced or aggravated by antibiotic treatment. Amongst others macrolide antibiotics are often associated with delirium- or confusional states. The pathophysiology, however is far from clear.

Methods: a case report of de novo absence status epilepticus (ASE) and review of the literature.

Results: A 57 year old woman received 500 mg/d azithromycin for respiratory tract infection over three days. On 4th day she was confused with semipurposeful movements, inappropriate reaction to commands and psychomotor slowing. Her quantitative consciousness was mildly impaired. The patient could recall admission, but then lost memory trace of following events. An emergency EEG revealed continuous generalized poly-spike –wave complexes correlating with ASE. The patient did not have seizures before but a brother with idiopathic generalized epilepsy (IGE) starting at age 18. De-novo absence status epilepticus was diagnosed and acute treatment with IV lorazepam 2 mg followed by IV levetiracetam 1000 mg initiated. The patient recovered fully within next hour. There was no documented SE in relation to azithromycin intake in previous literature, but one case in the structurally related clarithromycin was associated with non-convulsive status epilepticus (NCSE). A total of four patients with delirium in association with azithromycin were reported. EEG was not performed. Pathophysiology is unclear, but tendency of azithromycin to accumulate in brain with an up to 250-fold concentration may contribute to pathogenesis.

Conclusion: Azithromycin is a possible cause of ASE, in our patient with a first degree relative with IGE.

P55

Proposal of a Staging System for Risk Stratification and Cross Sectional Reporting of Status Epilepticus

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Background: Definitions for status epilepticus (SE) vary regarding their time points and –windows of treatment options. Clinical phenomena are highly dynamic and symptoms may gradually disappear, as status advances (electromechanical dissociation). Pragmatically, this may

cause problems, when transferring a patient in SE from one to another unit (e.g. emergency department to ICU). To date no standardized system exists for acquisition, documentation and communication of clinical core parameters to stage SE. Such a system would make research results better comparable for meta-analyses and serve as a tool for risk stratification.

Methods: Twenty consecutive patients with various types of status epilepticus of any cause were classified according to a proposed staging system for status epilepticus (SSSE) in a tertiary neurological university clinic in Salzburg, Austria. A data sheet was designed and explained to responsible physicians in charge. The SSSE uses a letter code comparable to the pTNM-system in tumors. A “D” denotes the definition based on clinical grounds, “T” for time/duration of symptoms, “t” for time to regain full consciousness, “E” for level of neurophysiological evidence, “L” for laboratory and “N” for results of neuroimaging.

Results: SSSE was easily applicable and well accepted by physicians, did not interfere with patient management and was suitable for communication in medical records.

Conclusion: The SSSE is applicable to various forms of SE in any clinical setting with low time consumption and no interference with acute patient management. Larger prospective studies are needed to perform risk stratification and to determine test characteristics such as inter-rater reliability.

P56

KCNQ2 Mutation in a patient with Ohtahara Syndrome

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Introduction/Objectives:

To present the clinical course of a child with Ohtahara syndrome due to a KCNQ2 mutation.

Participants, Materials/Methods:

Case presentation and analysis of clinical data.

Results:

The girl was born after an uneventful pregnancy at term and without a family history of seizures. At her second day of life she presented with short lasting (20-30s) tonic symmetrical seizures with apnea, bradycardia and desaturation. Furthermore asymmetric (hemi) clonic seizures could be observed, seizure frequency was high (5-50/d). Electroencephalogram (EEG) showed a burst suppression and an Ohtahara syndrome was diagnosed. At the age of 3 weeks a status epilepticus had to be treated with continuous midazolam at the intensive care unit. Inflammatory and an extensive metabolic screening was normal and cerebral magnet resonance imaging (MRI) without pathological findings. Tonic seizures responded transiently to phenobarbital, whereas vigabatrine, levetiracetam, midazolam, clobazam, valproic acid, ketogenic diet, pyridoxine, pyridoxal-phosphate and folinic acid did not influence seizure frequency. Zonisamide, topiramate, immunoglobuline, pulsatile dexamethasone resulted in minor improvement only. At the age of 4 months her development is severely delayed in all areas with impaired visual contact, missing head control and intermittent dystonic posturing of the body. Genetic testing revealed de novo KCNQ2 Mutation (c.629G>A, p.Arg210His).

Conclusions: In our patient a mutation of a potassium channel gene could be detected as a reason for the severe epileptic encephalopathy (Ohtahara syndrome) characterized by frequent tonic seizures, burst suppression in EEG and severe global developmental delay.

P57

Cerebral gas embolism presenting as Refractory Status Epilepticus

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Background

Cerebral gas embolism is a rare iatrogenic problem. It typically involves the migration of gas to small arteries and causes pathologic changes, reducing the perfusion distal to the obstruction and inducing an inflammatory response. The symptoms develop suddenly and the clinical presentation is determined by the quantity of gas and the areas of the brain that are affected. Epileptic seizures are one of the possible complications.

Case report

A 56 year-old male, with a history of diabetes mellitus with minor and major vascular complications such as coronary heart disease and chronic renal failure, presented with sudden loss of consciousness and left hemiparesis at the end of a dialysis session.

The patient was unresponsive, had forced oculocephalic deviation to the right and nystagmoid eye movements, left central facial palsy, left hemiparesis and bilateral Babinski sign. Myoclonic movements of the right upper extremity and masticatory movements were observed.

Brain CT revealed early signs of right frontal ischemia and multiple bihemispheric round lucencies of air density, suggestive of cerebral gas embolism. The EEG was consistent with status epilepticus. Despite the treatment with diazepam, phenytoin and valproic acid, status epilepticus persisted and the patient, who had a poor general condition, developed severe cardiorespiratory failure and died forty-eight hours after admission.

Conclusion

The diagnosis of cerebral gas embolism requires a high index of suspicion and the temporal relationship between the procedure and the sudden development of neurological deficit. Refractory status epilepticus is an uncommon complication, with a high morbidity and mortality rate.

P58

Febrile infection-related epilepsy syndrome in four Croatian boys

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Febrile infection-related epilepsy syndrome (FIREs) is a catastrophic epileptic encephalopathy with a yet undefined etiology. It is an increasingly recognized epileptic syndrome that presents with multifocal refractory status epilepticus (SE) in previously healthy children and evolves into chronic, refractory focal epilepsy followed by cognitive and behavioral difficulties.

Methods: We conducted a retrospective study of the first four patients diagnosed with FIREs in Croatia. Clinical, electroencephalography, neuroimaging and other investigative findings during the acute and chronic phases were reviewed.

Results: Four previously normal children presented with a febrile illness and SE that was refractory to numerous antiepileptic medications, burst-suppression coma, ketogenic diet, immunotherapies (corticosteroids, immunoglobulin, plasma exchange) as well as hypothermia (in two). Seizure semiology was similar in all our patients with perirolandic and perisylvian features. EEG ictal onset was lateralized in all recorded seizures with independent bilateral foci. Evolution to chronic epilepsy occurred in all patients. All four boys survived with severe intellectual impairment.

Conclusion: FIREs is a rare entity only recently more recognized in a small minority of all patients with SE and sometimes misdiagnosed as encephalitis (our first case). The outcome is poor and no therapeutic agent was efficacious in shortening the acute phase.

P59

Assessment of Status epilepticus and Seizures in Neurological Intensive Care Unit in Salzburg, Austria

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Status epilepticus (SE) as well as aggravation of epileptic seizures (SZs) are common reasons for admission to a neurological intensive care unit (NICU). They may also occur as complications during the stay in patients at the NICU. The aim of this study was to evaluate incidence and clinical data of SE and SZs at a NICU.

We retrospectively analysed all consecutive patients who were admitted to the NICU of the Department of Neurology, Paracelsus Medical University, in Salzburg, Austria, between from January 2010 to May 2011.

A total of 719 patients were admitted to the NICU, 121/719 (16.8%) patients (68 men; mean age 59.0 ± 19.6 years; range 14–91) had SE or SZs: 84/121 (69.4%) had the referral diagnosis "SE", 32/121 (25.5%) "SZs" and 5/121 (4.1%) developed SE or SZs during the stay. 116/119 (97.5%) patients had symptomatic aetiology: acute symptomatic in 43/119 (36.1%), remote symptomatic in 49/119 (41.2%) and progressive symptomatic in 24/119 (20.2%) patients. In acute and remote symptomatic aetiology, the most common reasons were cerebrovascular diseases (14/119; 11.8% vs. 27/119; 22.7%), while in progressive symptomatic aetiology brain tumors (8/119; 6.7%) were the most frequent cause. 70/119 (58.5%) patients suffered from epilepsies before admission to the NICU.

About a sixth of patients admitted to the NICU had SE or SZs. Aetiology was symptomatic in most of the cases. The main reasons for acute and remote symptomatic SE or SZs

were cerebrovascular diseases. Approximately two fifth of the patients had new-onset SZs or SE.

P60

Outcome of Status epilepticus in the elderly

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Status epilepticus (SE) has a bimodal distribution with the highest rates in the elderly population. The aim of our study was to analyse distribution, type, etiology, and the duration of stay on the neurological intensive care unit (NICU) and in hospital as well as the mortality rate of patients older than 60 years and compare it to the population younger than 60 years of age.

This retrospective study included all patients admitted to our Neurological Intensive Care Unit between Jan/2011 and Dec/2012.

A total of 1018 patients (504 in 2011, 514 in 2012) were admitted in the NICU. One hundred thirty-seven (13.5%) patients were admitted because of SE or had SE during their stay at the NICU. 38 % (52/137) were under 60 and 62% (85/137) over 60 years old. 52.3% (45/86) of the male and 78.4% (40/51) of the female patients were older than 60 years. The most common etiology of SE were cerebrovascular diseases (21.2%, 29/137). Non-convulsive SE (84.9%, 28/33) and convulsive SE (58.4%, 52/89) occur more frequent in patients over 60 years. A higher percentage of the old group stayed longer than 14 days in hospital (21.2 %; 18/85) compared to the young group (7.7%; 4/52). Mortality in the elderly group was high 91.7% (11/12).

SE is more frequent in patients over 60 years and is accompanied with a higher mortality. Older patients are longer hospitalized, suffer more frequent from non-convulsive SE and the most common etiology in the elderly are cerebrovascular disorders.

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Effect of Moon Phases and Other Time Variables on Frequency of Convulsive Status Epilepticus

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Introduction/Objectives. There are many superstitions about the effect of the moon phases on human health and behaviour; epilepsy is no exception. Various studies have shown either increased seizure frequency during full moon or shown no significant differences between moon phases. We aimed to assess the differences in frequency of convulsive status epilepticus (CSE) according to the days of the Moon, weekdays and months of the year.

Methods. We analyzed all (591) case histories of CSE in Vilnius hospitals over a 5-year period. According to CSE aetiology, we identified 2 groups of patients: cases with previous epilepsy (Epilepsy group, n=402) and those without (Non-epilepsy group, n=189). We judged differences in CSE frequency and outcomes using binomial, chi-squared best fit, Kruskal-Wallis and Pearson's correlation tests.

Results. We found no significant effect of the Moon on the frequency of CSE counting all cases. However, CSE was more frequent on the Moon day 12th and day 28th in Epilepsy group, and clearly thrust up on the day 13th in non-epilepsy group. CSE was more likely to strike on Sunday, Monday, and Friday) (χ²=24,538;p<0,001) and during the summer months (χ²=21,73;p=0,027). Moreover, the number of CSE episodes showed a strong correlation (r=0,625; p=0,03) with the average temperature of that month.

Conclusions. The CSE seems to be associated with the moon phase, weekday, month of the year, and air temperature. Surprisingly, tremendous increase of the CSE on the Moon day 13 in patients without previous epilepsy anamnesis was found.

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Status epilepticus and mortality in Latin-America: a systematic review

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Background: Studies of mortality in status epilepticus (SE) can estimate its severity and impact in health public in specific regions like Latin-America (LA).

Methods: MEDLINE, EMBASE and LILACS were interrogated, since their inception until December of 2012, searching for cohort studies of patients with SE. Searches were restricted to English, Spanish or Portuguese. Original documents dealing with any country of LA were selected. Abstracted data included source of cases, duration of follow-up, age group, type of SE, case-fatality rate (CF) and underlying causes.

Results: A total of 1681 references were identified using terms related to mortality and SE. After the first screening, 25 documents were read and critically reviewed. Ten final articles were selected. All the publications were hospital-based studies. Only three studies specified the duration of follow-up for the cohort. The CF ranged from 0% to 38%. There was no difference in regards to fatality between convulsive SE and non-convulsive SE. The percentage of deaths among elderly was greater than in any other age group. Mortality was higher in patients who had acute symptomatic SE. Central nervous system infections and strokes were the most common causes of mortality in children and adults/elderly, respectively.

Conclusions: Mortality in patients with SE varies widely in LA. Infectious and vascular are common causes of mortality. Population-based studies are necessary to avoid the selection bias that could be present in these studies series.

ViroPharma Symposium Abstracts

VS 1

Introducing the PERFECT™ Initiative: Aims, results highlights and key insights Professor Alexis Arzimanoglou, Department of Epilepsy, Sleep and Paediatric Neurophysiology, University Hospitals of Lyon, Lyon, France

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Prolonged epileptic seizures are a frequent manifestation of several epilepsy syndromes in childhood¹. If left untreated for >10 minutes, convulsive seizures can become established, and progression to status epilepticus (SE; seizures lasting >30 minutes) is increasingly likely. This creates a window of opportunity lasting from 5 to 10 minutes during which timely intervention with rescue medication can be effective in bringing the convulsive seizure under control, and prevent the resultant risks (35%) associated with SE.^{2,3} Timely intervention with anti-epileptic drug therapy in a non-hospital setting has been shown to reduce the incidence of prolonged seizures (seizures lasting <60 minutes).⁴

Prolonged seizures in children commonly occur outside of a hospital, most frequently the child's home and school. Despite the availability of anti-epileptic drugs, they are rarely administered *in situ*, resulting in unnecessary delays while the child is transported to the hospital for treatment.

The Practices in Emergency and Rescue medication For Epilepsy managed with Community administered Therapy (PERFECT™) Initiative was instigated and sponsored by ViroPharma in 2011 with the aim of improving our understanding of the challenges involved in the management of prolonged, acute, convulsive seizures (PACS) in children within a non-hospital setting. The PERFECT™ Initiative was conducted in 3 phases: 1) an analysis of policies and guidelines governing epilepsy management in select European countries; 2) a survey of health care professionals (HCPs); and 3) an ongoing patient/carer survey to explore their perspectives on the quality of non-hospital care. Results from the first 2 phases of the PERFECT™ initiative will be presented. They have highlighted unmet needs for: 1) a greater awareness and clarity in clinical guidelines and legal frameworks governing the management of PACS in children; 2) more training and education on epilepsy for those overseeing the care of these children.

1. Arzimanoglou A, Guerrini R, Aicardi J. Status epilepticus: *Aicardi's* epilepsy in children. 3rd ed. Philadelphia: Lippincott Williams &Wilkins; 2004. 188-209.
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4. Chin RF, et al. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. *Lancet Neurol.* 2008;7(8):696-703.

VS 2

Managing prolonged, acute, convulsive seizures in children in the community setting: perspectives from the PERFECT™ initiative investigator
Professor Dr. Bernd Wilken, Director Paediatric Neurology, Klinikum Kassel, Germany

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Neuropadiatrie Mit SPZ, Kassel, Germany

Background: Episodes of childhood prolonged, acute, seizures commonly start in the community setting. Therefore reducing the length of seizures and adverse effects is an important issue for emergency treatment.

Aim: The goal of the Practices in Emergency and Rescue medication For Epilepsy managed with Community administered Therapy (PERFECT™) initiative was to analyze and understand the current concepts and the state of play.

Diazepam, lorazepam and midazolam, via different administration routes, are available and commonly used in Europe for first-line intervention of prolonged (>5 minutes) epileptic seizures. In children of school age, rectal diazepam may be socially unacceptable and is

therefore less likely to be administered by teachers or other caregivers. Intravenous administrations of drugs are not allowed for parents and other caregivers if they do not have medical specialist training. However, effective treatment of prolonged, acute seizures requires robust intervention with available drugs in any situation. Midazolam administered via the oromucosal (buccal) route is becoming an increasingly popular option for rescue treatment in the community. With the approval of BUCCOLAM® (oromucosal midazolam), a new option for community based emergency treatment of a prolonged, acute, convulsive seizure exists, thus the likelihood of caregivers and teachers administering emergency drugs may increase.

Conclusion: Every child at risk for prolonged, acute, convulsive seizures needs a practical and useful emergency plan for the community situation. Training programmes for caregivers and teachers are mandatory in this setting. Current guidelines and treatment practice should be updated.

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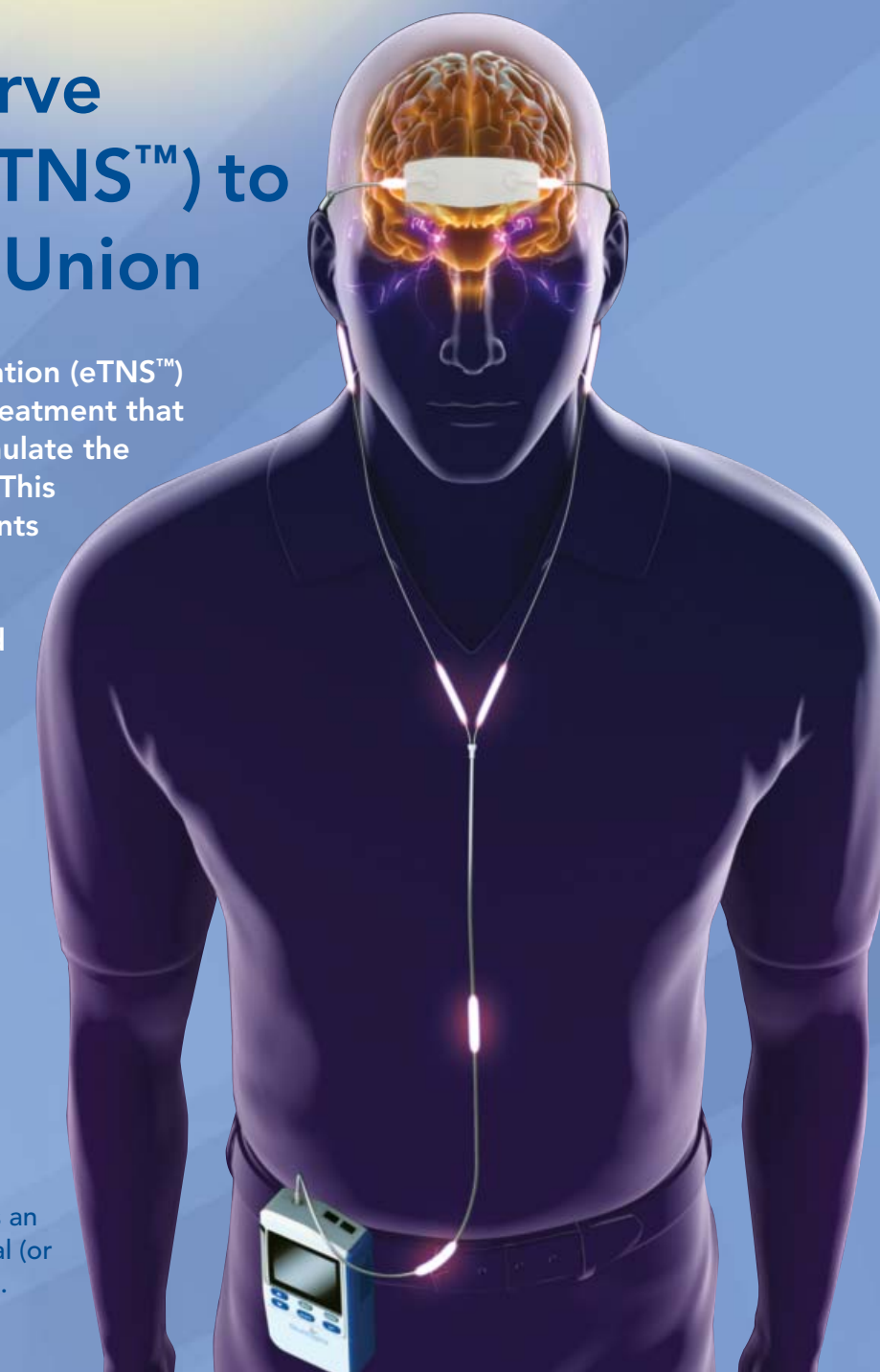
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A close-up portrait of a woman with light brown hair pulled back, resting her chin on her hand. She is wearing a blue and white striped shirt. The background is a soft, out-of-focus grey.

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