The 3rd London-Innsbruck Colloquium on Acute Seizures and Status Epilepticus

7-9 April 2011
Oxford, United Kingdom

Final Programme

www.statusepilepticus2011.eu

The colloquium is held under the auspices of the ILAE

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Dear colleagues and friends,

It is our sincere pleasure to welcome you all to Oxford as the venue for the 3rd London-Innsbruck Colloquium on Acute Seizures and Status Epilepticus. Oxford University is the second oldest surviving University and the oldest in the English speaking world. The University was founded in the 11th Century and teaching in medicine has been recorded continuously from the thirteenth century. Famous medical alumni include Harvey, Willis, Osler, Eccles, Sherrington, and Florey, and status epilepticus, the maximum expression of epilepsy, also has many Oxford links. Thomas Willis in 1667 wrote one of the earliest descriptions of the course of status:

> *"... whenas fits are often repeated, and every time grow more cruell, the animal function is quickly debilitated; and from thence, but the taint, by degrees brought on the spirits, and the Nerves serving the Praecordia, the vital function is by little and little enervated, till at length, the whole body languishing, and the pulse loosened, and at length ceasing, at last the vital flame is extinguished" .*

and this remains, unfortunately, a familiar situation - and one which the colloquium will address. Although 45 Nobel prizes have been awarded to University staff including 14 in Medicine, so far none have been for work in status and we ask the younger members of this conference to correct this glaring deficit.

The meeting is being held in the Examination Schools (commonly known in Oxford simply as the Schools), an architectural riot built in 1882 in the style of a Jacobean mansion (although James 1st would, we feel, turn in his grave at the sight of it). Sir Thomas Jackson was the architect responsible and he also built the preposterous cricket pavilion in the University Parks and the confection that is Brasenose College (both close to the Schools and both worth a visit, provided you take analgesia first).

The current Regius Professor in Medicine in Oxford, Sir John Bell, has recently written of research work in Epilepsy that *"Epilepsy and its associated syndromes give us a clear vision of what the future of medicine is likely to look like",* and it is our intention over the 3 days of the conference to explore research which is in the vanguard of medicine. We have left plenty of space in the programme for interaction, and hope that all in the audience will question and challenge - for academic debate is at the heart of all learning and discovery. 'All work and no play', though, is not good for the soul, and we have organized a reception in the Ashmolean Museum for all delegates at 7-9pm on April 8th. This will be a chance to see the spectacular new extension of the museum (which no doubt would have appalled Sir Thomas Jackson) and to sample the museum's wonderful collections.

We trust you will all have an entertaining time in Oxford, and find the colloquium stimulating and rewarding.

Simon Shorvon and Eugen Trinka
Co-Chairs

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.

Congress Venue

The congress will take place at the Examination Schools of the University of Oxford.

Examination Schools
75-81 High Street
Oxford, OX1 4BG
http://www.admin.ox.ac.uk/schools/

REGISTRATION DESK

The registration desk will be located on the ground floor of the Examination Schools. Opening hours are as follows:

Wednesday, 6 April	16:00 – 18:00
Thursday, 7 April	08:00 – 18:00
Friday, 8 April	08:00 – 18:00
Saturday, 9 April	08:00 – 13:00

CONGRESS ORGANISERS

pco tyrol congress
Congress und Messe Innsbruck GmbH
Rennweg 3, A-6020 Innsbruck, Austria
E: se2011@come-innsbruck.at
I: www.pco-tyrolcongress.at, www.cmi.at

During the conference you may reach us at the registration desk in Oxford on phone ++44 1865 286285 or fax ++44 1865 276904

INTERNET ACCESS

There will be an Internet café with 4 laptops in the exhibition area kindly sponsored by Upsher Smith.

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

med.ex GmbH
Rennweg 3, A-6020 Innsbruck
E: klaus@medex.co.at
I: www.medex.co.at

COFFEE BREAKS AND REFRESHMENTS

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

CITY TRANSPORTATION AND PARKING

Parking in the city of Oxford is very difficult, so if you have a car, it is highly recommended that you park at the park-and-ride just outside the city. Please see the website for more detailed information: http://www.parkandride.net/oxford/. Once in Oxford, transportation is provided by frequent buses and plentiful taxis. There is no train or metro system.

CURRENCY

The official currency is the British Pound (GBP). 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 any injury, loss or damage, arising from accidents or other situations during or as a consequence of the congress. Kindly check your personal insurance.

COLLOQUIUM RECEPTION - FRIDAY APRIL 8TH 7-9PM

This will be held at the Ashmolean Museum, which is the Museum of the University of Oxford and is Britain's first public museum, founded in 1683. It is home to the University of Oxford's extraordinary collections of art and archaeology. A spectacular new extension was opened at the end of last year, which has won a number of architectural awards. The reception will be held in a range of galleries allowing a viewing of many of the star attractions of the Museum and also of the original building and the new extension.

Drinks and canapés will be served.

The reception is open to all delegates and exhibitors, but it is important to bring name badges to allow entry to the museum.

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Thursday, April 7th, 2011

08:45 - 08:50 ILAE address and opening of the conference
S. Shorvon (London, United Kingdom)
E. Trinka (Salzburg, Austria)

08:50 - 11:10 Fundamental mechanisms of status epilepticus (I)
Chair: A. Nehlig (Strasbourg, France)
S. Shorvon (London, United Kingdom)

08:50 - 09:20 Receptors and their changes during development
E. Aronica (Amsterdam, The Netherlands)
09:20 - 09:40 Discussion

09:40 - 10:00 Mitochondrial function and pathology in status epilepticus
L. Bindoff (Bergen, Norway)
10:00 - 10:20 Discussion

10:20 - 10:40 Potentially pathogenic autoantibodies associated with epilepsy and encephalitis in children and adults
A. Vincent (Oxford, United Kingdom)
10:40 - 11:10 Discussion

11:10 - 11:30 Coffee break

11:30 - 13:10 Fundamental mechanisms of status epilepticus (II)
Chair: J. Engel (Los Angeles, USA)
C. Wasterlain (Los Angeles, USA)

11:30 - 12:00 Activity dependent trafficking of GABAa receptors
J. Kittler (London, United Kingdom)
12:00 - 12:20 Discussion

12:20 - 12:50 Computational modeling of epilepsy
I. Soltesz (Irvine, USA)
12:50 - 13:10 Discussion

13:10 - 14:30 Lunch and Poster session
Posters P01 – P48
for a detailed list of posters see p. 16

14:30 - 16:00 Fundamental mechanisms of status epilepticus (III)
Chair: F. Andermann (Montreal, Canada)
D. Kullmann (London, United Kingdom)

14:30 - 14:50 Light-activated channels in acute seizures
M. Kokaia (Lund, Sweden)

14:50 - 15:10 Discussion

15:10 - 15:40 Blood-brain barrier dysfunction, status epilepticus, seizures and epilepsy: a puzzle of a chicken and egg?
A. Friedman (Beer-Sheva, Israel)

15:40 - 16:00 Discussion

16:00 - 16:30 Coffee break

16:30 - 17:30 Satellite Symposium
sponsored and organised by GlaxoSmithKline

Friday, April 8th, 2011

08:30 - 10:30 EEG and Consciousness
Chair: G. Bauer (Innsbruck, Austria)
P. Kaplan (Baltimore, USA)

08:30 - 08:50 EEG patterns in coma and their taxonomic implications
L. Hirsch (New York, USA)
08:50 - 09:10 Discussion

09:10 - 09:30 Cellular mechanisms underlying EEG waveforms during coma
F. Amzica (Montreal, Canada)
09:30 - 09:50 Discussion

09:50 - 10:10 Febrile Infection-Related-Epilepsy-Syndrome (FIRES): does duration of anaesthesia affect outcome?
U. Kramer (Tel Aviv, Israel)
10:10 - 10:30 Discussion

10:30 - 10:50 Coffee break

10:50 - 12:10 New approaches to antiepileptic drug treatment
Chair: M. Bialer (Jerusalem, Israel)
F. Rosenow (Marburg, Germany)

10:50 - 11:10 Canine status epilepticus: a translational platform for human therapeutic trials
I. Leppik (Minneapolis, USA)
11:10 - 11:30 Discussion

11:30 - 11:50 Do we have enough evidence to use new AEDs in status epilepticus?
E. Trinka (Salzburg, Austria)
11:50 - 12:10 Discussion

12:10 - 13:00 Lunch

13:00 - 14:00 Satellite Symposium
sponsored and organised by UCB Pharma Ltd.
programme details see page 15

14:00 - 15:20 ICU management of status epilepticus
Chair: N. Fountain (Charlottesville, USA)
R. Kalviäinen (Kuopio, Finland)

14:00 - 14:20 Complications of the management of status epilepticus in the Intensive Care Unit
E. Schmutzhard (Innsbruck, Austria)
14:20 - 14:40 Discussion

14:40 - 15:00 Anaesthetic agents and status epilepticus
M. Smith (London, United Kingdom)
15:00 - 15:20 Discussion

15:20 - 15:50 Coffee break

15:50 - 18:00 Trials in status epilepticus
Chair: E. Perucca (Pavia, Italy)
S. Shinnar (New York, USA)

15:50 - 16:20 The RAMPART Trial
D. Lowenstein (San Francisco, USA)
16:20 - 16:40 Discussion

16:40 - 17:00 Prehospital randomized trial in convulsive status epilepticus
V. Navarro (Paris, France)
17:00 - 17:20 Discussion

17:20 - 17:40 Established Status Epilepticus Treatment Trial (and its tribulations)
H. Cock (London, United Kingdom)
17:40 - 18:00 Discussion

19:00 - 21:00 Reception at the Ashmolean Museum
All delegates and exhibitors are invited to attend

Saturday, April 9th, 2011

08:30 - 10:40 Future perspectives, novel therapy and innovation (I)
Chair: N. Bharucha (Mumbai, India)
J. Engel (Los Angeles, USA)

08:30 - 09:00 Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation
S. Shorvon (London, United Kingdom)
09:00 - 09:20 Discussion

09:20 - 09:40 Neuroanatomy of status epilepticus
O. Gröhn (Kuopio, Finland)
09:40 - 10:00 Discussion

10:00 - 10:20 Potential of brain stimulation in refractory status epilepticus
M. Walker (London, United Kingdom)
10:20 - 10:40 Discussion

10:40 - 11:10 Coffee break

11:10 - 13:10 Future perspectives, novel therapy and innovation (II)
Chair: P. Smith (Cardiff, United Kingdom)
P. Thomas (Nice, France)

11:10 - 11:30 What is the value of hypothermia in acute neurological diseases and status epilepticus?
A. Rossetti (Lausanne, Switzerland)
11:30 - 11:50 Discussion

11:50 - 12:20 Therapeutic potential of new anti-inflammatory drugs
A. Vezzani (Milan, Italy)
12:20 - 12:40 Discussion

12:40 -12:55 A new valproic acid derivative uniquely suppresses electrographic activity in the pilocarpine and organophosphate rat models of status epilepticus
M. Bialer (Jerusalem, Israel)

12:55 - 13:10 Mono- versus poly-therapy in the treatment of status epilepticus
C. Wasterlain (Los Angeles, USA)

13:10 - 13:30 Concluding remarks
S. Shorvon (London, United Kingdom)
E. Trinka (Salzburg, Austria)

Satellite Symposium
sponsored and organised by UCB Pharma Ltd.

Intravenous anti-epileptic drugs: past, present and future

Friday April 8th: 13.00 - 14.00

Chair: Claude Wasterlain (Los Angeles, USA)

13:00 - 13:05 Welcome and introduction
C. Wasterlain (Los Angeles, USA)

13:05 - 13:20 Pharmacokinetic profiles of intravenous AED treatments, drug-drug interactions and combination therapy
M. Walker (London, United Kingdom)

13:20 - 13:35 Tailoring treatment with intravenous AEDs: what do the clinical data tell us?
F. Rosenow (Marburg, Germany)

13:35 - 13:50 Indications and clinical use of intravenous AEDs: clinical experiences
S. Rüegg (Basel, Switzerland)

13:50 - 14:00 Question time
Chair's summary and close
C. Wasterlain (Los Angeles, USA)

P01

Diagnostic value of ictal neuroimaging techniques (Spect , angioTC, MRI) in patients with non diagnostic EEG and clinical suspicion of nonconvulsive status epilepticus

J. Miro, M. Veciana, J. Pedro, I. Moreno, M. Santurino, J. Mora, S. Castanyer, M. Falip (Hospitalet de Llobregat, Spain)

P02

Intravenous Lacosamide in clinical practice – patients to be reported to an independent registry

A. van Baalen, U. Stephani (Kiel, Germany)

P03

MicroRNA expression profiles in mice with spontaneous recurrent seizures following pilocarpine-induced status epilepticus

H.J. Moon, K. Chu, S.T. Lee, D.J. Jeon, K.H. Jung, K.I. Park, S.H. Kim, M.H. Kim, S.K. Lee, J.K. Roh, (Seoul, (South) Republic of Korea)

P04

Development and Characterization of Multi-Drug Resistant Epilepsy Model in Mice

H.J. Moon, D.J. Jeon, K. Chu, S.T. Lee, K.H. Jung, B.S. Kang, S.K. Lee (Seoul, (South) Republic of Korea)

P05

Does etiology of epilepsy predispose to status epilepticus?

G. Kuchukhidze, E. Trinka, I. Unterberger, C. Granbichler, G. Walser, M. Bergmann, J.P. Ndayisaba, J. Höfler, J. Dobesberger, G. Bauer, G. Luef (Innsbruck, Austria)

P06

Status epilepticus in patients with malformations of cortical development

G. Kuchukhidze, I. Unterberger, G. Walser, E. Haberlandt, K. Rostasy, F. Koppelstaetter, J. Höfler, J. Dobesberger, G. Bauer, G. Luef, E. Trinka (Innsbruck, Austria)

P07

Description of Four Cases of Simple-Partial Status Epilepticus Presenting as Epileptic Aphasia

J. Fernandez-Ferro, X. Rodriguez-Osorio, J. Pardo, E. Moreno, F.J. Lopez-Gonzalez, E. Corredera, M. Peleteiro (Santiago de Compostela, Spain)

P08

Non-convulsive status epilepticus (NCSE): The Greek experience after introducing EEG recording in the emergency department

D. Tsiptsios, G. Deretzi, X. Fitsioris, J. Rudolf, D. Kiourtidis, T. Tsironis, E. Mastrokosta, I. Tsiptsios (Thessaloniki, Greece)

P09

Clinical Characteristics and Prognosis of Febrile Status Epilepticus in Korean Children

S. Kwon, H.-E. Seo, S. Kim (Daegu, Republic of Korea)

P10

New Onset Refractory Status Epilepticus: Outcomes and role of immunotherapy

C. McHugh, R. Mohanraj (Salford, United Kingdom)

P11

Buccal midazolam or rectal diazepam for ongoing seizures - what is best?

K.O. Nakken, M.I. Lossius (Barum Postterminal, Norway)

P12

Investigations of neurophysiology in human health and disease: Effects of mental arithmetic and music on EEG

M. Mitra (Coventry, United Kingdom)

P13

Histopathology of Resistance Generalized Convulsive Status Epilepticus

V. Karlov (Moscow, Russia)

P14

Convulsive status epilepticus as initial manifestation in tetramethylenedisulfotetramine poisoning patients

D. Zhou, J. Mu, J.M. Li (Chengdu, China)

P15

The etiology of convulsive status epilepticus: a study of 220 cases in Western China

D. Zhou, L. Tian, B. Zhou (Chengdu, China)

P16

Status Epilepticus in the Intensive Care Unit: Frequency, Management and Impact on Outcome

L. Mantoan, Y. Amin, D. Kullmann, M. Walker (London, United Kingdom)

P17

Treatment of status epilepticus in a large community hospital

C. Kellinghaus, S. Berning (Osnabrueck, Germany)

P18

Successful Outcome of Episodes of Status Epilepticus after Implementation of Vagus Nerve Stimulator: A Multicenter Study

A. Sierra-Marcos, J. Aparicio, I. Maestro, M. Forcadas, J. Pardo, F. López González, X. Osorio, M. Carreño (Barcelona, Spain)

P19

Rapid cell-specific plasticity of AMPA receptors on the principal hippocampal neurons during experimental status epilepticus

J. Kapur, K. Rajasekharan (Charlottesville, United States)

P20

Pathophysiology and antiepileptic drug therapy in Tumour associated epilepsy and its implications in Status Epilepticus

J. Goonawardena (Townsville, Australia)

P21

Refractory Status Epilepticus: response to combo anaesthetic therapy

S. Sinha, K.A. Siddiqui (Riyadh, Saudi Arabia)

P22

Psychogenic Status Epilepticus

K.A. Siddiqui, S. Sinha, A. Benito (Riyadh, Saudi Arabia)

P23

A malignant variant of nonconvulsive status epilepticus

J.L. Fernández-Torre, P.W. Kaplan, M. Rebollo, A. Gutiérrez, M.A. Hernández-Hernández, J.L. Vázquez-Higuera (Santander, Spain)

P24

A multicenter, open-label trial to assess the safety and tolerability of a single intravenous loading dose of lacosamide followed by oral maintenance as adjunctive therapy in patients with partial-onset seizures

N.B. Fountain, G. Krauss, J. Isojarvi, D. Dilley, P. Doty, G.D. Rudd (Chicago, United States of America)

P25

A Case of Epilepsy Presenting as Insomnia Only; Insomnia Symptom may be related to Rhythmic Discharges

Y.W. Cho, D.H. Kim, W.C. Shin (Daegu, (South) Republic of Korea)

P26

Mood change and mutism in the elderly and status epilepticus

C.N. Lo, Y.L. Liang (Touliu, Taiwan)

P27

Efficacy of intravenous lacosamide in refractory nonconvulsive status epilepticus and simple partial status epilepticus

K. Rantsch, U. Walter, M. Wittstock, R. Benecke, J. Rösche (Rostock, Germany)

P28

Role of Mg-RBC and temporal-parietal-occipital EEG epileptiform activity in FSS and Complex partial epilepsy

A. Ibadi, A. Fredman, M. Czeczko (Warsaw, Poland)

P29

Topiramate and Status Epilepticus : Outcome of 8 Cases

S. Tiamkao, T. Suttichaimongkol, K. Sawanyawisuth (Khon Kaen, Thailand)

P30

Outcome of Status Epilepticus in North-East of Thailand

S. Tiamkao, P. Waleepitakdej, K. Sawanyawisuth, (Khon Kaen, Thailand)

P31

Intravenous Lacosamide as Treatment of Status epilepticus in Children – A Small Case Series

K. Frankenbusch, P. Herkenrath (Cologne, Germany)

P32

Sequencing of the ACCN2 gene in status epilepticus does not identify pathogenic mutations

C. Depondt, M. Rai, A. Lopes da Cruz, J. Parma, M. Pandolfo (Brussels, Belgium)

P33

Preliminary experience in the use of IV lacosamide in the treatment of refractory status epilepticus and seizure clusters

N. Gaspard, C. Depondt, S. Coppens, B. Legros (Bruxelles, Belgium)

P34

Autoimmune limbic encephalitis with antibodies to leucine-rich glioma inactivated 1 protein and N-type-voltage-gated-calcium-channels presenting as pilomotor status epilepticus

J. Hoefler, F. Ernst, A. Kunz, W. Kleindienst, H. Bartsch, E. Trinka (Salzburg, Austria)

P35

Variations in susceptibility to electroshock-induced seizures in rats with different degrees of brain dysplasia

Z. Setkowicz, K. Gzielo-Jurek, L. Uram, K. Janeczko (Krakow, Poland)

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IL1

Receptors and their changes during development

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The development of the human brain depends on a precisely orchestrated cascade of events, including proliferation, migration and maturation of neural progenitor cells (Rakic & Lombroso 1998). Different mechanisms coordinate these stages to reach a normal structural organization including synaptogenesis, producing appropriate excitatory and inhibitory networks. Among the mechanisms that control the late embryonic and early postnatal development, signaling of major neurotransmitters such as glutamate (Glu) and γ-aminobutyric acid (GABA), deserves particular attention. Transcriptional expression of Glu receptor (GluR) and GABA (GABAR) subunits is observed during the early phases of corticogenesis in human brain. Increasing evidence indicates that activation of both GABAR and GluR regulate critical developmental processes, such as proliferation, differentiation, growth and survival of neural progenitor cells (for reviews see (Catania et al. 2007; Henschel et al. 2008; Manent & Represa 2007)). Alterations in subunit expression and composition of GluR and GABAR are observed during the late gestational and early postnatal period of development and this developmental regulation is activity-dependent and region- and cell-type specific.

Both experimental and human studies indicate an early maturation of excitatory circuits and the subunit composition of ionotropic GluR (such as α-amino-3- hydroxy-5-methyl-4-isoxazole propionate, AMPA and N-methyl-d-aspartate, NMDA receptors) may also contribute to the enhanced excitability of the immature brain (Sanchez & Jensen 2001; Babb et al. 2005; Bettler et al. 2004; Catania et al. 2007; Henschel et al. 2008; Henson et al. 2008). A developmental switch of the NMDA receptor 2A (NR2A), NR2B and NR3A subunits has been shown to underlie functional changes of the NMDA receptor properties in different brain regions during the period when neural plasticity is most pronounced (Liu et al. 2004; van Zundert et al. 2004; Babb et al. 2005; Henson et al. 2008). A developmental regulation of AMPA receptor subunit expression has been observed in both rat and human brain, showing a correlation between the regional expression of GluR2-subunit lacking (Ca^{2+} permeable) AMPARs and the age windows of increased susceptibility to brain injury (Talos et al. 2006a; Talos et al. 2006b) .

Recent experimental evidence suggests critical functions for metabotropic GluR (mGluRs) during cortical development (Di Giorgi-Gerevini et al. 2004; Di Giorgi-Gerevini et al. 2005; Schlett 2006). The mGluR family includes eight subtypes that have been subdivided into three main groups on the basis of their sequence, second messenger systems and pharmacological profile. Group I includes mGluR1 and mGluR5, which are coupled to phosphoinositide (PI) hydrolysis, whereas the other subtypes are negatively coupled to adenylyl cyclase (Recasens et al. 2007). PI hydrolysis induced by activation of group I mGluRs is substantial in developing rat brain and particularly mGluR5 is highly expressed in rat brain during the early postnatal development (Catania et al. 2007). mGluR5 is highly expressed also in developing human cortex from the earliest stages (9 gestational weeks, GW), with strong expression in the ventricular/subventricular zones; in addition expression of group I mGluRs is detected in the Cajal-Retzius cells in human brain, supporting the potential role of these receptor subtypes in the regulation of Cajal-Retzius cell functions during human corticogenesis (Boer et al. 2010). Activation of group I and II mGluRs has been shown to modulate the expression of both glial and neuronal glutamate transporter proteins (Aronica et al. 2002). Temporal and regional changes in the expression of both Glu and GABA transporters represent additional factors that control synaptic transmission and neuronal excitability during development (Conti et al. 2004; Furuta et al. 2005).

The expression and function of both ionotropic and metabotropic GABA receptors ($GABA_A$ and $GABA_B$) are also developmentally regulated Billinton et al. 2001; Bettler et al. 2004; Henschel et al. 2008). Developmental differences in subunit expression contribute to alterations in

$GABA_A$ receptor function during postnatal development, influencing neuronal excitability (Brooks-Kayal et al. 2001; Henschel et al. 2008). Moreover, $GABA_A$ receptors expressed early in development initially mediate depolarizing responses to GABA. This paradoxical excitatory action of GABA observed in the immature brain (Owens & Kriegstein 2002; Ben-Ari 2002; Ben-Ari et al. 2007) has been shown to depend on the relatively high intracellular chloride ion content which is critically regulated by the cation-Cl- cotransporters (CCTs; (Payne et al. 2003; Yamada et al. 2004). Accordingly, in both rodent and human brain the CCTs (Na^+-K^+-$2Cl^-$-cotransporter, NKCC1 and K^+-Cl^--cotransporter, KCC2) are developmentally regulated (Clayton et al. 1998; Dzhala et al. 2005; Rivera et al. 1999; Aronica et al. 2007). The strong expression of NKCC1 observed early during development is considered to sustain the excitatory action of GABA and facilitates seizures in the immature human brain (Dzhala et al. 2005) probably through a synergistic action of GABA and GluR receptors (Khalilov et al. 2005).

Recent data support the involvement of the endocannabinoid signaling in early brain development, as well as the key role of cannabinoid receptors (CBR) in the regulation of neuronal excitability (for review see (Fernandez-Ruiz et al. 2000; Fernandez-Ruiz et al. 2004)). Depending on the cellular localization and the signal transduction pathways, CBR have been shown to regulate both glutamatergic and GABAergic synaptic transmission (for reviews see (Pacher et al. 2006; Onaivi 2009). Several studies show expression of cannabinoid receptors 1 (CB1) and their endogenous ligands early during brain development in rodents (Berrendero et al. 1998; Buckley et al. 1998; Fernandez-Ruiz et al. 1999; Mulder et al. 2008; Vitalis et al. 2008). Abundant levels of CB1 mRNA and protein have been also detected in early prenatal stages in human brain (Mato et al. 2003; Zurolo et al. 2010).

Of course, other ion channels (including sodium, potassium, calcium channels), other receptors (e.g. serotonin receptors, glucocorticoid receptors etc.) and numerous other signaling molecules (such as neuropeptides, neurohormones and adenosine) also regulate neuronal excitability during brain maturation.

Interestingly, there are several examples of protein expression (including receptor/channel, transporter and cytoskeleton proteins) in mature epileptic brain that resemble expression during early brain development and that suggest a recapitulation of a developmental program. Increased knowledge in the expression patterns and cellular functions of neurotransmitter receptors and other factors modulating synaptic transmission in human brain development, in particular during the late embryonic and early postnatal period, my lead to an improved understanding of the susceptibility to seizures not only in immature but also in adult brain and may contribute to develop age-specific therapeutic targets, as well as to prevent drug-induced long-term cognitive deficits.

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References

Aronica E, Gorter JA, Ijlst-Keizers H, Rozemuller AJ, Yankaya B, Troost D (2002) Expression and functional role of mGluR3 and mGluR5 in human astrocytes and glioma cells: opposite regulation of glutamate transporter proteins. *Neuropharmacology* 43:174.

Aronica E, Boer K, Redeker S, van Rijen PC, Troost D, Gorter JA (2007) Differential expression patterns of Chloride transporters, NKCC1 and KCC2, in epilepsy-associated malformations of cortical development. *Neuroscience* 145:185-196.

Babb TL, Mikuni N, Najm I, Wylie C, Olive M, Dollar C, MacLennan H (2005) Pre- and postnatal expressions of NMDA receptors 1 and 2B subunit proteins in the normal rat cortex. *Epilepsy Res.* 64:23-30.

Ben-Ari Y (2002) Excitatory actions of gaba during development: the nature of the nurture. *Nature Rev. Neurosci.* 3:728-739.

Ben-Ari Y, Gaiarsa JL, Tyzio R, Khazipov R (2007) GABA: a pioneer transmitter that excites immature neurons and generates primitive oscillations. *Physiol. Rev.* 87:1215-1284.

Berrendero F, Garcia-Gil L, Hernandez ML, Romero J, Cebeira M, de Miguel R, Ramos JA, Fernandez-Ruiz JJ (1998) Localization of mRNA expression and activation of signal transduction mechanisms for cannabinoid receptor in rat brain during fetal development. *Development* 125:3179-3188.

Bettler B, Kaupmann K, Mosbacher J, Gassmann M (2004) Molecular structure and physiological functions of GABA(B) receptors. *Physiological Reviews* 84:835-867.

Billinton A, Ige AO, Bolam JP, White JH, Marshall FH, Emson PC (2001) Advances in the molecular understanding of GABA(B) receptors. *Trends Neurosci.* 24:277-282.

Boer K, Encha-Razavi F, Sinico M, Aronica E (2010) Differential distribution of group I metabotropic glutamate receptors in developing human cortex. *Brain Res.*1324:24-33.

Brooks-Kayal AR, Shumate MD, Jin H, Rikhter TY, Kelly ME, Coulter DA (2001) gamma-Aminobutyric acid(A) receptor subunit expression predicts functional changes in hippocampal dentate granule cells during postnatal development. *J. Neurochm.* 77:1266-1278.

Buckley NE, Hansson S, Harta G, Mezey E (1998) Expression of the CB1 and CB2 receptor messenger RNAs during embryonic development in the rat. *Neuroscience* 82:1131-1149.

Catania MV, D'Antoni S, Bonaccorso CM, Aronica E, Bear MF, Nicoletti F (2007) Group I Metabotropic Glutamate Receptors: A Role in Neurodevelopmental Disorders? *Molecular Neurobiol.* 35:298-307

Clayton GH, Owens GC, Wolff JS, Smith RL (1998) Ontogeny of cation-Cl- cotransporter expression in rat neocortex. *Brain Res. Dev. Brain Res.*109:281-292.

Conti F, Minelli A, Melone M (2004) GABA transporters in the mammalian cerebral cortex: localization, development and pathological implications. *Brain Research - Brain Res. Rev.* 45:196-212.

Di Giorgi-Gerevini V, Melchiorri D, Battaglia G, Ricci-Vitiani L, Ciceroni C, Busceti CL, Biagioni F, Iacovelli L, Canudas AM, Parati E, De Maria R, Nicoletti F (2005) Endogenous activation of metabotropic glutamate receptors supports the proliferation and survival of neural progenitor cells. *Cell Death & Differentiation* 12:1124-1133.

Di Giorgi Gerevini VD, Caruso A, Cappuccio I, Ricci Vitiani L, Romeo S, Della Rocca C, Gradini R, Melchiorri D, Nicoletti F (2004) The mGlu5 metabotropic glutamate receptor is expressed in zones of active neurogenesis of the embryonic and postnatal brain. *Brain Res. Dev. Brain Res* 150:17-22.

Dzhala VI, Talos DM, Sdrulla DA, Brumback AC, Mathews GC, Benke TA, Delpire E, Jensen FE, Staley KJ (2005) NKCC1 transporter facilitates seizures in the developing brain.[see comment]. *Nature Med.* 11:1205-1213.

Fernandez-Ruiz J, Berrendero F, Hernandez ML, Ramos JA (2000) The endogenous cannabinoid system and brain development. *Trends Neurosci.* 23:14-20.

Fernandez-Ruiz J, Gomez M, Hernandez M, de Miguel R, Ramos JA (2004) Cannabinoids and gene expression during brain development. *Neurotoxicity Res.* 6:389-401.

Fernandez-Ruiz JJ, Berrendero F, Hernandez ML, Romero J, Ramos JA (1999) Role of endocannabinoids in brain development. *Life Sci.* 65:725-736.

Furuta A, Takashima S, Yokoo H, Rothstein JD, Wada K, Iwaki T (2005) Expression of glutamate transporter subtypes during normal human corticogenesis and type II lissencephaly. *Brain Res. Dev. Brain Res* 155:155-164.

Henschel O, Gipson KE, Bordey A (2008) GABAA receptors, anesthetics and anticonvulsants in brain development. *CNS & Neurol.l Dis. Drug Targ.* 7:211-224.

Henson MA, Roberts AC, Salimi K, Vadlamudi S, Hamer RM, Gilmore JH, Jarskog LF, Philpot BD (2008) Developmental regulation of the NMDA receptor subunits, NR3A and NR1, in human prefrontal cortex. *Cerebral Cortex* 18:2560-2573.

Khalilov I, Le Van Quyen M, Gozlan H, Ben-Ari Y (2005) Epileptogenic actions of GABA and fast oscillations in the developing hippocampus. *Neuron* 48:787-796.

Liu X, Murray KD, E.G. J (2004) Switching of NMDA Receptor 2A and 2B Subunits at Thalamic and Cortical Synapses during Early Postnatal Development. *Journal of Neuroscience* 24:8885– 8895

Manent JB, Represa A (2007) Neurotransmitters and brain maturation: early paracrine actions of GABA and glutamate modulate neuronal migration. *Neuroscientist* 13:268-279.

Mato S, Del Olmo E, Pazos A (2003) Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. *European Journal of Neuroscience* 17:1747-1754.

Mulder J, Aguado T, Keimpema E, Barabas K, Ballester Rosado CJ, Nguyen L, Monory K, Marsicano G, Di Marzo V, Hurd YL, Guillemot F, Mackie K, Lutz B, Guzman M, Lu HC, Galve-Roperh I, Harkany T (2008) Endocannabinoid signaling controls pyramidal cell specification and long-range axon patterning. *Proc Natl Acad Sci U S A.* 105:8760-8765.

Onaivi ES (2009) Cannabinoid receptors in brain: pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications. *Internat. Rev. Neurobiol.* 88:335-369.

Owens DF, Kriegstein AR (2002) Is there more to GABA than synaptic inhibition? *Nature Rev. Neurosci.* 3:715-727.

Pacher P, Batkai S, Kunos G (2006) The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol. Rev.* 58:389-462.

Payne JA, Rivera C, Voipio J, Kaila K (2003) Cation-chloride co-transporters in neuronal communication, development and trauma. *Trends Neurosci.* 26:199-206.

Rakic P, Lombroso PJ (1998) Development of the cerebral cortex: I. Forming the cortical structure. *J Am Acad Child Adolesc Psychiatry* 37:116-117.

Recasens M, Guiramand J, Aimar R, Abdulkarim A, Barbanel G (2007) Metabotropic glutamate receptors as drug targets. *Current Drug Targets* 8:651-681.

Rivera C, Voipio J, Payne JA, Ruusuvuori E, Lahtinen H, Lamsa K, Pirvola U, Saarma M, Kaila K (1999) The K+/Cl- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation.[see comment]. *Nature* 397:251-255.

Sanchez RM, Jensen FE (2001) Maturational aspects of epilepsy mechanisms and consequences for the immature brain. *Epilepsia* 42:577-585.

Schlett K (2006) Glutamate as a modulator of embryonic and adult neurogenesis. *Curr. Top. Med. Chem.* 6:949-960.

Talos DM, Fishman RE, Park H, Folkerth RD, Follett PL, Volpe JJ, Jensen FE (2006a) Developmental regulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor subunit expression in forebrain and relationship to regional susceptibility to hypoxic/ischemic injury. I. Rodent cerebral white matter and cortex. *J. Comp. Neurol.* 497:42-60.

Talos DM, Follett PL, Folkerth RD, Fishman RE, Trachtenberg FL, Volpe JJ, Jensen FE (2006b) Developmental regulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor subunit expression in forebrain and relationship to regional susceptibility to hypoxic/ischemic injury. II. Human cerebral white matter and cortex. *J. Comp. Neurol.* 497:61-77.

van Zundert B, Yoshii A, Constantine-Paton M (2004) Receptor compartmentalization and trafficking at glutamate synapses: a developmental proposal. *Trends Neurosci.* 27:428-437.

Vitalis T, Laine J, Simon A, Roland A, Leterrier C, Lenkei Z (2008) The type 1 cannabinoid receptor is highly expressed in embryonic cortical projection neurons and negatively regulates neurite growth in vitro. Eur. *J.Neurosci.* 28:1705-1718.

Yamada J, Okabe A, Toyoda H, Kilb W, Luhmann HJ, Fukuda A (2004) Cl- uptake promoting depolarizing GABA actions in immature rat neocortical neurones is mediated by NKCC1. *J. Physiol.* 557:829-841.

Zurolo E, Iyer A, Baayen JC, Spliet WGM, van Rijen PC, Troost D, Gorter JA, Aronica E (2010) CB1 and CB2 cannabinoid receptor expression during development and in epileptogenic developmental pathologies. Neuroscience, 29;170(1):28-41, 2010. *Neuroscience* 170:28-41

IL2

Mitochondrial Function and Pathology in SE

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Summary

Mitochondria are sub-cellular organelles with multiple roles the most important of which is the production of cellular energy in the form of ATP. The energy producing pathway, the mitochondrial respiratory chain (MRC), comprises 5 large multi-subunit complexes. Proteins making up this pathway are encoded by two genomes, the majority by chromosomal genes located in the nucleus and 13 by mitochondrial DNA (mtDNA), located inside the mitochondria themselves. Mutations in both mtDNA and nuclear genes can give rise to respiratory chain dysfunction.

Central nervous system neurones are terminally differentiated cells and this, coupled with a high energy demand, may explain their vulnerability to mitochondrial dysfunction. Since decreased intracellular ATP levels may also increase neuronal excitability, by impairing sodium-potassium ATPase activity, and mitochondria are an important store for intracellular calcium, mitochondrial dysfunction may impinge negatively on neuronal function in several different ways.

Epilepsy is common in MRC disease and can be the sole feature or, as usually happens, part of a syndrome that involves other parts of the central and peripheral nervous systems, the heart, pancreas and indeed any other organ. MRC disease can give rise to both focal and generalised epilepsy, but symptomatic, multifocal and thus, secondary generalised epilepsy combining focal and generalised features is the most common. Status epilepticus is a well recognised presenting feature of the epilepsy in MRC disease, and interestingly, several of these disorders show a clear occipital lobe predilection.

In order to understand the mechanisms involved in mitochondrial disease, we have studied the cortical damage seen in two mitochondrial syndromes that show a degree of clinical overlap, but which originate in different genomes; the first is caused by a point mutation in mtDNA (Tzoulis & Bindoff 2009), the other by mutation in the gene encoding the mitochondrial DNA polymerase gamma (POLG) (Tzoulis, et al. 2006). Both disorders are associated with a high risk of status epilepticus and, interestingly, both show occipital lobe predilection (Engelsen, et al. 2008). Using a combination of imaging and post-mortem studies, we find that cortical neuronal energy failure is an early part of the clinical evolution of both syndromes. Neuronal damage appears to be the trigger for status epilepticus and once started, it is generally difficult to control. Post mortem analysis shows evidence of cortical neuronal fall-out with features suggesting that energy failure is the main or sole cause.

References

Engelsen BA, Tzoulis C, Karlsen B, Lillebo A, Laegreid LM, Aasly J, Zeviani M, Bindoff LA. (2008) POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection. *Brain* 131:818-828.

Tzoulis C, Bindoff LA. (2009) Serial diffusion imaging in a case of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. *Stroke* 40:e15-17.

Tzoulis C, Engelsen BA, Telstad W, Aasly J, Zeviani M, Winterthun S, Ferrari G, Aarseth JH, Bindoff LA. (2006) The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. *Brain* 129:1685-1692.

IL3

Potoentially pathogenic autoantibodies associated with epilepsy and encephalitis in children and adults

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Antibodies against both voltage-gated and ligand-gated ion channels have been recognised in neurological diseases for some time. Classically, they cause neuromuscular junction disorders such as myasthenia gravis and the Lambert Eaton myasthenic syndrome. In addition, patients with acquired neuromyotonia, which is caused by peripheral nerve hyperexcitability, often have antibodies that bind to voltage-gated potassium channel (VGKC) complexes that can be labelled with ^{125}I-dendrotoxin and immunoprecipitated from digitonin extracts of mammalian brain tissue.

More recently, the role of antibodies in neurological diseases has expanded to include the central nervous system. VGKC-complex antibodies are associated with Morvan's syndrome a very rare condition that includes neuromyotonia, autonomic dysfunction, sleep and circadian rhythm disturbance (eg. Liguori et al 2001) and limbic encephalitis with severe memory loss, seizures, hyponatraemia and often high signal in the medial temporal lobes on MRI (Vincent et al 2004). It is now clear that the VGKC-complexes contain proteins, such as CASPR2 and LGI1 that are the actual targets for many of the patients' antibodies (Irani et al Brain 2010a; Lai et al 2010). CASPR2 antibodies are most often found in patients with Morvan's disease or neuromyotonia, but LGI1 antibodies are particularly common in patients with limbic encephalitis. Of particularly relevance to seizures, mutations in the gene for LGI1 are found in autosomal dominant lateral temporal lobe epilepsy (Morante-Redolat et al 2002), and IgG from one patient with LGI1 antibodies and limbic encephalitis increased the probability of release at the CA3 mossy fibre/pyramidal cell synapses in rodent brain slices in a manner that suggested impaired inhibitory mechanisms (Lalic et al 2010).

More evidence for the association of seizures with these antibodies in the increasing number of patients with a novel brief dystonic faciobrachial seizure identified with raised VGKC-complex antibodies (Irani et al 2011); most of these patients progress to limbic encephalitis but a small number have been identified and treated successfully without progression. Conversely, there are patients who have episodes of limbic encephalitis who then develop hippocampal sclerosis with temporal lobe epilepsy (Bien et al 2007).

Other CNS diseases associated with specific antibodies to ligand-gated ion channels, NMDA, AMPA and GABA(b) receptors, have now been identified and are also associated with seizures (Dalmau et al 2011; Lai et al 2009, Lancaster et al 2010). The most striking is the complex encephalopathy with NMDAR-antibodies. The patients present with neuropsychiatric disturbance and seizures but progress to bizarre movement disorders, orofacial dyskinesias and reduced consciousness. They respond to immunotherapies but improvement is often slow and recovery not always complete. A few patients have forme frustes of the disease with predominant seizures or psychosis and modest cognitive involvement (Dalmau et al 2011; Irani et al 2010b).

High titres of GAD antibodies are also proving useful in the clinical assessment of patients with adult onset seizures although they may not be directly pathogenic. Patients with these antibodies tend to be female and have temporal lobe epilepsy as a presenting feature, but cognitive features are also evident (Malter et al 2010).

Many of the patients with these antibodies do well with immunotherapies in combination with symptomatic treatments. Steroids, initially intravenous and then oral high dose, and plasma exchange followed by intravenous immunoglobulins are often used, although for the less severe cases, steroids or intravenous immunoglobulins may be sufficient. Recovery is not necessarily fast but the majority of patients can resume relatively normal lives although memory may remain somewhat impaired. Patients with GAD antibodies, however, have not yet shown good treatment responses and these patients need to be studied further.

Although autoimmunity is unlikely to be a major cause of idiopathic epilepsy, studies of cohorts of patients from epilepsy clinics are beginning to find patients with the antibodies described here who may well benefit from immunotherapies if identified promptly (eg McKnight et al 2006). Equally importantly, each of these antibodies is beginning to be found in children with a variety of different forms of

encephalitis or epilepsy (Florance et al 2010; Haberlandt et al 2010; Suleiman et al 2011; Granerod et al 2010). These CNS conditions are raising many challenging issues. How do the antibodies access the CNS compartment, where do they act and what are the mechanisms? Will this knowledge help in the design of better symptomatic treatments and which are the most suitable immunotherapies? Animal models are now being developed to try to answer some of these questions.

References

Liguori R, Vincent A, Clover L, Avoni P, Plazzi G, Cortelli P, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. Brain. 2001;124:2417-26

Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004;127:701-12.

Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133:2734-2748

Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9:776-85

Morante-Redolat JM, Gorostidi-Pagola A, Piquer-Sirerol S, et al. Mutations in the LGI1/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. Human Mol Genet 2002;11:1119-28.

Lalic T, Pettingill P, Vincent A, Capogna P. Human limbic encephalitis serum enhances hippocampal mossy fibre-CA3 pyramidal cell synaptic transmission. Epilepsia in press.

Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR et al. Faciobrachial dystonic seizures precede LGI1-antibody limbic encephalitis. Ann Neurol in press.

Bien CG, Urbach H, Schramm J, Soeder BM, Becker AJ, Voltz R, et al. Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. Neurology. 2007;69:1236-44.

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63-74

Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65:424-34

Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 2010;9:67-76.

Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133:1655-67.

Malter MP, Helmstaedter C, Urbach H, Vincent A, Bien CG. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol. 2010;67:470-478

McKnight K, Jiang Y, Hart Y, Cavey A, Wroe S, Blank M, et al. Serum antibodies in epilepsy and seizure-associated disorders. Neurology. 2005;65:1730-6.

Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66:11-8.

Haberlandt E, Bast T, Ebner A, Holthausen H, Kluger G, Kravljanac R, Kröll-Seger J, Kurlemann G, Makowski C, Rostasy K, Tuschen-Hofstätter E, Weber G, Vincent A, Bien C. Limbic encephalitis in children and adolescents. Arch Dis Child. 2010 Oct 19. [Epub ahead of print]

Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D et al ; on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010 Oct 15.

IL4

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Abstract not received

IL5

Computational Modeling of Epilepsy

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With the rapid rise in our knowledge about the structural and functional properties of neuronal microcircuits and the exponentially increasing power of computers, it has become possible to closely integrate experimental findings with large-scale, anatomically and biophysically realistic computational simulations of control and epileptic neuronal networks with unprecedented precision and predictive power. We are developing full-scale realistic network models of the control and injured temporal lobe in order to investigate fundamental questions related to the mechanistic bases of epilepsy. We will discuss the biological basis of the model development, and show specific applications, including exciting new computational and experimental results concerning the roles of aberrant hyper-connected hub-like neurons in seizures. The talk will highlight the unprecedented predictive and analytic power of increasingly user-friendly, freely shared, highly realistic, large-scale computational models in understanding the mechanistic bases of epilepsy.

IL6

Light-activated channels in acute seizures

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Halorhodopsin chloride pump (NpHR) from archaebacterium Natronomonas pharaonis is activated by orange light. When genetically adapted NpHR is expressed in mammalian brain by viral vectors and optically activated, it pumps chloride ions into transduced neurons and thus hyperpolarizes them, preventing firing of action potentials. This optical control of action potential generation could potentially be used in defined neuronal populations to prevent their excessive activation during seizures in specific focal brain regions containing epileptic focus. Selective hyperpolarization of principal neurons in the hippocampal network could result in suppression of synchronized epileptiform activity. However, intracellular accumulation of chloride in principal cells in the brain may theoretically convert inhibitory $GABA_A$ receptor-mediated hyperpolarizations into excitatory depolarizations, which in turn could promote more network excitability and seizures. We therefore investigated whether transduction of principal cells in the rat hippocampus by NpHR and its activation by light would inhibit action potential generation in these cells and thereby suppress seizure activity. More specifically we explored whether activation of NpHR would suppress epileptiform activity induced by electrical stimulation (stimulation-induced bursting - STIB) in hippocampal organotypic cultures, and whether such treatment influences $GABA_A$ receptor-mediated inhibition of the cells. Organotypic hippocampal slices closely resemble pharmacoresistant epileptic tissue in humans and animal models, characterized by cell death, axonal sprouting and synaptic reorganization, with resulting increased cellular and network excitability.

NpHR expression was assessed by including enhanced yellow fluorescent protein (EYFP) in the LV-NpHR-EYFP-pCaMKII_ vector construct. Injection of the lentiviral vector in vivo into the postnatal day (P) 4 mice pups resulted in expression of NpHR throughout the hippocampal formation at 21-28 days in culture.

Whole-cell patch-clamp recordings from NpHR transduced principal neurons revealed no significant alterations in input resistance, resting membrane potential (RMP), action potential threshold, duration, amplitude or accomodation, as well as rheobase of these cells, suggesting that expression of transgene NpHR has no significant effect on intrinsic properties and excitability of principal pyramidal cells in absence of light stimulation. All transduced neurons were hyperpolarized during optical stimulation of NpHR both CA1 and CA3 areas of organotypic hippocampal cultures. Light-induced hyperpolarization was effectively suppressing action potentials generated in response to injection of depolarizing currents in these cells. Hyperpolarizations were often accompanied by rebound depolarizations and action potentials during sustained depolarization by current injection. These rebound action potentials however were similar in frequency in NpHR-transduced and non-transduced pyramidal cells.

We also showed that activation of transgene NpHR does not alter the reversal potential for the $GABA_A$ receptor-mediated monosynaptic IPSCs in principal neurons. Thus, we confirmed that transgene NpHR activation does not convert GABAA receptor-mediated hyperpolarizations into depolarizations in the current in *vitro epilepsy* model.

Next we confirmed that transgene NpHR without light exposure does not affect the threshold for STIB induction, duration of STIB and frequencies of spikes during STIB. Further, we demonstrated that exposure of NpHR-transduced slices to orange light substantially shortened the duration of STIB discharges in the hippocampal organotypic cultures (Fig. 1). The blue light had no effect on STIB duration in the same slices. Inducing three consecutive STIBs without any light exposure showed a stable STIB induction.

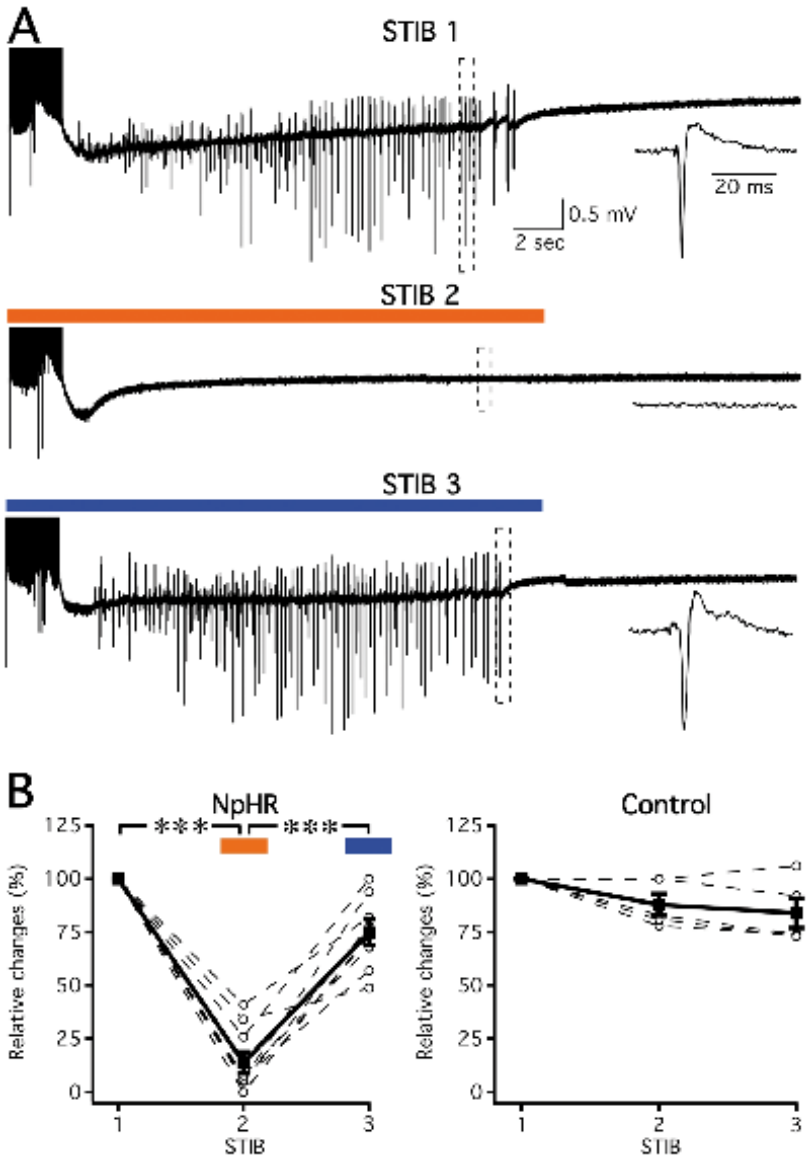

Figure 1. STIB in CA1 is strongly attenuated by orange light activation of transgene NpHR in organotypic hippocampal cultures. (A) Recordings of three consecutive STIB stimulations, with orange light illumination on second stimulation, in NpHR-transduced slices. *Inserts:* magnification of traces showing spikes during STIB. Scale bars apply for all traces. (B) Relative changes in STIB duration of individual recordings (dotted lines and open circles) and their average values (mean ± SEM; solid line and filled squares) for NpHR and non-transduced control slices, respectively, during three consecutive STIB. At STIB2, orange light is applied to NpHR-transduced slices as indicated by orange bar. At STIB3, blue light is applied to NpHR-transduced slices as indicated by blue bar. ***$p < 0.001$. From Tønnesen et al., PNAS, 2009: 106, 12162-12167.

These data show for the first time that optical activation of transgene NpHR can effectively suppress epileptiform activity in a relevant model of pharmacoresistant epilepsy in vitro. During STIB pyramidal neurons expressed a series of paroxysmal depolarizing shifts (PDS) with superimposed action potentials. Exposure of slices to light significantly shortened the duration of PDS occurrence in NpHR-transduced pyramidal cells. Inhibition of PDS occurrence was possible to induce repeatedly by orange light illumination. In addition, we used another in vitro model for epileptiform activity induced by bath application of picrotoxin (PTX, a GABAA receptor antagonist).

We observed that generation of high frequency action potential trains induced by PTX were strongly suppressed by optical activation of transgene NpHR in pyramidal neurons. Our preliminary data also show that even in acute hippocampal slices where strong epileptifrom activity is induced by chemical method, NpHR-based optogenetic treatment can effectively suppress such epileptiform activity.

These studies provide a proof-of-principle, that hyperpolarization of cortical neurons by transgene NpHR is an effective method to curtail paroxysmal activity in transduced neurons, and can inhibit epileptiform activity in hippocampal slices. These studies are first to demonstrate that optogenetic approach may become an useful method for controlling epileptiform activity, and opens novel avenues to develop alternative treatment strategies for epilepsy.

IL7

Blood-brain barrier dysfunction in status epilepticus

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Prolonged seizure and status epilepticus (SE) are neurological emergencies which may be followed by the development of unprovoked seizures as well as mental and neurologic deficits. Prolonged seizures have been shown to be associated with a robust vascular response (often vasodilation) and at some point, when a metabolic compromise occurs with an increased vascular permeability. The blood-brain barrier (BBB) is a functional and structural complex barrier characterizing the vasculature within the central nervous system and is crucial for the maintenance of strict extracellular environment. Recent studies in pilocarpine-exposed rats (van Vliet et al., 2007) found increased number of spontaneous seizures in animals showing greater BBB dysfunction following SE, suggesting a potential direct role for BBB dysfunction in epileptogenesis. Indeed, experiments in rodents demonstrated that dysfunction of the BBB underlies the initiation of transcriptional program within the neurovascular network (Cacheaux et al., 2009). This includes the transformation of astrocytes and microglia and upregulation of cytokines and chemokines. The transformation of astrocytes is associated specifically with disturbed extracellular homeostasis and activity-dependant accumulation of potassium and glutamate (David et al., 2009). These ionic changes are leading to neuronal depolarization, slower spike repolarization, increased transmitter release and enhancement of short-term synaptic facilitation and long-term synaptic modifications. In animals exposed to BBB opening, spontaneous unprovoked seizures develop within 4-10 days. Within 3-5 weeks, neurological dysfunction is found associated with loss of cortical volume (measured using in-vivo MRI imaging), reduced dendritic branching and neuronal loss with lasting astrogliosis (Tomkins et al., 2007). Specific attention has been given to serum albumin, which diffuses into the neuropil in SE-exposed animals and is taken up by specific cell populations; while hours following the initiation of SE a selective uptake into astroglial cell populations has been found, 1-2 days later we observed a massive uptake into neurons. Albumin was found to initiate an astroglial response via transforming growth factor beta (TGF-β) signaling and phosphorylation of the Smad-2/5 pathway (Ivens et al., 2007;Cacheaux et al., 2009). Preliminary data suggest that indeed, blocking TGF-β following experimental BBB opening, decreases albumin-induced transcriptional response and prevents epileptogenesis. Finally, although limited, clinical data support a frequent BBB dysfunction in human patients and its promoting effect in the development of seizures (Marchi et al., 2007;Tomkins et al., 2008). In summary, recent accumulating experimental evidence point to neurovascular interactions at the

BBB as key mechanisms underlying immune response, astroglial dysfunction and neuronal hyperexcitability in the SE-exposed brain, and thus as potential novel targets for treatment (Friedman et al., 2009).

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References

Cacheaux LP, Ivens S, David Y, Lakhter AJ, Bar-Klein G, Shapira M, Heinemann U, Friedman A, Kaufer D (2009) Transcriptome profiling reveals TGF-beta signaling involvement in epileptogenesis. J Neurosci 29:8927-8935.

David Y, Cacheaux LP, Ivens S, Lapilover E, Heinemann U, Kaufer D, Friedman A (2009) Astrocytic dysfunction in epileptogenesis: consequence of altered potassium and glutamate homeostasis? J Neurosci 29:10588-10599.

Friedman A, Kaufer D, Heinemann U (2009) Blood-brain barrier breakdown-inducing astrocytic transformation: novel targets for the prevention of epilepsy. Epilepsy Res 85:142-149.

Ivens S, Kaufer D, Flores LP, Bechmann I, Zumsteg D, Tomkins O, Seiffert E, Heinemann U, Friedman A (2007) TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. Brain 130:535-547.

Marchi N, Angelov L, Masaryk T, Fazio V, Granata T, Hernandez N, Hallene K, Diglaw T, Franic L, Najm I, Janigro D (2007) Seizure-promoting effect of blood-brain barrier disruption. Epilepsia 48:732-742.

Tomkins O, Friedman O, Ivens S, Reiffurth C, Major S, Dreier JP, Heinemann U, Friedman A (2007) Blood-brain barrier disruption results in delayed functional and structural alterations in the rat neocortex. Neurobiol Dis 25:367-377.

Tomkins O, Shelef I, Kaizerman I, Eliushin A, Afawi Z, Misk A, Gidon M, Cohen A, Zumsteg D, Friedman A (2008) Blood-brain barrier disruption in post-traumatic epilepsy. J Neurol Neurosurg Psychiatry 79:774-777.

van Vliet EA, da Costa AS, Redeker S, van SR, Aronica E, Gorter JA (2007) Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. Brain 130:521-534.

IL8

Lawrence Hirsch

Abstract not received

IL9

Cellular mechanisms underlying EEG waveforms during coma

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Despite the numerous etiologies leading to coma, the electroencephalographic (EEG) patterns accompanying comatose states are dominated by a few stereotyped patterns that also constitute relatively safe indicators of the depth of the coma (see Chatrian, 1990). Similarly to sleep, with whom coma also shares the abolition of consciousness, the EEG during the initial stages of coma mostly displays high amplitude slow delta waves. As deeper stages of coma are reached, the slow waves are interrupted by periods of isoelectric EEG that reflect absence of activity within cortical networks (Steriade et al,. 1994). This EEG pattern is termed burst-suppression (BS) and it was generally assumed that it would mark a further deafferentation of the brain from its sensory inputs. Recently it was shown that, at least in some iatrogenic comas, BS in fact results from a hyperexcitable state during which the bursting activity is triggered by low intensity stimuli that are unable to elicit overt responses under normal conditions (Kroeger and Amzica, 2007). On the other hand, the suppression episodes (isoelectric EEG) result from the exhaustion of cortical synaptic communication due to the transient depletion of extracellular calcium during the previous burst. It was further demonstrated that, contrary to the expected, BS is also associated with the suppression of cortical inhibition (Ferron et al., 2009), thus promoting the idea that hyperexcitability is rather the result of abolished inhibition than increased excitation.

Further deepening of the coma by increasing the anesthesia prolongs the duration of isoelectric periods and

shortens the bursts, to eventually result in a continuous EEG isoelectric line during which cortical neurons reach a hyperpolarized membrane potential devoid of any spontaneous or triggered synaptic potentials. However, deep intraparenchymal field potential recordings, especially in the hippocampus, reveal the presence of oscillatory activities at frequencies ranging within the theta-delta domain, with slower frequencies for deeper coma.

Till now, the isoelectric line was considered to be the final EEG expression of a living brain. We have found, however, that brain cells survived to even further increases of volatile anesthesia and that, under such circumstances, the EEG was displaying a regain of activity with the shape of pseudo-rhythmic spiky waves that we termed n-complexes (NCs). Intracellular recordings of cortical neurons showed that the cellular expression of NCs corresponded to short lasting (130 ms) depolarizing potentials. The origin of this type of activity was found in the hippocampus. Simultaneous intracellular recordings of cortical and hippocampal (mainly CA3) neurons showed that the hippocampal NCs always preceded the cortical NCs by about 43 ms. Both hippocampal neurons and local field potentials displayed ample NCs that were intermingled with faster oscillations in the delta frequency range henceforth termed delta ripples. These were present throughout the EEG isoelectric line but were expressed neither in the EEG nor the intracellular recordings of cortical neurons, and were not found in any other subcortical structure (thalamus, basal forebrain, midbrain, etc.) suggesting that these ripples were generated in the hippocampus.

These findings suggest that the progressive abolition of cortical activities with increased depth of coma is paralleled by an opposite evolution in the hippocampus where the inhibition exerted by forebrain neurons during wakefulness (Fernande de Sevilla and Buño, 2003) is gradually lifted by deepening of the coma, thus favoring the onset of self-oscillatory activities in CA3 pyramidal neurons (Buzsáki, 1989).

References

Buzsáki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31:551-570.

Chatrian GE (1990) Coma, other states of altered responsiveness, and brain death. In: Current Practice in Clinical Electroencephalography (Daly DD, Pedley TA, eds), pp 425-487. New York: Raven Press.

Fernandez de Sevilla D, Buño W (2003) Presynaptic inhibition of Schaffer collateral synapses by stimulation of hippocampal cholinergic afferent fibres. Eur J Neurosci 17:555-558.

Ferron J-F, Kroeger D, Chever O, Amzica F (2009) Cortical inhibition during burst-suppression induced with isoflurane anesthesia. J Neurosci 29:9850-9860.

Kroeger D, Amzica F (2007) Hypersensitivity of the anesthesia-induced comatose brain. J Neurosci 27:10597-10607.

Steriade M, Amzica F, Contreras D (1994) Cortical and thalamic cellular correlates of electroencephalographic burst-suppression. Electroencephalogr Clin Neurophysiol 90:1-16.

IL10

Febrile Infection Related Epilepsy Syndrome (FIRES): Does duration of anaesthesia affect outcome?

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Summary

Febrile infection related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy with yet undefined etiology. Treatment is disappointing and the outcome is poor with high death rate, refractory epilepsy and high rate of mental retardation at follow-up. This is a retrospective multicenter study that includes patients of eight pediatric studies that were published between November 2001 and July 2010. The cohort includes 77 patients. All patients presented with prolonged refractory status epilepticus. Forty six patients were treated with burst-suppression coma. Nine patients (11.7%) died during the acute phase. Of the rest only 12 patients (18%) retained normal cognitive level, however, with learning disabilities in most of them. Cognitive level at follow-up was significantly associated with duration of burst-suppression (p=0.005).

Introduction

Febrile infection related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy with yet undefined etiology.

Most patients described in these series share common clinical characteristics including febrile infection prior to the onset of the prolonged disease and absence of identified infectious agent. This entity is encountered both in adults and children, but is more frequent in children.

The seizure types at the onset of the disease are mainly partial or secondarily generalized. The partial seizures are often complex partial seizures, at times with facial myoclonia (Mikaelloff et al., 2006, Sakuma et al., 2010). The EEG except periods of induced burst-suppression (BS) is focal, multifocal or generalized and the origin of recorded seizures was usually temporal followed by frontal onset (Mikaeloff et al., 2006).

The initial MRI usually reveals normal results. In part of the patients hyperintensities can be seen, predominantly in the temporal regions but also in the insula and the basal ganglia (Sahin et al., 2001; Mikaeloff et al., 2006; van Baalen et al., 2010), probably secondary to long lasting epileptic activity.

Treatment with different antiepileptic drugs including immunosuppressive agents is disappointing (Sahin et al., 2001; Kramer et al., 2005).

The outcome is poor with death rate of up to 30% (Kramer et al., 2005; van Baalen et al., 2010), refractory epilepsy at follow-up, often immediately following the acute phase and mental retardation in 66-100% (Kramer et al., 2005; Mikaeloff et al., 2006). The survivors with normal cognitive level will usually present with learning disabilities (Kramer et al., 2005; Mikaeloff et al., 2006). Only a minority survive the episode without any neurological sequelae (Kramer et al., 2005; Lin et al., 2008). While there was no correlation between the duration of BS and outcome in some studies (Lin et al., 2008). There was a correlation between epilepsy and mental retardation at follow-up with the duration of clinical disease.

Methods

This is a retrospective multicenter study. The data includes the patients of eight pediatric studies that were published between November 2001 and July 2010.

The inclusion criteria included patients with acute onset catastrophic status epilepticus defined as either severe refractory status epilepticus, i.e. continuation of seizures following the first cycle of barbiturate come or BS, or continuation of multiple seizures per day for more than one week in spite prompt treatment, absence of identifiable etiology for SE in spite of thorough investigation and at least one year of follow-up.

Exclusion criteria included: infants younger than two years of age, children with previously reported seizures, known neurological disease, developmental delay prior to the acute disease, structural lesion on MRI and identification of infectious agent in blood or CSF.

A multivariate ordinal logistic regression model was applied to the data to predict the probability of cognitive scores as a function of log BS duration.

Results

The cohort includes 77 patients. The median age at the onset was eight years (range 2-17). All but two patients exhibited nonspecific disease prior to the SE. The fever preceded the onset of seizures with a median duration of four days (range 1-14).

Most patients (58/77) had partial seizures, either simple partial or complex partial with secondary generalizations in 31 patients. Nineteen patients displayed secondarily generalized seizures only. Five of the patients had gene-

ralized seizures accompanied by generalized discharges. The duration of the acute phase with very high seizures frequency was retrospectively estimated by the duration of mechanical ventilation irrespective weather BS coma was achieved. The median duration of mechanical ventilation in the surviving patients was 41 days (mean 49, STD 44.5, range 4-220).

Treatment

Forty six patients were treated with barbiturate (Phenobarbital, Penthotal or Thiopentol) or Midazolam BS coma. The median duration of the total BS coma cycles was seven days (mean 14.3, STD 14, range 1.5-49) days.

Outcome

Nine patients (11.7%) died during the acute phase. At follow-up, 66 of the 68 survivors had epilepsy. In 63 of them, the epilepsy was refractory to treatment.

Cognitive level at follow-up was as followed: Normal (with or without ADD and learning disabilities) – 12 (18%), borderline cognitive level – 11 (16%), mild mental retardation – 10 (14%), moderate mental retardation – 16 (24%), severe mental retardation – 8 (12%) and vegetative state – 11 (16%).

Poor cognitive outcome at follow-up was significantly associated with higher log of BS duration (Wald chi-square = 7.65, p =0.005).

Discussion

In the current study, sufficient information regarding cognitive level at follow-up and duration of BS was available for 32 of the survivors. The statistical analysis clearly demonstrated that BS coma was not associated with increased death rate. On the other hand, longer period of BS coma treatment was significantly associated with poorer cognitive level at follow-up (p=0.005). This association should be considered cautiously since longer BS coma duration is also the result of a longer disease process and possibly reflects the more extreme cases of the cohort.

References

Kramer U, Shorer Z, Ben-Zeev B, Lerman-Sagie T, Goldberg-Stern H, Lahat E. (2005) Severe refractory status epilepticus owing to presumed encephalitis. J Child Neurol 20: 184-187.

Lin JJ, Lin KL, Wang HS, Hsia SH, Wu CT. (2008) Analysis of status epilepticus related presumed encephalitis in children. European J Ped Neurol 12:32-37.

Mikaeloff Y, Jambaque I, Hertz-Pannier L, Zamfirescu A, Adamsbaum C, Ploin P, Dulac O, Chiron C. (2006) Devastating epileptic encephalopathy in school-aged childre (DESC): A pseudo encephalitis. Epilepsy Research 69:67-79.

Sahin M, Menache CC, Holmes GL, Riviello JJ (2001) Outcome of severe refractory status epilepticus in children. Epilepsia 42:1461-1467.

Sakuma H, Awaya Y, Shiomi M, Yamaguochi H, Takahashi Y, Saito Y, Sugai K, Sasakl M. (2010) Acute encephalitis with refractory, repetitive partial seizures (AERRPS): a peculiar form of childhood encephalitis. Acta Neurol Scand 121:251-256.

van Baalen A, Häusler M, Boor R, Rohr A, Sperner J, Kurlemann G, Panzer A, Stephani U, Kluger G. (2010) Febrile infection-related epilepsy syndrome (FIRES): A non-encephalitic encephalopathy in childhood. Epilepsia 51:1323-1328

IL11

Canine Status Epilepticus: A Translational Platform for Human Therapeutic Trials

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Introduction

Treatment of human status epilepticus (HSE) is based on studies performed more than two decades ago using drugs developed 10 to 50 years or more before the studies. Successful treatment rates were only 67% with lorazepam and 44% with phenytoin (Trieman 1998). These drugs now form the basis of the international HSE treatment guidelines (Kalviainen 2007). A major barrier to the development of new drugs for HSE is providing enough

pre-clinical evidence of safety and efficacy to justify the of conduct human studies.Resutls from studies performed in small animals with experimental SE may not be sufficient to convince trial sponsors to proceed with development of drugs in humans. Further, the available drugs for HSE were initially developed for chronic treatment of epilepsy, and only used for HSE after intravenous preparations became available. The mechanisms driving HSE may differ from the triggers of isolated seizures, and the best drugs for chronic epilepsy may not be the best choices to abort HSE. The small animal SE models have two shortcomings, which make it difficult to apply results to treating HSE. First, none of the models have counterparts in the human condition; they are usually induced by chemicals or electrical kindling (Sloviter et al, 2007). Secondly, scaling doses from rodents to humans involves a body size difference of more than 4000 fold and scaling is not linear (Leppik, 1998). This enormous difference may lead to substantial errors in selecting doses for humans. Clearly a test species having naturally occurring SE similar to humans and closer in terms of pharmacokinetic characteristics would be very useful.

Canine Status Epilepticus (CSE)

Naturally occurring CSE has many similarities to the human condition, and evaluating drugs for SE in dogs has three advantages: 1) canine SE studies could provide proof of principle evidence for efficacy and safety; 2) distribution volumes in dogs are similar to those in humans, and using an animal closer to humans in size would provide much better information regarding the effective dose and target plasma concentrations for humans; and 3) the ability to perform a placebo-controlled study in dogs significantly increases the power of the study. CSE is commonly encountered in veterinary practice, and the causes are similar to those seen in humans (Platt and Haag, 2002; Bateman and Parent, 1999). Because FDA-approved treatments for canine SE are not available, approval for a placebo-controlled study is possible. Such study design has many advantages, including relatively few subjects. For example, a pilot study of levetiracetam in CSE was able to show a very statistical trend ($p = 0.053$) for efficacy with only 9 active and 10 placebo subjects (Patterson 2010). Demonstrating that CSE studies could be done successfully was instrumental in obtaining an NIH grant for a proof of principle study to further explore the usefulness of this new approach. Additional advantages of using CSE to evaluate potential agents are: 1) a small (approximately 5 fold) difference in body size; 2) ability to perform pharmacokinetic and pharmacodynamics studies; 3) opportunity to identify effective drug concentrations which can be used as target values for human studies; and 4) evaluate acute and chronic safety issues.

Current Developments

During the 2007 London Colloquium on SE, it became clear that many agents tested in small animal SE models had the potentially significant advantages over current agents. However, many of these are not candidates for chronic epilepsy therapy, thus they will not proceed to clinical development. This led us to consider using CSE as a translational platform. We were successful in obtaining an NIH R-21 grant to evaluating drugs in CSE as a proof of principal for HSE.

The proposal is to treat dogs with established CSE with loading doses of fosphenytoin (FOS) designed to attain PHT concentrations similar to those attained in humans following loading doses of 18 mg/kg. The trial is a randomized, double-blind, placebo-controlled investigation of FOS vs. saline. Validation of the platform will be based on: 1) statistical superiority of the FOS (50% response) vs. placebo (10% response), powering the study for a 40% difference; and 2) a response rate of approximately 50% for FOS, similar to that observed for PHT in HSE trials. The study is being conducted at 3 veterinary hospitals: University of Minnesota Veterinary Medical Center (Dr. Edward Patterson); The Chicago Veterinary Emergency and Specialty Center, (Dr. Michael Podell); and The University of Pennsylvania Matthew J. Ryan Veterinary Hospital (Dr. Charles H. Vite). The study involves 2 phases: phase 1 is a pharmacokinetic study to determine the dose needed to attain the desired PHT levels and the second phase is the actual evaluation of efficacy and safety involving 60 subjects. Phase 1 has been completed and results analyzed by the Center for Orphan Drug Research laboratory, University of Minnesota (Dr. James Cloyd). An initial test dose of 25mg/kg produced unbound PHT levels in the 3.0-4.5 ug/ml range, but this dose was associated with unacceptable side effects. A dose of 15 mg/kg was tolerated, and because of less protein binding in dogs, attained unbound PHT concentrations (2.0-2.5 ug/ml) that are in the range used for HSE. This dose is now being used at the three centers.

Future plans

If we are able to demonstrate the validity of CSE as a platform for testing drugs discovered in animal models, a process of therapeutic development can be initiated that will enable: 1) establishment of a national network of veterinary emergency care departments similar to the human Neurological Emergencies Treatment Trials (NETT) system; 2) use the CNETT to test specific novel agents, and 3) make the CNETT available to basic scientists and industry to test new compounds for HSE. The results from 2 and 3 may be used to inform IND applications and support for treatment of HSE.

References

Cranford RE Leppik IE Patrick B Anderson CB Kostick B (1978) Intravenous phenytoin: clinical and pharmacokinetic aspects. Neurology 28:874-880.

Kalviainen, R (2007) Status epilepticus treatment guidelines. Epilepsia 48 (Suppl 8): 99-102.

Leppik IE (1998) AED doses: from animals to humans. Adv. Neurol ;76:89-93.

Patterson E Hardy B Cloyd J Craig A Hardy R Rarick J Leppik I (2010) Results of a Double Blind, Placebo-Controlled Study of Levetiracetam for the Emergency Treatment of Seizures in Canine Clinical Patients. The American Epilepsy Society Annual Meeting, San Antonio TX. December 3-7.

Platt SR Hagg M. (2002) Canine status epilepticus: a retrospective study of 50 cases. J of Small Animal Practice. 43:151-153.

Saito M Munana KR, Sharp NJ Olby NJ (2001) Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effect of status epilepticus on outcome3 and survival time:32 cases (1990-1996). AM Vet Med Assoc 219:618-13.

Sloviter RS, Zappone CA, Bumanglag AV, Norwood BA, Kudrimoti H (2007) On the relevance of prolonged convulsive status epilepticus in animals to the etiology and neurobiology of human temporal lobe epilepsy. Epilepsia 48 Suppl 8:6-10.

Treiman DM Meyers PD Walton NY Walton NY Collins JF Colling C Rowan J Handforth A Faught E Calabtrese VP Uthman BM Ramsay RE Mamdani MB (1998). A comparison of four treatments for generalized convulsive status epilepticus. N Eng J med 339:792-798.

IL12

What is the evidence to use new intravenous AEDs in Status epilepticus?

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1. Introduction

Status epilepticus (SE) in its convulsive forms is one of the most common neurological emergencies, which is associated with high morbidity and mortality. Its successful treatment requires (i) life support measures, (ii) identification and treatment of the underlying cause, and (iii) rapid institution of intravenous antiepileptic drugs. Current First-line treatment for CSE is intravenous (IV) administration of lorazepam (LZP) or diazepam (DZP) directly followed by phenytoin or fosphenytoin (Meierkord et al., 2006;Prasad et al., 2005;Prasad et al., 2007;Shorvon et al., 2008;Treiman et al., 1998;Trinka, 2007a). However, two large randomised controlled trials investigated the efficacy of LZP in the first stage of SE and found, that only 65% and 59% were adequately controlled with Benzodiazepines (Alldredge et al., 2001;Treiman et al., 1998). Therefore at least one third of patients with SE will need a second stage treatment with IV AEDs. The relative use of VPA and PHT as well as fPHT have been recently reviewed at the first and second London-Innsbruck Colloquium 2007 and 2009 (Trinka, 2007b;Trinka and Dobesberger, 2009). This summary will give a brief overview on the clinical evidence to use levetiracetam (LEV) and lacosamide (LCM) status epilepticus (SE).

2. Levetiracetam

Levetiracetam (LEV) was the first new AED to be licensed in oral forms and intravenous solution at the same time in 2006. Although the approval for the IV formulation was "for the treatment of patients with epileptic seizures who are temporary unable to swallow", it has been widely used since its availability to treat all forms of acute seizures and status epilepticus. Several open case series in adults and children have been published since 2007 (Abend et al., 2008;Altenmuller et al., 2008) (Farooq et al., 2007;Goraya et al., 2008;Knake et al., 2007;Ruegg et al., 2008;Schulze-Bonhage et al., 2007) (Trinka and Dobesberger, 2009) (Aiguabella et al., 2011) (Chen et al., 2011;Cilio et al., 2009;Fattouch et al., 2010;Gamez-Leyva et al., 2009;Kirmani et al., 2009;Reiter et al., 2010;Weber, 2010) (Berning et al., 2009) (Beyenburg et al., 2009;Callen-Soto et al., 2008;Gallentine et al., 2009;Haase and Hopmann, 2009;Haberlandt et al., 2009) .

Levetiracetam (LEV) has a wide spectrum of action and a favourable pharmacokinetic profile. The mechanism of action is distinct from that of classic AEDs and unrelated to known mechanisms of neurotransmission but seems to involve the synaptic vesicle protein 2A (SV2A) (Surges et al., 2008). In addition to that, LEV inhibits HVA CA 2 channels (N-type), at reverses the inhibition of negative allosteric modulators like zinc and beta-carbolines of GABA- and glycine-gated currents, and reduces the calcium release from intra-neuronal stores (for review see (Surges et al., 2008)). In addition neuroprotective effects have been described in animal models (Gibbs et al., 2006). The IV formulation is bioequivalent to the oral preparation and it is well tolerated even at higher doses and/or at faster infusion rates than proposed (Ramael et al., 2006a;Ramael et al., 2006b). The maximum dose applied to healthy adults was 4000 mg in a person with 70 kg (corresponding to 57 mg/kg), which was well tolerated. Therefore a maximum dose of up to 60 mg/kg seem to be justified in clinical use although formal safety studies with this dose in patients with SE are missing (Ramael et al., 2006a;Ramael et al., 2006b).

Overall 707 patients with various form of SE were treated with IV LEV. The success rate of was around 70%. The most often used initial dose was 2000-3000 mg per day over 15 minutes. Adverse events were reported in less than 10% and were mild and transient.

3. Lacosamide

Recently Lacosamide (LCM) became available as the second IV solution of a new AEDs based on bioequivalence to the oral formulation (Biton et al., 2008). LCM is a functionalized amino acid with anticonvulsant properties. LCM has a novel dual mechanism of action, that is, selective enhancement of sodium channel slow inactivation and modulation of CRMP-2 activity (Beyreuther et al., 2007). LCM was effective in different rodent seizure models for generalized and complex partial seizures as well as for status epilepticus (Beyreuther et al., 2007;Stohr et al., 2007;Wasterlain et al., 2011). Experimental evidence (Beyreuther et al., 2007;Errington et al., 2006;Wasterlain et al., 2011), safety studies in healthy individuals and in patients (Biton et al., 2008)as well as first case series with status epilepticus in humans (Albers et al., 2011;Chen et al., 2011;Goodwin et al., 2011;Kellinghaus et al., 2009;Kellinghaus et al., 2011;Koubeissi et al., 2011;Parkerson et al., 2011;Tilz et al., 2010) suggest that IV LCM is a potential alternative to common standard treatments in this field. The first patients who received LCM for the treatment of SE was reported by Tilz and co-workers (Tilz et al., 2010): A 48 year old man who had a series of complex focal seizures with secondary generalisation leading to refractory convulsive SE (CSE) was refractory to 22.5 mg diazepam, 12 mg etomidate, 5 mg midazolam, and 1500 mg levitiracetam. After 200 mg lacosamide via percutaneous gastric fistula, the status remitted within 30 minutes. The first intravenous treatment of SE with LCM was reported by Kellinghaus et al. (Kellinghaus et al., 2009) in a patient with non convulsive SE: a 42 year old woman with post-stroke epilepsy with complex focal SE was not controlled with 2.5 mg diazepam and 6 mg lorazepam. Intravenous LCM (200 mg applied over 3-5 minutes) led to a complete control of seizure symptoms and normalized the EEG. The same author reported the first larger series, which was the result of a collaborative work of five neurological departments in Germany, Austria and Switzerland (Kellinghaus et al., 2011). Thirty nine patients with various types of SE (generalized convulsive in 6, complex focal in 17 and simple focal in 16). In all patients IV LCM was administered after the failure of benzodiazepines or other standard drugs, except in 1 case. The usual dose was median 400 mg (range 200 – 400 mg) which was administered at a rate of 14-18 mg per minute. The SE was fully controlled in 17 of 39 patients (44%). There

was a clear order effect according to the stage of status in which LCM was used. There were no serious adverse events attributed to LCM documented (Kellinghaus et al., 2011). Koubeissi and co-worker reported a small series of 4 patients with refractory non convulsive SE to conventional treatment (Koubeissi et al., 2011). All patients responded readily to LCM with an initial dose of 50 to 100 mg, which was titrated to a maintenance dose of 200 to 400 mg. Non convulsive status was resolved between 2 and 48 hours after LCM initiation in all patients. There were no side effects attributable to LCM identified (Koubeissi et al., 2011). Albers reported 7 patients with focal SE were refractory to other antiepileptic drugs before LCM IV was added (Albers et al., 2011). The median age 77 years and range between 34 and 84 years. SE was terminated within 24 hours in all patients with a bolus of 400 mg and a daily dose of 400 mg after the bolus. There were no significant adverse events reported (Albers et al., 2011). These positive reports contrast with a retrospective series covering 9 patients who received LCM after failure of at least two other agents (Goodwin et al., 2011). In their observational study on patients where admitted to intensive – care unit with refractory SE none of the patients where controlled with LCM, which was applied in an initial dose of 200 mg followed by 200 mg every 12 hours. One of 9 patients developed angioedema after two doses of LCM and another one developed angioedema later in the course (Goodwin et al., 2011). Another reasoned report included patient with acute recurrent seizures ore with periodic epileptic – form patters in critically ill patients (Parkerson et al., 2011). A total of 17 patients received IV LCM because of refractory focal seizures with no further specification whether these was status or not. The seizures were well controlled in 15 out of 17 patients without adverse effects for doses up to 300 mg. Eleven of 17 patients were discharged with LCM. The initial dose ranged from 50 to 300 mg. In our one serious presented as poster at the 4th London-Innsbruck Colloquium on Status epilepticus 49 patients, aged 17 to 95 years, have received IV LCM for various forms of status epilepticus with 11 convulsive status epilepticus (Höfler et al, poster). In total 39 of 48 patients (88%) were responders. Again the drug was well tolerated with no reported adverse events. Overall 126 patients, who had received intravenous lacosamide for a SE and acute seizures / seizures clusters, were reported with an overall success – rate of 67%. One has to emphasise that all series were retrospective and the actual number of convulsive status epilepticus in all serious together was 21. In addition with the use of a new antiepileptic drug there is a publication buyer to be accepted especially in the first retrospective series.

Conclusion

Although IV LEV and IV LCM are interesting alternatives for the treatment of SE due to the lack of centrally depressive effects and low potential of drug interactions, one has to be aware of the non randomised retrospective study design, the heterogenous patient population and treatment protocols, as well as the publication bias inherent in these types of studies. Only a large randomised controlled trial (see Cock et al. in this issue) with an adequate power cans solve this problem and inform the clinicians appropriately on the treatment choices in status epilepticus.

Reference List

Abend,N.S., Florance,N., Finkel,R.S., Licht,D.J., Dlugos,D.J., 2008. Intravenous Levetiracetam Terminates Refractory Focal Status Epilepticus. Neurocrit Care.

Aiguabella,M., Falip,M., Villanueva,V., de la,P.P., Molins,A., Garcia-Morales,I., Saiz,R.A., Pardo,J., Tortosa,D., Sansa,G., Miro,J., 2011. Efficacy of intravenous levetiracetam as an add-on treatment in status epilepticus: a multicentric observational study. Seizure 20, 60-64.

Albers,J.M., Moddel,G., Dittrich,R., Steidl,C., Suntrup,S., Ringelstein,E.B., Dziewas,R., 2011. Intravenous lacosamide-An effective add-on treatment of refractory status epilepticus. Seizure.

Alldredge,B.K., Gelb,A.M., Isaacs,S.M., Corry,M.D., Allen,F., Ulrich,S., Gottwald,M.D., O'Neil,N., Neuhaus,J.M., Segal,M.R., Lowenstein,D.H., 2001. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 345, 631-637.

Altenmuller,D.M., Kuhn,A., Surges,R., Schulze-Bonhage,A., 2008. Termination of absence status epilepticus by low-dose intravenous levetiracetam. Epilepsia 49, 1289-1290.

Berning,S., Boesebeck,F., van Baalen,A., Kellinghaus,C., 2009. Intravenous levetiracetam as treatment for status epilepticus. J Neurol.

Beyenburg,S., Reuber,M., Maraite,N., 2009. Intravenous levetiracetam for epileptic seizure emergencies in older people. Gerontology 55, 27-31.

Beyreuther,B.K., Freitag,J., Heers,C., Krebsfanger,N., Scharfenecker,U., Stohr,T., 2007. Lacosamide: a review of preclinical properties. CNS Drug Rev 13, 21-42.

Biton,V., Rosenfeld,W.E., Whitesides,J., Fountain,N.B., Vaiciene,N., Rudd,G.D., 2008. Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. Epilepsia 49, 418-424.

Callen-Soto,A., Perez-Perez,S., Robles-Del Olmo,B., 2008. [Non-convulsive epileptic status reverted with intravenous levetiracetam]. Rev Neurol 47, 501-502.

Chen,L.L., Haneef,Z., Dorsch,A., Keselman,I., Stern,J.M., 2011. Successful treatment of refractory simple motor status epilepticus with lacosamide and levetiracetam. Seizure 20, 263-265.

Cilio,M.R., Bianchi,R., Balestri,M., Onofri,A., Giovannini,S., Di Capua,M., Vigevano,F., 2009. Intravenous levetiracetam terminates refractory status epilepticus in two patients with migrating partial seizures in infancy. Epilepsy Res 86, 66-71.

Errington,A.C., Coyne,L., Stohr,T., Selve,N., Lees,G., 2006. Seeking a mechanism of action for the novel anticonvulsant lacosamide. Neuropharmacology 50, 1016-1029.

Farooq,M.U., Naravetla,B., Majid,A., Gupta,R., Pysh,J.J., Kassab,M.Y., 2007. IV levetiracetam in the management of non-convulsive status epilepticus. Neurocrit Care 7, 36-39.

Fattouch,J., Di Bonaventura,C., Casciato,S., Bonini,F., Petrucci,S., Lapenta,L., Manfredi,M., Prencipe,M., Giallonardo,A.T., 2010. Intravenous Levetiracetam as first-line treatment of status epilepticus in the elderly. Acta Neurol Scand 121, 418-421.

Gallentine,W.B., Hunnicutt,A.S., Husain,A.M., 2009. Levetiracetam in children with refractory status epilepticus. Epilepsy Behav 14, 215-218.

Gamez-Leyva,G., Aristin,J.L., Fernandez,E., Pascual,J., 2009. Experience with intravenous levetiracetam in status epilepticus: a retrospective case series. CNS Drugs 23, 983-987.

Gibbs,J.E., Walker,M.C., Cock,H.R., 2006. Levetiracetam: antiepileptic properties and protective effects on mitochondrial dysfunction in experimental status epilepticus. Epilepsia 47, 469-478.

Goodwin,H., Hinson,H.E., Shermock,K.M., Karanjia,N., Lewin,J.J., III, 2011. The Use of Lacosamide in Refractory Status Epilepticus. Neurocrit Care.

Goraya,J.S., Khurana,D.S., Valencia,I., Melvin,J.J., Cruz,M., Legido,A., Kothare,S.V., 2008. Intravenous levetiracetam in children with epilepsy. Pediatr Neurol 38, 177-180.

Haase,C.G., Hopmann,B., 2009. Epilepsia partialis continua successfully treated with levetiracetam. J Neurol 256, 1020-1021.

Haberlandt,E., Sigl,S.B., Scholl-Buergi,S., Karall,D., Rauchenzauner,M., Rostasy,K., 2009. Levetiractam in the treatment of two children with myoclonic status epilepticus. Eur J Paediatr Neurol 13, 546-549.

Kellinghaus,C., Berning,S., Besselmann,M., 2009. Intravenous lacosamide as successful treatment for nonconvulsive status epilepticus after failure of first-line therapy. Epilepsy Behav 14, 429-431.

Kellinghaus,C., Berning,S., Immisch,I., Larch,J., Rosenow,F., Rossetti,A.O., Tilz,C., Trinka,E., 2011. Intravenous lacosamide for treatment of status epilepticus. Acta Neurol Scand 123, 137-141.

Kirmani,B.F., Crisp,E.D., Kayani,S., Rajab,H., 2009. Role of intravenous levetiracetam in acute seizure management of children. Pediatr Neurol 41, 37-39.

Knake,S., Gruener,J., Hattemer,K., Klein,K.M., Bauer,S., Oertel,W.H., Hamer,H.M., Rosenow,F., 2007. Intravenous levetiracetam in the treatment of benzodiazepine-refractory status epilepticus. J Neurol Neurosurg Psychiatry.

Koubeissi,M.Z., Mayor,C.L., Estephan,B., Rashid,S., Azar,N.J., 2011. Efficacy and safety of intravenous lacosamide in refractory nonconvulsive status epilepticus. Acta Neurol Scand 123, 142-146.

Meierkord,H., Boon,P., Engelsen,B., Gocke,K., Shorvon,S., Tinuper,P., Holtkamp,M., 2006. EFNS guideline on the management of status epilepticus. Eur J Neurol 13, 445-450.

Parkerson,K.A., Reinsberger,C., Chou,S.H., Dworetzky,B.A., Lee,J.W., 2011. Lacosamide in the treatment of acute recurrent seizures and periodic epileptiform patterns in critically ill patients. Epilepsy Behav 20, 48-51.

Prasad,K., Al Roomi,K., Krishnan,P.R., Sequeira,R., 2005. Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev CD003723.

Prasad,K., Krishnan,P.R., Al Roomi,K., Sequeira,R., 2007. Anticonvulsant therapy for status epilepticus. Br J Clin Pharmacol 63, 640-647.

Ramael,S., Daoust,A., Otoul,C., Toublanc,N., Troenaru,M., Lu,Z.S., Stockis,A., 2006a. Levetiracetam intravenous infusion: a randomized, placebo-controlled safety and pharmacokinetic study. Epilepsia 47, 1128-1135.

Ramael,S., De Smedt,F., Toublanc,N., Otoul,C., Boulanger,P., Riethuisen,J.M., Stockis,A., 2006b. Single-dose bioavailability of levetiracetam intravenous infusion relative to oral tablets and multiple-dose pharmacokinetics and tolerability of levetiracetam intravenous infusion compared with placebo in healthy subjects. Clin Ther 28, 734-744.

Reiter,P.D., Huff,A.D., Knupp,K.G., Valuck,R.J., 2010. Intravenous levetiracetam in the management of acute seizures in children. Pediatr Neurol 43, 117-121.

Ruegg,S., Naegelin,Y., Hardmeier,M., Winkler,D.T., Marsch,S., Fuhr,P., 2008. Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. Epilepsy Behav 12, 477-480.

Schulze-Bonhage,A., Hefft,S., Oehl,B., 2007. Termination of complex partial status epilepticus by intravenous levetiracetam - a case report. J Neurol Neurosurg Psychiatry.

Shorvon,S., Baulac,M., Cross,H., Trinka,E., Walker,M., 2008. The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London Colloquium on Status Epilepticus. Epilepsia 49, 1277-1285.

Stohr,T., Kupferberg,H.J., Stables,J.P., Choi,D., Harris,R.H., Kohn,H., Walton,N., White,H.S., 2007. Lacosamide, a novel anti-convulsant drug, shows efficacy with a wide safety margin in rodent models for epilepsy. Epilepsy Res 74, 147-154.

Surges,R., Volynski,K.E., Walker,M.C., 2008. Is levetiracetam different from other antiepileptic drugs? Levetiracetam its cellular mechanism of action in epilepsy revisited. Therap Adv Neurol Dis 1, 13-24.

Tilz,C., Resch,R., Hofer,T., Eggers,C., 2010. Successful treatment for refractory convulsive status epilepticus by non-parenteral lacosamide. Epilepsia 51, 316-317.

Treiman,D.M., Meyers,P.D., Walton,N.Y., Collins,J.F., Colling,C., Rowan,A.J., Handforth,A., Faught,E., Calabrese,V.P., Uthman,B.M., Ramsay,R.E., Mamdani,M.B., 1998. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 339, 792-798.

Trinka,E., 2007a. Emergencies in Epilepsy: What must and must not be done. Nervenheilkunde 26, 981-992.

Trinka,E., 2007b. The Use of Valproate and New Antiepileptic Drugs in Status Epilepticus. Epilepsia 48, 49-51.

Trinka,E., Dobesberger,J., 2009. New Treatment Options in Status Epilepticus: a critical review on levetiracetam. Therap Adv Neurol Dis 2, 79-91.

Wasterlain,C.G., Stohr,T., Matagne,A., 2011. The acute and chronic effects of the novel anticonvulsant lacosamide in an experimental model of status epilepticus. Epilepsy Res 94, 10-17.

Weber,P., 2010. Levetiracetam in nonconvulsive status epilepticus in a child with Angelman syndrome. J Child Neurol 25, 393-396.

IL13

Complications of the Management of Status epilepticus in the Intensive Care Unit

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Introduction

Status epilepticus (SE) is a neurologic emergency, sometimes a neurocritical care catastrophy. A status epilepticus not responding to initial anticonvulsants is termed refractory, a condition which warrants urgent admission to a neurocritical care unit. Insight into relevant underlying pathophysiologic processes of SE is still not sufficient, hence, treatment options being still unsatisfactory, morbidity and mortality rates are still high. Recently guidelines on the management of a generalized convulsive SE, of non-convulsive SE, including subtle status epilepticus have been published (Meierkord et al, 2010). Although these guidelines aim to provide best possible care for patients with status epilepticus, high morbidity and mortality still remain a challenge (Holtkamp 2010, Neligan & Shorvon 2010, 2011).

It is beyond doubt, that appropriate diagnostic and therapeutic management of underlying diseases are the prerequisite for optimal management of patients in ICUs with severe, therapy refractory status epileptic (Holtkamp 2010; Meierkord et al, 2010; Tan et al, 2010; van Gestel et al, 2008).

Treatment of refractory SE requires the use of continuous infusions of GABA-mediated anaesthetic agents to control seizures or to achieve burst suppression in EEG. Commonly used agents include barbiturates, propofol and midazolam. While these therapeutic strategies may control seizures, adverse effects of these anaesthetic agents frequently limit the dose, limit the duration of necessary therapy and add to morbidity and mortality (Arnold et al, 2010). In patients, who do not respond to the these therapeutic agents (barbiturates, propofol, midazolam) or who experience excess morbidity due to side effects, other even unconventional therapeutic management strategies may be necessary (Hattori et al, 2008; Prüss & Holtkamp 2008; Holtkamp 2010; Meierkord et al, 2010).

For this reason such unconventional therapeutic strategies are also discussed, concentrating on ketamine and lidocaine.

Adverse effects of GABA-mediated anaesthetic agents to control seizures or to achieve burst suppression

Barbiturates:

Barbiturates may be highly efficacious, used as third line therapeutic agents, in controlling generalized convulsive SE (Holtkamp 2010; Meierkord et al, 2010). It is recommended to titrate the dosage of barbiturates against an EEG burst suppression pattern, which should be maintained for at least 24 hours. Thiopental is started with a bolus of 3-5 mg/kg bodyweight, followed by continuous infusion at a rate of 3-7 mg/kg/hour. If necessary, further boluses 1-2 mg/kg bodyweight are given, until seizures are controlled. Depending on the dosage and duration of barbiturate therapy, side effects include hemodynamic instability, leading to distributive shock, immuno-suppression and reduced gastrointestinal motility. All these side effects may limit the dose and the duration of therapy with barbiturates (Robakis et al, 2006).

Patients with cardiopulmonary instability, i. e. distributive shock, need invasive blood pressure monitoring, invasive and hemodynamic monitoring, e. g. PiCCO or even more invasive monitoring methods like pulmonary artery catheter (Belda et al, 2010; Gassanov et al, 2010; Hadian et al, 2010; Proulx et al, 2011). Depending on these monitoring findings, patients on barbiturate-therapy need sufficient fluid management, aggressive fluid balancing and, in most instances, catecholamines.

Hemodynamic instability potentially leading to distributive shock, reduces the cerebral perfusion and adds to injury of neuronal intracranial structures.

It must be borne in mind that barbiturates lead to immunosuppression, increasing the risk of nosocomial infections, e. g. catheter associated bloodstream infections, nosocomial ventilator associated pneumonia, urinary tract infection and even intestinal infection (see below). Therefore every monitoring strategy must be on high alert in order to recognize at the earliest possible point of time any incipient nosocomial infection; regular culturing of body fluids, C-reactive protein, procalcitonin, white blood cell count, differential count on (at least) a daily basis include these monitoring recommendations.

Barbiturates lead to reduced gastrointestinal motility, which is particularly important in patients with hemodynamic instability, or even distributive shock, necessitating a liberal use of catecholamines. The effect of these catecholamines onto the peripheral vascular system increases the blood pressure by peripheral vasoconstriction; exactly this effect may add to severe nosocomial infection since this vasoconstriction may lead to (incomplete) ischemia in the gastrointestinal wall. This specifically holds true in patients on therapeutic agents which reduce, per se, gastrointestinal motility. For this reason patients on barbiturates with reduced gastrointestinal motility and – at the same time – on high dose catecholamines are at high risk to experience transmural translocation of intestinal bacteria, e. g. gram-negative rods (as Enterobacteriacae, E. coli, or, even Clostridia species etc.). This fact urges the intensivist to be on high alert and to react towards rapidly increasing clinical signs and symptoms of septic shock and rapid increase of "inflammatory parameters" (C-reactive proteine, white blood cell count, procalcitonin) with the appropriate empiric antimicrobial chemotherapy. This requires best knowledge of the resistance pattern, in particular, of the gram-negatives seen in patients of the respective ICU. Therefore, a thorough knowledge of surveillance data is essential to optimize empiric or semiempiric antimicrobial chemotherapy. In case of the occurrence of extended-spectrum beta-lactamases (ESBL) or carbapenemase producing gram-negatives, the empiric antimicrobial chemotherapy might even necessitate the use of polymyxin B (or E), tigecycline or similar third line antimicrobials (Benenson et al, 2011; Fircanis & McKay 2010; Oteo et al, 2010).

Impaired gastrointestinal motility, in particular, of the large intestine, may be the consequence of or even be caused by antibiotic associated ulcerative colitis due to Clostridia species. Constipation does not preclude the presence of a clostridial colitis, a disease with mortality rates of up to 50%, if diagnosis and appropriate management is delayed unnecessarily.

Propofol:

Beside similar concerns as discussed with barbiturates propofol may, in rare instances, cause the so-called propofol infusion syndrome (PRIS) (Fodale & La Monaca 2008; Guitton et al, 2010; Roberts et al, 2009; Wong et al, 2010). Patients on specific anticonvulsive therapies, like ketogenic diet, may be even at higher risk to develop PRIS (Baumeister et al, 2004).

Almost 20 years ago in pediatric ICU patients a propofol related syndrome with metabolic acidosis, brady-arrhythmia and progressive myocardial failure has been described (Parke et al, 1992). In a recent analysis by the FDA PRIS has carried a 30% mortality rate (Wong et al, 2010). The incidence of PRIS slightly exceeds 1% (Roberts et al, 2009), postulated risk factors include use of a high propofol dose (>83 µg/kg/min.), a duration of therapy of more than 48 hours and concomitant vasopressor therapy. Both high dose and concomitant vasopressor therapy are frequently necessary in patients with refractory convulsive SE. However, it needs to be stressed that PRIS can occur soon after the initiation of propofol therapy and even also at rather low dose (Roberts et al, 2009). In former publications mortality rate was high and rhabdomyolysis was frequently seen. Although, so far, the co-incidence of convulsive SE triggered rhabdomyolysis and PRIS has been reported only once (Zarovnaya et al, 2007) it is conceivable that patients with myglobinuria or even frank rhabdomyolysis might be even at higher risk to develop PRIS (Kreft et al, 2008). Therefore, careful observation is necessary when patients with refractory convulsive SE are treated with propofol.

Unconventional therapies, ketamine and lidocaine

As seizures persist, GABA-receptors become downregulated and GABA-mediated treatments may become more and more ineffective. At the end, excitatory NMDA receptors and glutamate are thought to play a more important role (Robakis & Hirsch, 2006). Ketamine being a non-competitive NMDA receptor antagonist might play a role in effectively treating electrographic seizures once they

have persisted for prolonged time. Beside animal models, in which ketamine has been shown not to be affected in early SE, but to be effective in reducing electrographic seizures after 1 hour or longer, several case reports have been suggesting that this substance may have a role in the treatment of refractory SE. Prüss et al reported on a successful termination of a malignant SE after initiation of ketamine therapy (Prüss & Holtkamp, 2008). Unlike the above mentioned anesthetic agents, in particular, barbiturates and propofol, ketamine has less hemodynamic effects being more likely to cause hypertension than hypotensive shock.

Lidocaine is another possible alternative for the treatment of refractory SE in the ICU (Walker & Slovis, 1997). Lidocaine is used as antiarrhythmic, this property is attributed to the capacity to stabilize the cardiac membrane by blocking the fast voltage gated sodium channels. Possibly, its antiepileptic activity may also to be related to sodium channel blockade. Several small case series have described rapid cessation of seizures following administration of a lidocaine bolus, however, its effective duration being rather short. In more than half of the responders - in one of the key series (Walker et al 1997) – seizures recurred within _ hour. Either a second (1-3 mg/kg bw.) bolus or continuous infusion (0,06 mg/kg/min – up to a maximum infusion rate of 5 mg/min.) need to be administered. Adverse effects include paradoxical pro-arrhythmic and, rarely, proconvulsant effects. Lidocaine must be avoided in patients with significant heart disease, in particular, bradyarrhythmia or conduction block. Even worse, lidocaine being metabolized by the liver, it should be avoided in patients with liver dysfunction.

Both substances need careful monitoring of both neurological and cardiopulmonary as well as regular monitoring of routine laboratory values, including inflammatory parameters, kidney and renal parameters as well as coagulation parameters.

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References

Arnold HM, Hollands JM, Skrupky LP, Mice ST (2010). Optimizing sustained use of sedation in mechanically ventilated patients: focus on safety. Curr Drug Saf; 5:6-12

Baumeister FA, Oberhoffer R, Liebhaber GM, Kunkel J, Eberhardt J, Holthausen H, Peters J (2004). Fatal propofol infusion syndrome in association with ketogenic diet. Neuropediatrics; 35:250-252

Belda FJ, Aguilar G, Teboul JL, Restana D, Redondo FJ, Malbrain M, Luis JC, Ramasco F, Umgelter A, Wendon J, Kirov M, Fernández-Mondéjar E; for the PICS Infestigators Group. Complications related to less-invasive haemodynamic monitoring. Br J Anaesth; Dec 26 [Epub ahead of print]

Benenson S, Temper V, Cohen MJ, Schwartz C, Hidalgo-Grass C, Block C (2011). Imipenem disc for the detection of KPC carbapenemase-producing Enterobacteriaceae in clinical practice. J Clin Microbiol; Feb 2 [Epub ahead of print]

Fircanis S, McKay M (2010). Recognition and management of extended spectrum beta lactamase producing organisms (ESBL). Med Health R I; 93:161-162

Fodale V, La Monaca E (2008). Propofol Infusion Syndrome: An Overview of a perplexing Disease. Drug Safety; 4:293-303

Gassanov N, Caglayan E, Nia A, Erdmann E (2010). The PiCCO catheter. Dtsch Med Wochenschr; 135:2311-2314

Guitton C, Gabillet L, Latour P, Rigal JC, Boutoille D, Al Habash O, Derkinderen P, Bretonniere C, Villers D (2010). Propofol Infusion Syndrome During Refractory Status Epilepticus in a Young Adult: Successful ECMO Resuscitation. Neurocrit Care; May 25 [Epub ahead of print]

Hadian M, Kim HK, Severyn DA, Pinsky MR (2010). Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. Crit Care; Nov 23; 14:R212 [Epub ahead of print]

Hattori H, Yamano T, Hayashi K, Osawa A, Kondo K, Aihara M, Haginoya K, Hamano S, Izumi T, Kaneko K, Kato I, Matsukura M, Minagawa K, Miura T, Ohtsuka Y, Sugai K, Takahashi T, Yamanouchi H, Yamamoto H, Yoshikawa H (2008). Effectiveness of lidocaine infusion for status epilepticus in childhood: a retrospective multi-institutional study in Ja-

pan. Brain Dev; 30:504-512

Holtkamp M (2010). Treatment strategies for refractory status epilepticus. Curr Opin Crit Care; Dec 21 [Epub ahead of print]

Kreft A, Rasmussen N, Hansen LK (2008). Refractory status epilepticus in two children with lethal rhabdomyolysis. Ugeskr Laeger; 170:3339

Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, Holtkamp M; European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol; 17:348-355

Neligan A, Shorvon SD (2010). Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. Arch Neurol; 67:931-940

Neligan A, Shorvon SD (2011). Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus: a review. Epilepsy Res; 93:1-10

Oteo J, Pérez-Vázquez M, Campos J (2010). Extended-spectrum [beta]-lactamase producing Escherichia coli: changing epidemiology and clinical impact. Curr Opin Infect Dis; 23:320-326

Parke TJ, Stevens JE, Rice AS, Greenaway CL, Bray RJ, Smith PJ, Waldmann CS, Verghese C (1992). Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. BMJ; 305:613-616

Proulx F, Lemson J, Choker G, Tibby SM (2011). Hemodynamic monitoring by transpulmonary thermodilution and pulse contour analysis in critically ill children. Pediatr Crit Care Med; Jan 21 [Epub ahead of print]

Prüss H, Holkamp M (2008). Ketamine successfully terminates malignant status epilepticus. Epilepsy Res; 82:219-222

Robakis TK, Hirsch LJ (2006). Literature review, case report, and expert discussion of prolonged refractory status epilepticus. Neurcrit Care; 4:35-46

Roberts RJ, Barletta JF, Fong JJ, Schumaker G, Kuper PJ, Papadopoulos S, Yogaratnam D, Kendali E, Xamplas R, Gerlach AT, Szumita PM, Anger KE, Arpino PA, Voils SA, Grgurich P, Ruthazer R, Devlin JW (2009). Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. Crit Care; 13:R169

Tan RY, Neligan A, Shorvon SD (2010). The uncommon causes of status epilepticus: a systematic review. Epilepsy Res; 91:111-122

Van Gestel JP, Blussé van Oud-Alblas HJ, Malingré M, Ververs FF, Braun KP, van Nieuwenhuizen O (2005). Propofol and thiopental for refractory status epilepticus in children. Neurology; 65:591-592

Walker IA, Slovis CM (1997). Lidocaine in the treatment of status epilepticus. Acad Emerg Med; 4:918-922

Wong J (2010). Propofol Infusion Syndrome. Am J Therapeutics; 17:487-491

Zarovnaya EL, Jobst BC, Harris BT (2007). Propofol-associated fatal myocardial failure and rhabdomyolysis in an adult with status epilepticus. Epilepsia; 48:1002-1006

IL14

Anaesthestic agents and status epilepticus

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Short title: Anaesthestics and status epilepticus

Summary

There is little evidence to guide the choice of intravenous anaesthetic agent to treat refractory status epilepticus (RSE) but midazolam, propofol and barbiturates are widely used. It is impractical to use inhalational anaesthetic agents in most circumstances and there is little experience

with non-GABA-ergic agents such as ketamine. A more aggressive treatment approach, aiming for EEG suppression, is most likely to result in sustained cessation of seizure activity but this is associated with increased treatment-related complications. Side effects of treatment, including hypotension, gastric paresis and pneumonia, are common and contribute independently to poor outcome and death.

Although general anaesthetics are widely used to treat refractory status epilepticus (RSE), there are no randomized studies comparing agents and little evidence to guide the choice of agent or duration of treatment (Claassen et al., 2002). Although most experts agree on first and second line therapy, there is much less consensus on when to introduce general anaesthetics (Claassen et al., 2003; Holtkamp et al., 2003). In a European study, around one-third of respondents recommended rapid administration of intravenous anaesthetic agents after a failed trial of benzodiazepines and phenytoin, whereas two-thirds introduced a third line, non-anaesthetic agent, prior to institution of general anaesthesia (Holtkamp et al., 2003).

Intravenous general anaesthetic agents

The intravenous anaesthetic agents most widely used to treat generalized convulsive RSE (GCSE) are midazolam, propofol and barbiturates; thiopental is widely used in Europe but it is not available in the USA where its first metabolite, pentobarbital, is used. A systematic review (of 193 patients in 28 studies) found that, although barbiturates are more effective than midazolam or propofol in controlling clinical or electrophysiological seizures, and in preventing breakthrough seizures, there is no difference between these agents in terms of early mortality (Claassen et al., 2002). However, the studies included in this review are not comparable. In particular, EEG suppression was the treatment end point in 96% of patients treated with barbiturates, in only 38% of those treated with propofol and in none treated with midazolam. Anaesthesia should be maintained for the minimum period required to achieve long term seizure control irrespective of the agent used (Rossetti et al., 2005).

Propofol is the first line intravenous anaesthetic agent for RSE in many centres because it allows rapid control of the depth of anaesthesia and has a short duration of action, even after prolonged infusion. In an early retrospective study propofol controlled seizures in 67% of cases of RSE (Rossetti et al., 2004) and, in a more recent study, it was effective in 24 of 27 (88.9%) patients (Power et al., 2011). A retrospective study also confirmed rapid termination of clinical and electrophysiological seizures by propofol, but maintaining a burst suppression EEG pattern required incremental doses to a high median (range) infusion rate of 9.5 (8.2 – 11.0) mg/kg/h (Parviainen et al., 2006).

Because the side effects of treatment might outweigh its potential benefits in non-convulsive SE (NCSE), there remains debate about whether NCSE should be treated as aggressively as GCSE. Although NCSE should be terminated early to minimize neurological and other complications, it is generally agreed that administration of anaesthetic agents should be postponed until a trial of a third-line non-anaesthetic anticonvulsant has been completed (Meierkord et al., 2010).

Inhalational anaesthetic agents

Inhalational halogenated anaesthetic agents have been used to control seizures in small numbers of patients who do not respond to intravenous agents. In a case series, isoflurane and desflurane produced EEG burst suppression and terminated seizure activity rapidly in seven patients with RSE, six of whom had not responded to previous therapy with midazolam, propofol and pentobarbital. EEG burst suppression was maintained throughout the period of inhalational agent administration, which was continued for a mean (range) of 11 (2-26) days (Mirsattari et al., 2004). The logistical and safety implications of providing inhalational anaesthesia on the ICU are substantial and such treatment is not a realistic option in most circumstances.

Ketamine

The progressive loss of GABAA-receptor subunits with ongoing seizure activity limits the efficacy of agents with predominantly GABA-ergic mechanisms of action, which, in association with the increasing expression of NMDA receptors as SE progresses, has prompted interest in the role of excitatory amino acid antagonists. Ketamine, an NMDA antagonist, has been used to terminate seizure activity in highly refractory cases and, because it has sympathomimetic properties, the (often profound) hypotension associated with other anaesthetic agents is avoided (Pruss

& Holtkamp, 2008). There are currently limited data on the use of ketamine in RSE and there is some concern that it might have neurotoxic effects when used for prolonged periods.

Treatment endpoints

Current data suggest that a more aggressive treatment approach, aiming for EEG burst suppression, is most likely to result in sustained cessation of seizure activity, although mortality and functional outcome is similar in those with and without EEG suppression (Claassen et al., 2002). This raises the important question of whether the potential benefits are worth the increased risks associated with the higher doses of anaesthetic agents required to achieve EEG suppression. Current European guidance recommends titration of propofol and barbiturate to EEG burst suppression, and midazolam to seizure suppression, maintained for at least 24 h (Meierkord et al., 2010).

Complications

The side effects of general anaesthetics are considerable, are often underestimated during the treatment of RSE and contribute independently to poor outcome and death. The most frequent complication is hypotension, often requiring aggressive fluid resuscitation and vassopressor or inotropic support. In addition, immunusuppression, gastric paresis and pneumonia are common. Barbiturates are associated with the greatest incidence of systemic complications, particularly hypotension, splanchnic hypoperfusion (leading gastric, pancreatic and hepatic sequelae) and pneumonia (Claassen et al., 2002). There is also concern about the safety of prolonged infusion of propofol in this setting. A recent retrospective study identified propofol-related systemic complications in 17 of 27 episodes of RSE, the most common of which was pneumonia (Power et al., 2011). The high doses of propofol in association with prolonged infusion times during the treatment of RSE increase the likelihood of the propofol infusion syndrome (PRIS), which is characterized by unexplained metabolic acidosis, elevated creatinine kinase, rhabdomyolysis and widespread ECG changes. In a recent retrospective study, propofol was used in 31 patients with RSE and 14 showed one or more signs of PRIS (Iyer et al., 2009). Two of these patients died after an unexpected cardiac arrest and a third suffered a malignant arrhythmia requiring emergency resuscitation.

Conclusion

There are currently no high quality prospective data supporting one anaesthetic agent over another in the treatment of RSE. A randomized, controlled trial identifying efficacy and side effects of commonly used agents is urgently required.

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Conflict of interest: None

References

Claassen J, Hirsch LJ, Emerson RG, Mayer SA (2002) Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 43: 146-153.

Claassen J, Hirsch LJ, Mayer SA (2003) Treatment of status epilepticus: a survey of neurologists. *J Neurol Sci* 211: 37-41.

Holtkamp M, Masuhr F, Harms L, Einhaupl KM, Meierkord H, Buchheim K (2003) The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists. J *Neurol Neurosurg Psychiatry* 74: 1095-1099.

Iyer VN, Hoel R, Rabinstein AA (2009) Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. *Crit Care Med* 37: 3024-3030.

Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, Holtkamp M (2010) EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 17: 348-355.

Mirsattari SM, Sharpe MD, Young GB (2004) Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 61: 1254-1259.

Parviainen I, Uusaro A, Kalviainen R, Mervaala E, Ruokonen E (2006) Propofol in the treatment of refractory status epilepticus. *Intensive Care Med* 32: 1075-1079.

Power KN, Flaatten H, Gilhus NE, Engelsen BA (2011) Propofol treatment in adult refractory status epilepticus. Mortality risk and outcome. *Epilepsy Res* Feb 5 [Epub ahead of print]

Pruss H, Holtkamp M (2008) Ketamine successfully terminates malignant status epilepticus. *Epilepsy Res* 82: 219-222.

Rossetti AO, Logroscino G, Bromfield EB (2005) Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol* 62: 1698-1702.

Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J (2004) Propofol treatment of refractory status epilepticus: a study of 31 episodes. *Epilepsia* 45: 757-763.

IL15

RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial): A double-blind randomized clinical trial of the efficacy of IM midazolam versus IV lorazepam in the pre-hospital treatment of status epilepticus by paramedics

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Background

Early treatment of status epilepticus (SE) by paramedics reduces the number of patients with persistent seizures on ED arrival and the number admitted to the ICU for refractory status. However, the optimal agent for prehospital treatment of SE is unknown. Intramuscular midazolam is an increasingly popular choice because of its ease of administration and practicality for EMS use, but the safety and efficacy of midazolam or the intramuscular route of administration have not been studied in a randomized controlled trial. We hypothesized that in the prehospital treatment of SE, the efficacy of intramuscular (IM) midazolam is not inferior to that of intravenous (IV) lorazepam, as determined by the proportion of subjects with termination of clinically evident seizure at arrival in the Emergency Department (ED) after a single dose of study medication and without use of rescue medication.

Methods

This is a double-blind randomized non-inferiority clinical trial of the efficacy of IM midazolam versus IV lorazepam in the prehospital treatment of status epilepticus by paramedics. 1,024 adult and pediatric patients with continuing seizure activity after EMS arrival and meeting all inclusion and exclusion criteria are being enrolled and randomized in this trial. All subjects receive active treatment by either IM or IV routes of administration. Adults and children greater than or equal to 40 kg who are randomized to active IM therapy are treated with 10 mg midazolam IM followed by IV placebo. Adults and children greater than or equal to 40 kg who are randomized to IV active therapy are treated with IM placebo followed by 4 mg lorazepam IV. The weight of children is estimated from their length using a length based weight estimation tape which is included in each study box. Active therapy in children estimated to be less than 40 kg is either 5 mg midazolam IM or 2 mg lorazepam IV. Children estimated to be less than 13 kg are not enrolled. The study is conducted under an FDA Investigational New Drug application using Exception from Informed Consent for Emergency Research.

Outcomes

The primary outcome measure is the binary outcome variable measuring whether or not there is termination of convulsive seizure activity prior to arrival in the ED after an initial dose of study medication without the need for a

second "rescue" dose of benzodiazepine by EMS. Determination of termination of convulsive seizure activity upon arrival at the receiving emergency department is made clinically by the attending emergency physician treating the subject. Key secondary outcome measures include times from EMS arrival to termination of seizure and from initiation of treatment to termination of seizure. Other secondary outcomes include frequency of endotracheal intubation, the frequency and duration of hospitalization and of ICU admission, and the frequency of acute seizure recurrence. Time data are collected using an instrumented logger device that determines time of arrival and records voice time stamps when medications are given or convulsions are noted to have stopped.

Analysis

The primary analysis used in this trial will test the hypothesis that IM midazolam is not less effective than IV lorazepam on the primary endpoint by more than an absolute difference of 10% (i.e., non-inferiority margin). Based on preliminary studies we estimate that 70% of subjects will terminate seizure prior to ED arrival after the initial dose of IV lorazepam. An absolute difference in the proportion of terminated seizures at ED arrival of less than 10% between the two treatment groups is considered to be clinically unimportant and is defined as the non-inferiority margin. The value of this margin is based on a combination of statistical and clinical judgement and was chosen to ensure that the overall success (termination of seizure) of the new treatment (IM midazolam) has a clinically relevant superiority over a putative placebo as well as a clinically unimportant difference from the currently used benzodiazepines. Based on the above information and taking into consideration the planned interim analysis, the study is powered to assure greater than 90% likelihood of identifying less than a 10% absolute difference in success rates between the two treatment groups. Sample size estimation is based on the comparison of independent proportions with a 1:1 randomization scheme and a one-sided type I error rate of 0.025. The maximum sample size required for randomization is 890 subjects (445 per treatment group). Due to the potential recurrence rate in patients with status epilepticus, the total sample size is inflated by 15% to account for multiple enrollments of a study subject. Subjects will be independent for the primary analysis. Thus a minimum of 1,024 subjects will be randomized.

Network

The trial is being conducted in the Neurological Emergencies Treatment Trials (NETT) network, which is composed of 17 academic medical center Hubs, each with several academic or community based Spokes. Over 40 EMS systems and more than 4000 medics are involved. Enrollment began in June 2009 and ended successfully in January 2011. Final data collection and monitoring are currently being completed.

This work is supported by award 5U01NS056975-04 from the National Institute of Neurological Disorders and Stroke (NINDS), the Office of the Director, National Institutes of Health (OD), BARDA, and the NIH CounterACT program. This trial is registered with ClinicalTrials.gov (NCT00809146).

IL16

A Prehospital randomized trial in convulsive status epilepticus

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Generalized convulsive status epilepticus (GCSE) is associated with high levels of morbidity and mortality. The therapeutic management of patients with GCSE must be improved. Clinical and experimental data suggest that the earliest is the drug administration, the highest is the percentage of controlled GCSE (Lowenstein, 2006; Kapur and Macdonald, 1997; Bleck, 2006). However few studies have examined therapeutic options before patients are admitted to hospital (Alldredge et al., 2001). It is suggested that combining two drugs, acting on different pathways, may be more efficient to interrupt the status (Wasterlain, 2006).

We are conducting a prehospital, randomized, double blind, placebo-controlled, phase III clinical trial, to compare the efficacy for GCSE, of intravenous levetiracetam in association with clonazepam versus clonazepam alone (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 prehospital physicians, are included in the study. Post-anoxic and subtle status epilepticus are excluded, as is 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.

Therapeutic treatment consists of the co-injection of 1 mg clonazepam and 2500 mg levetiracetam over 5 min. Control treatment consists of the injection of 1 mg clonazepam with a placebo over 5 min. If status persists, a second injection of clonazepam is made after 5 min.

The primary outcome measure is the percentage of patients with cessation of convulsions within 15 minutes of the onset of initial injections. Secondary outcome measures include i) the time between the first injection and the interruption of the convulsion, ii) the time between the first injection and signs of awakening, iii) duration of hospitalization, iv) percentage of patient receiving the second injection of clonazepam after 5 min. Further secondary outcome measures are given at ClinicalTrials.gov.

Emergency medical consent is obtained from family members, if possible. An informed consent for continued participation is also obtained from patients when they wake.

We will present data on recruitment and preliminary results.

References

Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR and Lowenstein DH (2001) A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med.* 345:631-7.

Bleck T (2006) In Status *Epilepticus : Mechanisms and Managements* (Ed, Wasterlain, T.) MIT Press, Boston.

Kapur J and Macdonald RL (1997) Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. *J Neurosci.* 17:7532-40.

Lowenstein DH (2006) The management of refractory status epilepticus: an update. *Epilepsia.* 47 Suppl 1:35-40.

Wasterlain C (2006) In *Status Epilepticus : Mechanisms and Managements* (Ed, Wasterlain, T.) MIT Press, Cambridge.

IL17

Established Status Epilepticus Treatment Trial (ESETT)

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Background: The need for an adequately powered, randomised, controlled trial (RCT) to determine the best treatment for convulsive status epilepticus (SE) where initial benzodiazepines have failed has been recognized for some years, and continues to be highlighted in recent reviews and guidelines. Treatment prior to or without consent is an essential pre-requisite for such a study, but permissible in the USA and most European countries when clinical equipoise exists. This is the case for valproate (VPA), levetiracetam (LEV) and phenytoin (PHT). Whilst there are also emerging data for lacosamide, this is insufficient at present to be considered in equipoise.

Study proposal: Building on the workshop at the 2009 SE Colloquium, an international team led by HC put forward a funding application to the UK Health Technology Assessment program in summer 2010. This proposed a pragmatic (unblinded) RCT to determine whether VPA or

LEV were superior in efficacy, safety or cost-effectiveness in comparison to the current standard PHT for the treatment of convulsive SE ongoing or recurring despite adequate first line benzodiazepines. The proposed study was powered to detect a 10% superiority (80% power, 5% significance). Costs were estimated at around £6 million recruiting for 4 years, though expected to be closer to £4million by use of an adaptive trial design, and with an additional feasibility stop point. The proposal failed at the prioritization round. Building on this, and the success of the USA Neurological Emergency Treatment Trials (NETT) network in recruiting to Rapid Anticonvulsant Medication Prior to Arrival (RAMPART) trial, a team now lead by Jaideep Kapur, HC and others is currently working on an application to the National Institute of Neurological Disorders and Stroke (NINDS), largely based on the original protocol with the exception of now including a blinded design. Blinding has obvious scientific advantages, though will increase costs and requires the use of fos-PHT (fPHT) as the comparator to minimize artificial delays to drug administration time (a treatment dose for a 70Kg adult at maximum recommended infusion rates is 3-5mins for VPA, 7-10mins for LEV, 10mins for fPHT, but almost 30minutes for PHT). Adults and children (though excluding infants/toddlers) with clinically obvious convulsive status epilepticus which has not responded to adequate doses of initial benzodiazepines will be eligible. Exclusions include known pregnancy, known allergy to a study drug, hypo or hyperglycaemia, and cardiac arrest as a cause. The study drugs will be prepared in concentrations to deliver the required dose at equal infusion rates, and pre-packaged in identical vials with instructions for administration as mls/kg/min. Proposed doses are 30mg/kg VPA, 20mg/kg fPHT, and up to 60mg/kg LEV, which will be infused over up to 13.3mins (100kg adult). The primary outcome will be cessation of seizure activity (convulsions/signs of seizure activity, improving responsiveness, EEG supported where available) without serious adverse events or additional antiepileptic drug treatment, maintained at 2 hours post infusion. Serious adverse events will include sustained hypotension (<90mm Systolic, > 5 minutes, not responding to fluid challenge); cardiac arrhythmias requiring anti-arrhythmics or cardioversion; respiratory depression requiring intubation. Secondary outcomes will include time to seizure cessation; need for intubation/anaesthesia; disposition from emergency room (ICU, hospital, home); ICU bed days; functional outcome (death, return to baseline, new disability) at discharge. EEG data where available, as soon as possible after presentation, will also be collected and centrally reported. Data on seizure types, cause, prior and discharge medication, comorbidities and demographics will also be obtained.

Sample size, centres and timescales: Good evidence on which to estimate the likely success rate with fPHT is lacking. The European group had originally estimated 55% success with PHT, and the USA group 25% based on published literature. Sample size estimates (10% group difference in proportions, 85% power) vary depending on this, with maximum numbers being needed if the true success for fPHT is around 50%. In this worst case scenario in terms of feasibility/numbers needed, and assuming 5% missing data (protocol deviation, refused consent in UK) approximately 500 patients in each arm would be needed. Using an adaptive trial design, if interim analysis reveals one arm as clearly inferior (then dropped), or that the difference between all three groups is negligible, the total number may reduce to nearer 1000. Estimating recruitment rates/centre from the published literature and RAMPART data indicates that 50-60 centres, each recruiting 6-8 patients/year over 4 years, will be needed (approximately 30 USA, 15-20UK, utilizing a network already recruiting for other emergency trials, 10-15 from up to 4 additional European Countries). The study will be primarily managed from the USA, with a smaller project team based in the UK. Work on further protocol refinements and costings is ongoing, with a provisional estimate of up to $15-20million, including the use of a CRO to facilitate navigation through international regulatory processes, training, site initiation and monitoring in Europe.

ESETT GROUP: *Original ESETT Team:* Tim Coats, Hannah Cock (lead), Simon Dixon, Steve Goodacre, Steven Julious, Dan Lowenstein, Simon Shorvon, Eugen Trinka. Contributors: Ulrich Stephani, Patient representative, Sheffield Clinical Trials Unit Staff.

Current ESETT Team: Co-PIs: Hannah Cock, Jordan Elm, Nathan Fountain, Jaideep Kapur (lead), Dan Lowenstein, Robert Sibergleit, David Treiman. Co-applicants: Thomas Bleck, James Cloyd, Omotola Hope, Elizabeth Jones, Yuko Palesch, Eugen Trinka

Declaration: I have received hospitality from all major AED manufacturers; Invited talks & consultancy honoraria from UCB Pharma, Janssen-Cilag, Sanofi-Synthelabo,

GSK; Unrestricted Research Grants from UCB Pharma, Johnson&Johnson & Pfizer

IL18

Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation

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The choice of therapy of status epilepticus (SE) will depend greatly on the SE type and the clinical context - and particularly on the extent to which the SE is life-threatening. This abstract is largely concerned with tonic-clonic status epilepticus, which is the most severe form, and not for instance non-convulsive status epilepticus nor epilepsia partialis continua which require totally different therapeutic approaches.

The treatment protocols for treating the earlier stages of tonic-clonic status epilepticus are now well defined and there is a good degree of international consensus about these (see for instance, Shorvon et al 2009, for the consensus report from the 2nd London-Innsbruck colloquium). Refractory SE is defined as SE which has neither responded to first-line therapy (benzodiazepine) nor second-line therapy, and which, according to the treatment protocols, requires the application of general anaesthesia (the conventional choices of anaesthetic are either IV propofol, IV pentobarbital/thiopental, or IV midazolam).

Super-refractory status epilepticus can be defined as SE which has continued or recurred despite 24 hours of general anaesthesia.

It is a well-recognised clinical problem, which is encountered typically, but not exclusively, in two quite distinctive clinical situations: (a) in patients with severe acute brain injury; (b) in patients with no prior history of epilepsy in whom status epilepticus develops out of the blue with no overt cause. This latter situation has been considered by some to be a 'syndrome' (entitled NORSE (new-onset refractory status epilepticus); Rathakrishnan and Wilder Smith 2009), although it seems to this author at least that a syndromic sobriquet is not appropriate based as it is on the fact that the SE has occurred without any cause found.

Therapy is difficult. There are no randomized or controlled studies of therapy. The published evidence base consists largely of case reports or small series, and so any recommendations on therapy must be considered anecdotal at best. The following approaches to therapy have been recommended:

Anaesthesia

In super-refractory SE, continued general anaesthesia remains the bedrock of therapy. It is usual to continue anaesthesia for a period of initially 24 hours and then slowly to reverse this. If seizures recur, the anaesthesia is re-established. This pattern of instituting and withdrawing anaesthesia is continued in 24 - 48 hour cycles initially and then at 5-7 day cycles. The role of anaesthesia is largely to prevent complications and to maintain stable clinical parameters whilst the epilepsy settles down. Whether they confer useful 'antiepileptic' action is debatable. Anaesthesia is usually administered to the level of 'burst suppression'. This is an arbitrary decision and in occasional cases, focal spikes on an EEG can be seen to be breaking through even at this level.

(a) Conventional anaesthesia (propofol, pentobarbital/thiopental or midazolam): The choice of anaesthesia depends on largely on side-effects (Shorvon 1994). Propolol is the easiest anaesthetic to use from the pharmacokinetic and pharmacological points of view, and pentobarbital/thiopental the most difficult. Propofol carries a particular risk of Propofol Infusion syndrome (Iyer et al 2009), especially in children and when used in combination with steroids or catecholamines. Midazolam suffers a particular risk of acute tolerance. All three anaesthetics carry serious problems of hypotension and cardiac depression, and these are probably most prominent with the barbiturate anaesthetics. (b) Alternative anaesthetics: Ketamine is an anaesthetic frequently described as a potentially useful therapy, although published experience is extremely slight (Mar-

tin and Kapur 2009, Pruss and Holtkamp 2008, Hsueh et al 2010). It has two advantages over the conventional anaesthetics: firstly, it has no cardiac depressant properties (in fact the reverse) and does not cause hypotension; and secondly, it is potentially neuroprotective, because it is a strong N-methyl-d-aspartate (NMDA) antagonist, although by the time it is employed glutaminergic damage may already have been incurred. Other anaesthetics which have been occasionally reported in case reports and small series to be useful in super-refractory SE include etomidate and the inhalational anaesthetics such as isoflurane and desflurane. In one report of isoflurane or desflurane given for up to 26 days in 7 subjects, with end-tidal volumes of 1.2-5%. Four patients had good outcomes. Three patients died (one of acute hemorrhagic leukoencephalitis, one of bowel infarction, and 1 remained in a persistent vegetative state until death 5.5 months after the onset of seizures due to toxic encephalopathy). Complications included hypotension (7/7), atelectasis (7/7), infections (5/7), paralytic ileus (3/7), and deep venous thrombosis (2/7). (Mirsattari et al 2004).

Antiepileptic drugs

A wide range of antiepileptic drugs have been used in patients in super-refractory SE in addition to anaesthesia. Whether any is superior to others is quite unclear and it is likely that no drug has strikingly different rates of efficacy than others. The author's advice is to retain a combination of 2 or 3 antiepileptic drugs at high doses, without switching too often (as is the usual temptation in a severe case). It is sensible where possible to avoid drugs which have a strong allergic potential or commonly interact with other drugs. Other side effects can be troublesome and acute pancreatitis, hepatic or renal failure may be induced IV antiepileptics. High dose IV valproate also carries theoretical risks of platelet and clotting disorders and severe hyperammonemia in predisposed patients.

Magnesium and other drugs

IV magnesium retains a unique place and is frequently given in status epilepticus, even in the absence of evidence of deficiency (Robakis and Hirsch 2006; Visser et al 2010). The infusion is given at doses which increase serum level from 0.81mmol/L to 3.5 mmol/L (loading dose and then continuous infusion). Other drugs which have been used include IV lidocaine and the old fashioned but highly effective IV paraldehyde. Verapamil has been reported to have terminated refractory status epilepticus in one patient, and the authors postulate that this was via an inhibition of p-Glycoprotein or other drug transporter processes.

Immunotherapy

The most interesting development in the therapy of SE in recent years has been the vogue for initiating immunotherapy, even in the absence of any evident immunological cause for the SE. The rational is that many of the episodes without known cause may be due to overt immunological disease. The recent discovery of anti NMDA-receptor antibodies and the recognition that this is a common condition has stimulated interest in the possibility that other, as yet undiscovered antibodies, may be playing a part in the pathogenesis of SE. Emergency treatment is usually attempted with high dose methylprednisolone (Igm prednisolone per day), and then followed if there is no response, by one or two courses of IVIG. If there is a response, longer term treatment with steroids, IVIG and later other immunomodulatory agents such as cyclophosphamide or rituximab may be necessary.

Hypothermia

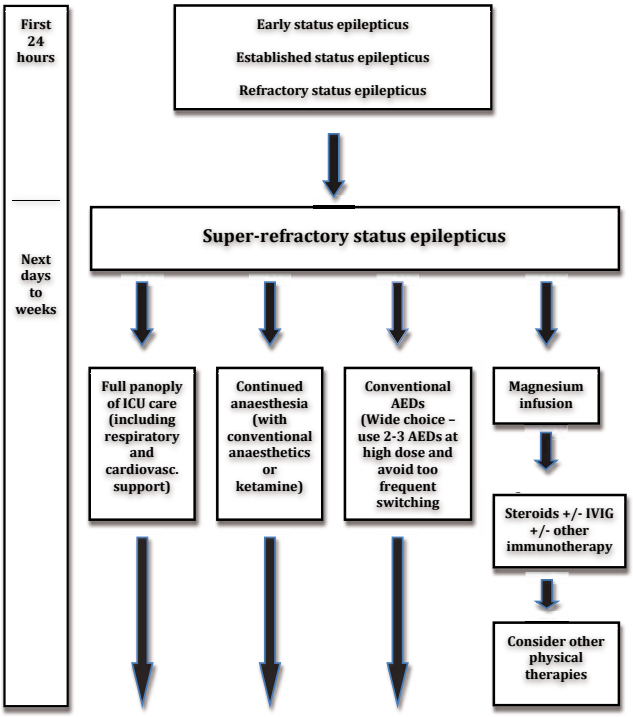
Hypothermia for status epilepticus, with thiopental anaesthesia, was reported in three children with generalized SE in 1984 (Orlowski et al 1984). In this report, moderate hypothermia (30+/- to 31+/-C) and anaesthesia to the level of burst suppression was continued for 48-120 hours resulting the cessation of SE. There has been a recent resurgence of interest in this mode of therapy, and Corry et al (2008) reported 4 patients with refractory tonic-clonic SE in whom hypothermia to 30-35C was achieved for 20-61 hrs using endovascular cooling , who were also receiving barbiturate or benzodiazepine anaesthesia. Hypothermia is not without its risks, and can cause acid–base and electrolyte disturbances, DIC, coagulation disorders, thrombosis, infection, cardiac arrhythmia, and paralytic ileus (Corry et al 2008), Nevertheless, it is now applied routinely to patients in super-refractory SE in some units.

Other physical treatments

There are individual reports of a range of disparate physical therapies used to treat super-refractory SE. These include ECT (an old therapy; Cline and Roos 2007), Transcranial Magnetic Stimulation (Misawa et al 2005, Rotenberg et

al 2009), vagal nerve stimulation (Winston et al 2001, De Herdt et al 2009) and drainage of the CSF (Kohrmann et al 2006; a very old therapy – see Neligan and Shorvon 2009). Other cases have been treated by emergency neurosurgery (Lhatoo and Alexopoulos 2009). An emergency ketogenic diet has also been reported to be successful (Francois et al 2003, Bodenant et al 2008). These therapies are most convincing then used against a chronic status syndrome such as EPC, but whether any really have an influence on the course of acute tonic-clonic status epilepticus is quite unclear.

Table 1: Flow chart summarizing the authors approach to the treatment of super-refractory status epilepticus



In table 1, the authors recommendations for therapy of super-refractory SE are summarized in a flow chart.

NB. In parallel to the treatment of seizures outlined above, emergency therapy should also be directed where possible at the underlying cause of the SE.

ICU = intensive Care Unit; AEDs = antiepileptic drugs.

Treatment of the underlying condition

Whilst efforts are made to control seizures, it is vital that the therapy is directed where possible at the underlying condition. Indeed, where this is not done, there is a significant risk of prolonging the status epilepticus and rendering it harder to control. The range of conditions which typically cause status epilepticus are different from those that result in ordinary epilepsy, and this topic was reviewed recently (Tan et al 2010).

The prognosis of super-refractory SE depends largely on the underlying aetiology. A recent study looked at the prognosis of 14 patients with SE lasting 7 days or more (Cooper et al 2009). 8 patients died during the SE or in its aftermath. Six patients survived (median duration of status epilepticus was 33 days) and despite initial deficits, 4 of the 5 patients who could be assessed showed a satisfactory cognitive outcome. It is common experience, backed up by this study, that good recovery can occur even after prolonged and severe status epilepticus and the neurologist has a role in the intensive care situation to ensure that premature withdrawal of care is not contemplated in the face of super-refractory status epilepticus.

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References

Bodenant M, Moreau C, Sejourne C, Auvin S, Delval A, Cuisset JM, Derambure P, Destée A, Defebvre L, (2008) Interest of the ketogenic diet in a refractory status epilepticus in adults.
Rev Neurol (Paris) 164:194–199.

Cline JS, Roos K. (2007) Treatment of status epilepticus with electroconvulsive therapy. *J. ECT* 23:30–32.

Cooper AD, Britton JW, Rabinstein AA. (2009) Functional and cognitive outcome in prolonged refractory status epilepticus. *Arch Neurol* 66:1505-9.

Corry JJ, Dhar R, Murphy T, Diringer MN. (2008) Hypothermia for refractory status
epilepticus. *Neurocrit Care* 9:189-97.

De Herdt V, Waterschoot L, Vonck K, Dermaut B, Verhelst H, Van Coster R, De Jaeger A, Van Roost D, Boon P. (2009) Vagus nerve stimulation for refractory status epilepticus. *Eur J Paediatr Neurol* 13: 286–289.

Francois LL, Manel V, Rousselle C, David M. (2003) Ketogenic regime as anti-epileptic treatment: its use in 29 epileptic children. *Arch Pediatr* 10:300–306.

Hsieh CY, Sung PS, Tsai JJ, Huang CW. (2010) Terminating prolonged refractory status
epilepticus using ketamine. *Clin Neuropharmacol* 33:165-7.

Iyer VN, Hoel R, Rabinstein AA. (2009) Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. *Crit Care Med* 37:3024-30.

Kohrmann M, Huttner HB, Gotthardt D, Nagel S, Berger C, Schwab S. (2006)
CSF-air-exchange for pharmacorefractory status epilepticus. *J Neurol* 253:1100–1101.

Lhatoo SD, Alexopoulos AV. (2007) The surgical treatment of status epilepticus. *Epilepsia* 48(suppl 8):61–65.

Martin BS, Kapur J. (2009) A combination of ketamine and diazepam synergistically controls refractory status epilepticus induced by cholinergic stimulation. *Epilepsia* 49:248–255.

Mirsattari SM, Sharpe MD, Young GB. (2004) Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 61:1254-9.

Misawa S, Kuwabara S, Shibuya K, Mamada K, Hattori T. (2005) Low-frequency transcranial magnetic stimulation for epilepsia partialis continua due to cortical dysplasia. *J Neurol Sci* 234:37–39.

Neligan A, Shorvon SD. (2009) The history of status epilepticus and its treatment. *Epilepsia* 50 (Suppl 3):56-68.

Orlowski JP, Erenberg G, Lueders H, Cruse RP (1984) Hypothermia and barbiturate coma for refractory status epilepticus. *Crit Care Med* 12:367-72.

Pruss H, Holtkamp M. (2008) Ketamine successfully terminates malignant status epilepticus.
Epilepsy Res 282:219–222.

Rathakrishnan R, Wilder-Smith EP. New onset refractory status epilepticus (NORSE). (2009) *J Neurol Sci.* 284:220.

Robakis TK, Hirsch LJ. (2006).
Literature review, case report, and expert discussion of prolonged refractory status epilepticus. *Neurocrit Care* 4:35–46.

Rotenberg A, Bae EH, Takeoka M, Tormos JM, Schachter SC, Pascual-Leone A. (2009) Repetitive transcranial magnetic stimulation in the treatment of epilepsia partialis continua. *Epilepsy Behav* 14:253–257.

Schmitt FC, Dehnicke C, Merschhemke M, Meencke HJ. (2010) Verapamil attenuates the malignant treatment course in recurrent status epilepticus. *Epilepsy Behav* 17:565-8

Shorvon SD (1994). Status Epilepticus: its Clinical Form and Treatment in Children and Adults.
Cambridge University Press, Cambridge, 1994. 382pp.

Shorvon SD, Baulac TM, Cross H, Trinka E, Walker M (for the TaskForce on Status Epilepticus of the ILAE). (2008) The drug treatment of status epilepticus in Europe: Consensus document from a workshop at the first London Colloquium on Status Epilepticus. *Epilepsia* 49: 2177-2184

Tan RY, Neligan A, Shorvon SD. (2010) The uncommon causes of status epilepticus: a systematic review. *Epilepsy Res* 91:111-22.
Visser NA, Braun KP, Leijten FS, van Nieuwenhuizen O, Wokke JH, van den Bergh WM. (2011) Magnesium treatment for patients with refractory status epilepticus due to POLG1-mutations. *J Neurol* 258:218-22

Winston KR, Levisohn P, Miller BR, Freeman J.(2001) Vagal nerve stimulation for status epilepticus. *Pediatr Neurosurg* 34:190–192.

IL19

Assessment of damage and plasticity caused by status epilepticus in the rat brain by multimodal MRI

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Status epilepticus or other brain damaging insults launch a cascade of events that may lead to the development of epilepsy. Non-invasive detection of these often progressive changes would have a great value for understanding better the basic pathophysiological mechanism of epileptogensis and for finding novel treatment strategies to prevent epilepsy. MRI is probably the most versatile non-invasive imaging modality available nowadays to study different aspects of these progressive changes *in vivo*. Contemporary MRI techniques are able to assess in addition to major structural changes also for example, axonal reorganization, brain function, blood flow and metabolism. Our special interest in recent years has been to develop MRI approaches for detection of the plastic recovery processes in the brain. Initial damage launches not only progressive damage but also enhances brain plasticity as a recovery mechanism. Optimal balance between damage and recovery processes is a key for planning of possible treatment, and non-invasive imaging has potential to greatly facilitate that process and to make individualised treatment plans possible.

The time period during (prolonged status epilepticus) and immediately after status epilepticus are associated with cytotoxic oedema (disturbance of water balance between intracellular an extracellular water) which causes decreased diffusion of the water in the tissue. This can be detected by diffusion MRI and is most often described by using orientation independent measure of water diffusion (several different abbreviations used in literature including Trace D, D_{av}, ADC_{av}, mean diffusivity MD; accurately 1/3 of the trace of the diffusion tensor). This is followed by a net accumulation of water in following days, causing vasogenic oedema which is typically assessed using T_2 or T_1 weighted MRI where contrast peaks 24-48 h after the initiation of insult (Fig 1A, B). Resorption of water decreases the relaxation based MRI contrast. Consequently, MRI visibility of the lesion can be low during the following weeks. Secondary increase in signal intensity in T2 weighted (or decrease in T1 weighted) MRI and increased mean diffusivity can be seen when progressive tissue damage evolves during the several weeks – months after status epilepticus in rat (for review of typical pattern of relaxation and diffusion changes see Gröhn and Pitkänen, 2007).

As described above, the time course of the changes in relaxation and diffusion (mean diffusivity) MRI can be used to follow tissue changes that are associated predominantly to damage process. The question that we asked a few years ago is: can MRI also assess recovery processes in the brain which occur in parallel to progressive neurodegenration. One of the best known example of plastic changes in the brain after status epilepticus is the sprouting of the mossy fibers in the dentate gyrus. To demonstrate that in vivo imaging of axonal plasticity is possible we injected $MnCl_2$ into enthorhinal cortex of rats two weeks after systemic kainate injection (Nairismagi, 2006). Mn^{2+} is a paramagnetic ion that behaves like Ca^{2+} in the brain, which form a basis for so called manganese enhances MRI (MEMRI). Mn^{2+}-ions were transported via perforant pathway to granule cells in the dentate gyrus which resulted in visualizing of mossy fibers in T_1 weighted MRI (Fig 1C). We were able to show that after kainate injection the area enhanced by Mn^{2+} was increased and that the increase was correlated with mossy fiber sprouting (Nairismagi, 2006). After the initial demonstration that MRI can detect cellular level reorganization after status epilepticus we decided to look for less invasive MRI approaches. We and others (Kuo, 2008; Laitinen, 2010) recently showed that fractional anisotropy (FA, a parameter derived from diffusion tensor MRI data showing degree of anisotropic diffusion) increases in the dentate gyrus weeks-months after status epilepticus. We attributed these changes to axonal reorganization due to increased density of myelinated fibers in the outer 2/3 of the molecular layer and mossy fiber sprouting in the inner molecular layer (Laitinen, 2010), thus showing that also diffusion tensor MRI (DTI) can indeed detect damage induced structural plasticity in hippocampus. These demonstrations of the value of DTI to detect changes also

outside of the main white matter bundles implies that DTI can provide additional information about the dynamics of ongoing plasticity in other areas of hippocampus and other brain areas undergoing circuitry reorganization. This can be seen in Figure 1D and E showing changes in the direction of main diffusion direction 6 months after kainic acid -induced status epilepticus in different subfields of the hippocampus.

The examples above describe hypothesis driven approaches where known features of epileptogensis/epilepsy were imaged using MRI. Novel voxel based imaging approaches also make possible to conduct fishing expeditions such as (anat)omics-like approaches were 3D imaging data are aligned, and analysis is done in the group level in order to find out which anatomical structures are changed as a results of insult. We recently applied tract based spatial statistics (TBSS, Smith, 2006) to high resolution *ex vivo* DTI data obtained from kainic acid treated animals **(Fig 1F)**. The TBSS analysis highlighted more than 10 different anatomical brain areas, of which almost half have not been previously described to undergo structural changes after kainate injection. Histological analysis of some of these areas revealed, for example, altered myelination, neurodegeneration, and/or calcification (Sierra, 2011).

Also functional plasticity and increased excitability can be potentially assessed by MRI. Functional MRI (fMRI) has been used to assess sensory recovery after stroke in rats (Dijkhuizen, 2001). However typical rodent fMRI protocols based on sensory stimulation of the fore paw or whisk are not well suited to asses functional changes after status epilepticus. This is an obvious field where experimental MRI approaches should be developed further. Potential approaches include pharmacological stimulation (for example pentylenetetrazole, or kainic acid) combined with fMRI **(Figure 1G)** and simultaneous EEG or field potential measurements (Blummenfeld, 2007; Airaksinen, 2010), which also could help to assess origin of the seizures.

MRI can also be used to characterize hemodynamic changes after status epilepticus (Choy 2010, Hayward, 2010). Arterial spin labelling (ASL, **Figure 1H**) MRI makes possible also non-invasive imaging of blood flow in the brain (CBF) without contrast agent and intravascular contrast agents can be used to measure cerebral blood volume (CBV). CBF, being closely coupled with metabolic demand of tissue, provides an insight into general tissue state and may also shed light to devascularization and angiogenesis after status epilepticus (Ndode-Ekane, 2010, Hayward 2010).

There are also some novel MRI approaches which likely will become to play a role in the assessment of changes caused by status epilepticus in the brain. Susceptibility weighted imaging (SWI) or phase contrast MRI in high magnetic field is rapidly expanding new application areas in different fields of neuroimaging. These techniques detect local magnetic field changes caused in tissue by different magnetic susceptibilities. It has been recently shown that phase images obtained with gradient echo sequence creates excellent white-grey matter contrast in high magnetic field and may have sensitivity to detect axonal damage or plasticity. Also changes in vascularization (Ndode-Ekane, 2010), iron accumulation or calcification (Lehto, 2011) could possibly cause contrast changes detectable by SWI or phase imaging **(Figure 1I).**

To summarize, MRI techniques available today can detect not only damage caused by status epilepticus but also plastic changes in brain as a response to damage. MRI is still rapidly evolving imaging technique and the approaches currently available in high field experimental MRI systems are likely to become available also in clinical settings, in future.

References

Gröhn O, Pitkänen A. (2007) Magnetic resonance imaging in animal models of epilepsy-noninvasive detection of structural alterations. *Epilepsia.* 48 Suppl 4:3-10

Nairismägi J, Pitkänen A, Narkilahti S, Huttunen J, Kauppinen RA, Gröhn OH (2006) Manganese-enhanced magnetic resonance imaging of mossy fiber plasticity in vivo. *Neuroimage.* Mar;30(1):130-5.

Kuo LW, Lee CY, Chen JH, Wedeen VJ, Chen CC, Liou HH, Tseng WY (2008) Mossy fiber sprouting in pilocarpine-induced status epilepticus rat hippocampus: a correlative study of diffusion spectrum imaging and histology. *Neuroimage.* Jul 1;41(3):789-800.

Laitinen T, Sierra A, Pitkänen A, Gröhn O. (2010) Diffusion tensor MRI of axonal plasticity in the rat hippocampus. *Neuroimage.* Jun;51(2):521-30.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage.* Jul 15;31(4):1487-505.

Sierra A, Laitinen T, Lehtimäki K, Rieppo L, Pitkänen A, Gröhn O. Diffusion tensor MRI with tract-based spatial statistics and histology reveals undiscovered lesioned areas in kainate model of epilepsy in rat. *Brain Struct Funct.* 2011 Jan 12.

Dijkhuizen RM, Ren J, Mandeville JB, Wu O, Ozdag FM, Moskowitz MA, Rosen BR, Finklestein SP. (2001) Functional magnetic resonance imaging of reorganization in rat brain after stroke. *Proc Natl Acad Sci U S A.* Oct 23;98(22):12766-71.

Airaksinen AM, Niskanen JP, Chamberlain R, Huttunen JK, Nissinen J, Garwood M, Pitkänen A, Gröhn O. (2010) Simultaneous fMRI and local field potential measurements during epileptic seizures in medetomidine-sedated rats using raser pulse sequence. *Magn Reson Med.* 2010 Oct;64(4):1191-9

Choy M, Wells JA, Thomas DL, Gadian DG, Scott RC, Lythgoe MF. (2010) Cerebral blood flow changes during pilocarpine-induced status epilepticus activity in the rat hippocampus. *Exp Neurol.* Sep; 225(1):196-201.

Hayward NM, Ndode-Ekane XE, Kutchiashvili N, Gröhn O, Pitkänen A. (2010) Elevated cerebral blood flow and vascular density in the amygdala after status epilepticus in rats. *Neurosci Lett.* Oct 22;484(1):39-42

Ndode-Ekane XE, Hayward N, Gröhn O, Pitkänen A. (2010) Vascular changes in epilepsy: functional consequences and association with network plasticity in pilocarpine-induced experimental epilepsy. *Neuroscience.* Mar 10;166(1):312-32.

Wu Z, Mittal S, Kish K, Yu Y, Hu J, Haacke EM. (2009) Identification of calcification with MRI using susceptibility-weighted imaging: a case study. *J Magn Reson Imaging.* Jan;29(1):177-82.

Lehto L, Sierra A, Corum CA, Idiyatullin D, Garwood M, Gröhn O (2011) Calcification imaging with SWIFT in rat brain Proceedings of the 19th *International Society for Magnetic Resonance in Medicine meeting,* in press

Table 1: MRI techniques which have been used or have potential to be used to detect changes after status epilepticus in rat

MRI technique	What is detected after status epilpeticus in rat	References
T2-weighted MRI	• vasogenic oedema, peaks 24-48 hours after SE • secondary increase in signal intensity weeks-months after SE • atrophy, enlarged ventricles	Gröhn and Pitkänen , 2006
Diffusion (mean diffusivity)	• detection of cytotoxic oedema in hyperacute phase (decreased diffusion) • increased diffusion weeks-months after	Gröhn and Pitkänen , 2006
Diffusion tensor imaging	• axonal plasticity and reorganization • axonal damage • when combined with TBSS – identification of novel brain areas associated with epileptogenesis/epilepsy	Kuo, 2008 Laitinen, 2010 Sierra, 2011
fMRI	• seizures • potentially: functional plasticity	Blummenfeld, 2007 Airaksinen, 2010
Arterial spin labelling CBV-MRI using intravascular contrast agent	• detection of the hypo/hyperperfusion, coupled with metabolic demand • structural changes in vascularization	Choy, 2010 Hayward, 2010
SWI, phase imaging	• calcifications • potentially: myelinization and vascularization changes	Wu, 2009 Lehto 2011

CBV, cerebral blood volume; fMRI, functional MRI; SWI, susceptibility weighted imaging

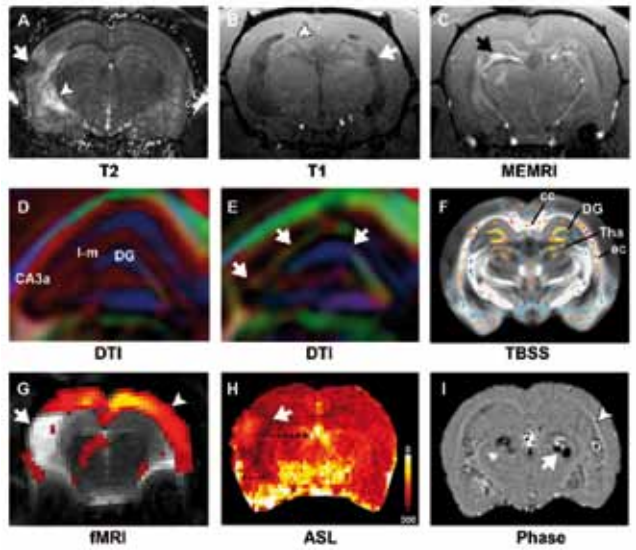

Figure 1: Examples of different MRI approaches to detect changes after initial insults potentially causing epileptogenesis. **A)** T_2 map measured 3 days after traumatic brain injury (TBI). White arrow shows oedemic tissue at the site of the impact, arrow head an enlarged ventricle. **B)** T_1 weighted MR image showing enlarged ventricles and deformation of the hippocampus 2 months after status epilepticus induced by KA. **C)** T_1 weighted manganese enhanced MRI (MEMRI) image 3 days after injecting $MnCl_2$ into enthorhinal cortex shows enhancement of the mossy fibers two weeks after systemic kainic acid (KA) injection (black arrow). Colour coded FA images from **D)** control animal and E) KA treated animal, ex vivo, show changes in several subfields of hippocampus as marker as a result of axonal reorganization (white arrows). Color coding: blue, dorsal-ventral; green, medial-lateral; red, rostral-caudal. **F)** Tract based spatial statistics (TBSS) reveals several brain areas where fractional anisotropy (FA) is decreased (blue) or increased (yellow) 6 months after KA induced status epilepticus. **G)** fMRI activation map describing activated areas after pentylenetetrazole injection 8 weeks after traumatic brain injury. **H)** CBF map measured with arterial spin labelling (ASL) shows hypoperfused area (arrow) around the impact site 6 hours after induction of TBI. Colorbar in ml/100g/min **I)** High pass filtered gradient echo phase image shows calcification 9 months after systemic pilocarpine injection. Abbreviations: cc: corpus callosum; DG: dentate gyrus; ec: external capsule; *l-m:* stratum lacunosum-moleculare; *Tha:* thalamus.

IL20

The potential of brain stimulation in status epilepticus

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The use of brain stimulation in the treatment of epilepsy has a long and checkered history. Cerebellar stimulation was amongst the first structures to be stimulated by Cooper and colleagues in the early 1970's and initial results showed considerable promise, a promise that was not borne out in subsequent trials (Rosenow et al., 2002). In 1979, Cooper also carried out the first thalamic stimulation for the treatment of epilepsy (Rosenow et al., 2002). More recently, the efficacy of stimulation of the anterior nuclei of the thalamus has been confirmed in a double-blind, randomized control study (Fisher et al., 2010). The use of direct brain stimulation to control status epilepticus has, however, not been the subject of controlled trials, and in humans, there have been only case reports, and small case series. As a result, there remain a number of critical questions that need to be answered: does brain stimulation work in status epilepticus? What areas should be stimulated? How should the brain be stimulated? What are the stimulation parameters that should be used?

Brain stimulation can be targeted at the focus, at structures that modulate brain excitability (e.g. thalamus, basal ganglia) or at the whole brain (e.g. electroconvulsive therapy). In humans, there have been reports of the efficacy of electroconvulsive therapy (ECT) in the treatment of established status epilepticus with success reported in 6 out of 7 cases (Carrasco Gonzalez et al., 1997; Griesemer et al., 1997; Lisanby et al., 2001; Cline & Roos, 2007; Kamel et al., 2010). The use of ECT is supported by the concept of a refractory period after electroconvulsive therapy perhaps mediated by a large release of inhibitory transmitters such as GABA (Sackheim et al., 1983;Sanacora et al., 2003). In addition, the clinical observation that nonconvulsive status epilepticus is often terminated by a convulsion supports this hypothesis (Shorvon & Walker 2005). Interestingly, the reports of ECT in status epilepticus indicate that single ECT is not sufficient and that a course over 3-8 days may be necessary. Furthermore, anticonvulsants should be

stopped during the ECT in order to increase its effectiveness, supporting the contention that it is the induced tonic-clonic seizure that terminates the status epilepticus rather than the stimulation per se (Kamel et al., 2010).

The other method of stimulation that has received attention in the literature is transcranial magnetic stimulation (TMS).In contrast to ECT, this is a targeted therapy and so requires a focal epilepsy. This has, therefore, been mainly used in the treatment of epilepsia partialis continua. Success has been variable with seizure suppression in 8 out of 13 patients of whom only 4 had a lasting improvement (Rotenberg et al. 2009). The protocols used have, however, varied considerably from prolonged low frequency trains (0.5-1Hz) to high frequency (20-100Hz) bursts over the putative seizure focus. These protocols appear to have been equally (in)effective. In contrast to ECT, TMS is likely to work by reducing cortical excitability through a mechanism akin to long term synaptic depression (a form of synaptic plasticity).

The use of deep brain stimulation has not been extensively reported in status epilepticus but it is mentioned in discussions (see for example Robakis & Hirsch, 2006). Data from animal seizure models have indicated that high frequency stimulation of the anterior thalamic nucleus can increase seizure threshold, and delay the occurrence of status epilepticus following administration of the convulsant pilocarpine (Hamani et al. 2009). However, the same stimulation protocol does not terminate established status epilepticus, indicating that the mechanisms underlying induction and maintenance of status epilepticus differ (Hamani et al. 2009). This raises a further question: are the stimulation protocols for prevention of spontaneous seizures effective for status epilepticus termination?

Notwithstanding this, even the most effective stimulation protocols for seizure prevention are still uncertain, not only the frequency, but also the pattern of stimulation. Indeed, recent evidence in an animal model suggests that a Poisson distributed (random) stimulation protocol is more effective than a constant frequency stimulation protocol in reducing seizure frequency (Wyckhuys et al., 2010). Moreover, the kinetics of slow GABA(B) receptor mediated- and fast GABA(A) receptor mediated-inhibition may determine the frequency and intensity of stimulation that will shift the system into or out of an oscillatory state (Adhikari et al., 2009), and there may be inter-individual differences in these. However, perhaps one of the most intriguing observations has been that seizure termination is associated with increased synchronization in the EEG (Schindler et al., 2007a). This observation has been extended to status epilepticus and, again, termination of the status epilepticus is preceded by increased synchronization of activity in the EEG (Schindler et al., 2007b). The explanation of this could be that highly synchronized neuronal activity may be more effective at recruiting inhibitory mechanisms (whether these be release of inhibitory transmitters or forms of spreading depression) and that status epilepticus is maintained by inadequate neuronal synchronization. This observation has considerable implications for the stimulation protocols that we should use to terminate status epilepticus. In particular, low frequency bulk stimulation, which can result in oscillatory behavior in healthy brains, may, by synchronizing neuronal activity, help terminate status epilepticus. This contrasts with the high frequency stimulation protocols usually used in seizure prevention. Moreover, the concept of synchronized activity terminating seizures may provide an explanation for the efficacy of ECT in status epilepticus.

Lastly, the targets for stimulation are unclear. Should we be stimulating the whole cortex (ECT), the seizure focus or subcortical structures? There is growing evidence that targeting specific areas of the thalamus such as the centro-median nucleus and the anterior thalamic nuclei is effective in reducing seizures. However, other subcortical structures, such as the subthalamic nuclei and the basal ganglia (in particular, the caudate and the substantia nigra), may offer alternative, more effective approaches (Kahane & Depaulis 2010).

In conclusion, brain stimulation for the treatment of status epilepticus is an exciting field where much work remains. It is still unclear where and how we should stimulate, and what is the most effective method. In addition, the mechanisms by which brain stimulation terminates seizures are uncertain and are likely to involve more than one process. It is probable that the most effective protocols and methods fro the treatment of status epilepticus will differ from those used in the prevention of seizures; in particular the use of protocols that increase neuronal synchronization and oscillatory behavior may be effective in the termination status epilepticus.

References

Adhikari MH, Heeroma JH, di Bernardo M, Krauskopf B, Richardson MP, Walker MC, Terry JR. (2009) Characterisation of cortical activity in response to deep brain stimulation of ventral-lateral nucleus: modelling and experiment. *J Neurosci Methods.* 183(1):77-85

Carrasco Gonzalez MD, Palomar M, Rovira R. (1997) Electroconvulsive therapy for status epilepticus. *Ann Intern Med.* 127:247–8.

Cline JS, Roos K. (2007) Treatment of status epilepticus with electroconvulsive therapy. *J ECT.* 23:30–2.

Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, Handforth A, Stern J, DeSalles A, Chung S, Shetter A, Bergen D, Bakay R, Henderson J, French J, Baltuch G, Rosenfeld W, Youkilis A, Marks W, Garcia P, Barbaro N, Fountain N, Bazil C, Goodman R, McKhann G, Babu Krishnamurthy K, Papavassiliou S, Epstein C, Pollard J, Tonder L, Grebin J, Coffey R, Graves N; SANTE Study Group. (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51(5):899-908

Griesemer DA, Kellner CH, Beale MD, Smith GM.(1997) Electroconvulsive therapy for treatment of intractable seizures. Initial findings in two children. *Neurology* 49:1389-92.

Hamani C, Ewerton FI, Marcolin de Almeida F, Bonilha SM, Covolan L, Fantin Cavarsan C, Ballester G, Mello LE, Lozano AM. (2009) Bilateral anterior thalamic nucleus lesions are not protective against seizures in chronic pilocarpine epileptic rats. *Stereotact Funct Neurosurg.* 87(3):143-7

Kahane P, Depaulis A. (2010) Deep brain stimulation in epilepsy: what is next? *Curr Opin Neurol.* 23(2):177-82

Kamel H, Cornes SB, Hegde M, Hall SE, Josephson SA (2010) Electroconvulsive therapy for refractory status epilepticus: a case series. *Neurocrit Care.* 12(2):204-10

Lisanby SH, Bazil CW, Resor SR, Nobler MS, Finck DA Sackeim HA. (2001) ECT in the treatment of status epilepticus. *J ECT.* 17:210–5.

Robakis TK, Hirsch LJ. (2006) Literature review, case report, and expert discussion of prolonged refractory status epilepticus. *Neurocrit Care.* 4(1):35-46.

Rosenow J, Das K, Rovit RL, Couldwell WT. Irving S. (2002) Cooper and his role in intracranial stimulation for movement disorders and epilepsy. *Stereotact Funct Neurosurg.* 78(2):95-112.

Rotenberg A, Bae EH, Takeoka M, Tormos JM, Schachter SC, Pascual-Leone A. (2009) Repetitive transcranial magnetic stimulation in the treatment of epilepsia partialis continua. *Epilepsy Behav.* 14(1):253-7

Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR.(1983) Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. *Biol Psychiatry.* 18(11):1301-10.

Sanacora G, Mason GF, Rothman DL, Hyder F, Ciarcia JJ, Ostroff RB, Berman RM, Krystal JH. (2003) Increased cortical GABA concentrations in depressed patients receiving ECT. *Am J Psychiatry.* 160(3):577-9.

Schindler K, Elger CE, Lehnertz K. (2007b)Increasing synchronization may promote seizure termination: evidence from status epilepticus. *Clin Neurophysiol.* 118(9):1955-68

Schindler K, Leung H, Elger CE, Lehnertz K. (2007a) Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. *Brain* 130(Pt 1):65-77

Shorvon S, Walker M. Status epilepticus in idiopathic generalized epilepsy. (2005) *Epilepsia.* 46 Suppl 9:73-9.

Wyckhuys T, Boon P, Raedt R, Van Nieuwenhuyse B, Vonck K, Wadman W. (2010) Suppression of hippocampal epileptic seizures in the kainate rat by Poisson distributed stimulation. *Epilepsia.* 51(11):2297-304

IL21

What is the value of Hypothermia in acute neurological diseases and SE

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Although the beneficial effects of low body temperature on head injury were already recognized more than two millenniums ago by Hippocrates ((Adams, 1939), cited in (Harris et al., 2002)), and despite several animal and clinical studies on various indications carried out in the last decades, the evidence-based use of therapeutic hypothermia (TH) has only been recently recommended in the setting of adult and pediatric postanoxic encephalopathy and reduction of intracranial pressure (Polderman, 2008). Its indication for the treatment of other acute brain disorders, including status epilepticus (SE), remains essentially anecdotic.

A low brain temperature exerts several beneficial effects on the pathophysiological cascades implicated in acute cerebral injuries; several seminal studies have been recently reviewed in (Holzer, 2010; Polderman, 2008). Globally, hypothermia reduces brain metabolism, oxygen utilization, and ATP consumption; furthermore, it leads to inhibition of glutamate release, mitochondrial dysfunction and calcium overload. Conversely, brain-derived neurotrophic factor is increased. Following these changes, and reduction of free radical production and oxidative stress, apoptosis is inhibited. Other favorable modifications also corroborate the neuroprotective properties of hypothermia: mitigation of reperfusion injury, reduced permeability of the blood-brain barrier resulting in limitation of edema, and depression of proinflammatory reactions. Since several aforementioned mechanisms are implicated in neuronal suffering during SE (Chen and Wasterlain, 2006; Lothman, 1990), it would be straightforward to infer that TH is beneficial in this clinical indication.

TH may be applied with external devices and/or core cooling methods (infusion of cold fluids through peripheral or central approaches (Holzer, 2010)). Deep hypothermia (15°C-22°C) leads to marked greater complications as compared to mild TH (30°C-35°C) (Harris et al., 2002). Adverse effects may be related to the cooling devices or the low temperature itself. In 41 clinical trials using mild TH on postanoxic encephalopathy, complications related to the cooling device involved only 29/3133 patients (1%), suffering from bleeding, infection, vein thrombosis, or pulmonary edema (Holzer, 2010). Conversely, in the few major comparative clinical trials in the same clinical setting, side-effects were recorded in 223/300 patients treated with TH (74%) versus 201/285 controls (71%; P=0.31) (Holzer, 2010). These included pneumonia (probably related to mechanical ventilation), hyperglycemia, cardiac arrhythmias, and electrolyte disturbances.

Various rodent models of SE support the neuroprotective effects of TH. Hypothermia reduces seizure severity and epileptic discharges in SE triggered by electrical stimulation of the perforant path, especially if coadministered with diazepam (Schmitt et al., 2006); it reduces seizures, brain edema, and cognitive deficits in animals with kainate-induced SE (Wang et al.); and temperature lowering before pilocarpine injection in immature rats protects against SE and apopotosis in the hippocampus (Yu et al.). Somewhat surprisingly, however, clinical observations are scarce.

A pioneer description published more than 25 years ago on three children with generalized SE, successfully treated with TH (30°C-31°C) and thiopental (Orlowski et al., 1984) was only followed by a handful reported cases. Four adult patients with SE due to limbic encephalitis (2 patients), hepatic encephalopathy (1 patient) and of unknown origin (1 patient) were treated with TH (31°-35°C) together with midazolam; SE was controlled in all, but two subjects died subsequently (Corry et al., 2008). Shivering had to be controlled with neuromuscular blockade; other side effects included vein thrombosis and pulmonary embolism. One additional adult patient with cryptogenic SE was treated with TH (34°C) and thiopental, developing paralytic ileus that required emergency intestinal resection; she survived (Cereda et al., 2009). Finally, an infant with SE due to hemimegalencephaly had his ongoing seizures controlled by hypothermia at 35°C-36°C, together with ketamine; later, hemispherectomy was performed (Elting et al., 2010). Reported TH durations are markedly variable, ranging between 20 hours and several days.

It has been increasingly recognized that postanoxic SE does not necessarily imply a poor outcome. In this setting, recent observations suggest that SE occurring during TH,

mostly as a "seizure suppression" EEG pattern, represents a situation of extreme brain damage, and patients are extremely unlikely to survive (Rossetti et al., 2010b; Thenayan et al., 2010); conversely, SE arising after rewarming may be treated with AED if the EEG background is reactive, and somatosensory evoked potentials and brainstem reflexes are preserved (Rossetti et al., 2009). In those cases (representing about 10% of patients with postanoxic SE) survival with reasonable functional outcome may be obtained (Rossetti et al., 2010a). This suggests that TH (together with moderate midazolam or propofol doses) is sufficient to transitorily control "benign" postanoxic SE forms (illustrating its antiepileptic properties), while it does not prevent a dismal outcome in more severe forms.
In conclusion, considering the current lack of clinical evidence, it seems reasonable to reserve mild TH (32°C-35°C) for extremely refractory SE, on a patient by patient basis. Should this option be chosen, barbiturates should be avoided (thus favoring midazolam or propofol) and limit hypothermia duration at 24-48 hours, in order to minimize potential side effects such as paralytic ileus. A routine check of cardiovascular indices, coagulation parameters and lactate counts (metabolic acidosis following intestinal necrosis or severe infections), and limbs inspections (vein thrombosis), are mandatory. A well-designed, prospective study would be necessary to implement TH in the treatment of SE.

References

Adams F. The genuine works of Hippocrates. Baltimore, MD: Williams & Wilkins, 1939.

Cereda C, Berger MM, Rossetti AO. Bowel ischemia: a rare complication of thiopental treatment for status epilepticus. Neurocrit Care 2009; 10: 355-8.

Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol 2006; 5: 246-56.

Corry JJ, Dhar R, Murphy T, Diringer MN. Hypothermia for refractory status epilepticus. Neurocrit Care 2008; 9: 189-97.

Elting JW, Naalt J, Fock JM. Mild hypothermia for refractory focal status epilepticus in an infant with hemimegalencephaly. Eur J Paediatr Neurol 2010; 14: 452-5.

Harris OA, Colford JM, Jr., Good MC, Matz PG. The role of hypothermia in the management of severe brain injury: a meta-analysis. Arch Neurol 2002; 59: 1077-83.

Holzer M. Targeted temperature management for comatose survivors of cardiac arrest. N Engl J Med 2010; 363: 1256-64.

Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990; 40: 13-23.

Orlowski JP, Erenberg G, Lueders H, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. Crit Care Med 1984; 12: 367-72.

Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008; 371: 1955-69.

Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology 2009; 72: 744-9.

Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010a; 67: 301-7.

Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. Crit Care 2010b; 14: R173.

Schmitt FC, Buchheim K, Meierkord H, Holtkamp M. Anticonvulsant properties of hypothermia in experimental status epilepticus. Neurobiol Dis 2006; 23: 689-96.

Thenayan EA, Savard M, Sharpe MD, Norton L, Young B. Electroencephalogram for prognosis after cardiac arrest. J Crit Care 2010; 25: 300-4.

Wang Y, Liu PP, Li LY, Zhang HM, Li T. Hypothermia Reduces Brain Edema, Spontaneous Recurrent Seizure Attack, and Learning Memory Deficits in the Kainic Acid Treated Rats. CNS Neurosci Ther, in press.

Yu L, Zhou Y, Chen W, Wang Y. Mild hypothermia pretreat-

ment protects against pilocarpine-induced status epilepticus and neuronalapoptosis in immature rats. Neuropathology, in press.

IL22

Therapeutic potential of new anti-inflammatory drugs

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Purpose

In the last decade, accumulating evidence have supported an important role of brain inflammation in the etiopathogenesis of seizures (Vezzani et al., 2011). In particular, the activation of specific proinflammatory signals, such as *the Interleukin-1 receptor/Toll-like receptor (IL-1R/TLR)* pathway, is involved in the precipitation and recurrence of seizures in experimental models (Balosso et al., 2008; Maroso et al., 2010). Expression studies of components of the *IL-1R/TLR* signaling in surgically resected human epileptic tissue supports its activation in human epilepsy (Ravizza et al., 2006; Ravizza et al., 2008; Boer et al., 2010; Zurolo et al., 2011). This new knowledge opens up the possibility of a new target system for anticonvulsant drug intervention to control pharmaco-resistant seizures.

Methods

Pharmacological studies in experimental models of seizures and epilepsy have used selective tools to block the activation of specific pro-inflammatory pathways, to evaluate their effects on induced and spontaneous seizures, as assessed by quantitative EEG analysis.

Key findings

ICE/Caspase-1 is the enzyme involved in IL-1b biosynthesis. Its blockade using pralnacasan or VX-765 reduces by 50% acute recurrent seizures in rats and in mice. Moroever, the systemic administration of VX-765 reduces up to 70% AED-resistant chronic epileptic activity in mice (Ravizza et al., 2006; Maroso et al., 2011). Another strategy to preclude the activation of IL-1b signaling is to block its receptor *IL-1R1* using anakinra (i.e. IL-1 receptor antagonist). Anakinra strongly reduces seizures (Vezzani et al., 2000; Vezzani et al., 2002) and the incidence of status epileticus in rats (Marchi et al., 2008). Acute and chronic seizures suppression was attained in mice also using specific blockers of Toll-like receptor 4 (*TLR4*) (Maroso et al., 2010). These receptors are activated by endogenous *danger signals* released by cells undergoing biological stress or injury, as well as by mimicry of microbial pathogens. High Mobility Group Box 1 (*HMGB1*) is a protein identified as the endogenous ligand which activates TLR4 after a proconvulsant challenge. Inhibitors of HMGB1's biological actions, such as the peptide Box A, drastically reduce experimental seizures. Notably, the blockade of TLR4-mediated signaling delays the onset of seizures indicating its role in the mechanisms of seizure precipitation (Maroso et al., 2010).

These pharmacological findings are supported by genetic studies showing that mice with a defective *IL-1R/TLR* signaling are intrinsically resistant to seizures.

Molecular studies showed that the activation of *IL-1/TLR* signaling results in rapid post-translational changes in NMDA and voltage-gated ion channels; these effects increase neuronal excitability thus contributing to seizure activity.

Significance

These results support a new target system for epilepsy intervention, and open new perspectives for the clinical use of this anti-inflammatory strategy for treating established drug-resistant epileptic conditions (ClinicalTrials.gov, 2010). Considering that chronic administration in epilepsy is likely to be required, and the constraints imposed by the BBB, it will be important to further understand both the efficacy and the safety of long duration treatment with drugs that impair the over-activation of specific inflammatory mechanisms in the brain. Some of these drugs are already in clinical use showing anti-inflammatory and therapeutic effects in chronic peripheral inflammatory conditions; these

drugs might relieve or reduce inflammatory processes in the epileptic brain and thereby ease hyperexcitability, thus they may have great therapeutic potential in epilepsy.

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AV owns intellectusl properties on a patent on the use of ICE inhibitors in epilepsy issued from Vertex Pharmaceuticals, Cambridge, USA, that does not involve any financial interest.

References

Balosso S, Maroso M, Sanchez-Alavez M, Ravizza T, Frasca A, Bartfai T, Vezzani A. (2008) A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1beta. *Brain* 131: 3256-3265.

Boer K, Jansen F, Nellist M, Redeker S, van den Ouweland AM, Spliet WG, van Nieuwenhuizen O, Troost D, Crino PB, Aronica E. (2008) Inflammatory processes in cortical tubers and subependymal giant cell tumors of tuberous sclerosis complex. *Epilepsy Res* 78: 7-21.

ClinicalTrials.gov (2010) *Study of VX-765 in subjects with treatment-resistant partial epilepsy* [online],http://clinicaltrials.gov/ct2/show/NCT01048255.

Marchi N, Fan Q, Ghosh C, et al. (2009) Antagonism of peripheral inflammation reduces the severity of status epilepticus. *Neurobiol Dis* 33: 171-181.

Maroso M, Balosso S, Ravizza T, et al. (2010) Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. *Nat Med* 16: 413-419.

Ravizza T, Boer K, Redeker S, Fazio V, Bertolini F, Betto G, Batra A, Carlton E, Najm I, Granata T, Janigro D. (2006) The IL-1beta system in epilepsy-associated malformations of cortical development. *Neurobiol Dis* 24: 128-143.

Ravizza T, Lucas SM, Balosso S, Bernardino L, Ku G, Noé F, Malva J, Randle JC, Allan S, Vezzani A. (2006) Inactivation of caspase-1 in rodent brain: a novel anticonvulsive strategy. *Epilepsia* 47: 1160-1168.

Ravizza T, Gagliardi B, Noé F, Boer K, Aronica E, Vezzani A. (2008) Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy. *Neurobiol Dis* 29: 142-160.

Vezzani A, Moneta D, Conti M, Richichi C, Ravizza T, De Luigi A, De Simoni MG, Sperk G, Andell-Jonsson S, Lundkvist J, Iverfeldt K, Bartfai T. (2000) Powerful anticonvulsant action of IL-1 receptor antagonist on intracerebral injection and astrocytic overexpression in mice. *Proc Natl Acad Sci U S A* 97: 11534-11539.

Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ, Ravizza T, Perego C, De Simoni MG. (2002) Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. *Epilepsia* 43 (Suppl 5): 30-35.

Vezzani A, French J, Bartfai T, Baram TZ. (2011) The role of inflammation in epilepsy. *Nat Rev Neurol* 7: 31-40.

Zurolo E, Iyer A, Maroso M, Fluiter K, Spliet WGM, van Rijen PC, Baayen JB, Vezzani A, Aronica E. (2011) Activation of TLR, RAGE and HMGB1 signaling in malformations of cortical development. *Brain*, in press.

IL23

A New Derivative of Valproic Acid Amide Uniquely Suppresses Electrographic Activity and is Neuroprotective in the Lithium-Pilocarpine and Organophosphate Models of Status Epilepticus

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Status epilepticus

(SE) that is resistant is benzodiazepine (BZ) therapy is a major medical emergency with high morbidity and mortality. The current standard-of-care for patients with SE, when BZ fails to stop the seizures, is to administer either barbiturates or anesthetics to induce coma. Clearly, there is an unmet medical need for anticonvulsants that can stop the seizures associated with BZ-resistant SE, and have a high margin of safety so that they have potential utility in an out-patient or field setting, particularly for nerve-agent protection.

Valproic acid (VPA), a leading anti-seizure drug for people with chronic epilepsy, is however not a particularly potent drug among the established anti-seizure drugs and its clinical use is limited by two rare, but potentially life-threatening side effects: hepatotoxicity and teratogenicity. In order to overcome VPA's severe side effects and improve its beneficial antiepileptic and CNS activity, numerous VPA analogues and derivatives have been designed and evaluated. The present study aimed to evaluate the efficacy of one such compound in two animal models of severe BZ-resistant SE.

As the present report demonstrates, sec-butyl-propylacetamide (SPD) is a unique compound that possesses potent anticonvulsant activity in the rat pilocarpine-induced SE model. SPD is a one carbon homologue of valnoctamide (VCD) that is a constitutional isomer of VPA's corresponding amide valpromide. Racemic-VCD was used in Europe as an anxiolytic drug between 1964-2005 and has recently completed successfully phase IIa clinical trials in bipolar disorder. When SPD was given 30 min after pilocarpine injection, it was found to suppress convulsive seizures. The calculated ED_{50} and ED_{97} values were 84mg/kg and 149mg/kg, respectively. In addition, SPD (130 mg/kg) had an acute suppressive effect (1 h and 3h after dosing) on benzodiazepine-resistant electrographic SE in this model when administered 30 min as well as 45 min after the first motor seizure. Moreover, SPD at 30 min prevented pilocarpine-induced cognitive impairment and produced wide-scale neuroprotection of the hippocampus as determined by Fluoro-Jade staining. Because SPD did not confer neuroprotection in an *in vitro* excitoxicity assay, this result suggests that the neuroprotection observed in vivo was due to termination of the seizures. SPD (100-174 mg/kg) also protected against soman-induced seizures when administered 20 min and 40 min after the first seizure. All of these experiments make SPD a unique compound that blocks SE and organophosphate neuronal damage in a manner that is superior to diazepam.

Successful translation of this compound to the clinic may provide neurologists and emergency response teams with an important and novel drug to prevent the devastating effects of BZ-resistant SE. Of particular importance is our observation that SPD directly blocks electrographic seizure activity in two severe models of SE, and furthermore, that cognitive impairment is mitigated. The search for new and highly efficacious anti-seizure drugs is one of the most important areas of neurological research, particularly for people with pharmacoresistant epilepsy and status epilepticus. In addition to generating strong, multi-disciplinary data for a new compound to suppress BZ-resistant SE, the present experiments provide proof-of-principle support for the strategy of developing new anti-seizure drugs by fine-tuning older compounds with the modern methods of medicinal chemistry.

IL24

Mono- versus poly-therapy in the treatment of status epilepticus

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Monotherapy is widely accepted as the best option for treatment of epilepsy, and controlled studies of the treatment of status epilepticus (SE) have shown lorazepam monotherapy to be as effective as any treatment tested (Treiman et al, 1998). However, the major reasons for preferring monotherapy in the treatment of chronic epilepsy, such as minimizing lifelong exposure to potentially toxic drugs, may not apply to SE, an acute, life-threatening event of limited duration. There is a paucity of experimental or clinical evidence supporting the superiority of monotherapy in the treatment of acute seizures and SE. There is also no consensus on the criteria which allow comparisons between the benefits and adverse effects of mono- and polytherapy.

Recent studies have shown that seizure-induced trafficking of synaptic GABA and glutamate receptors causes both a reduction of GABAergic inhibition and an increase in glutamatergic excitation in hippocampus during SE (Naylor et al 2005, Goodkin et al 2008). This might suggest that combination therapy aimed at correcting the consequences of both changes may be more effective than monotherapy targeting only one of those pathophysiological mechanisms (Chen & Wasterlain, 2006). In the present study, we propose the use of a key measure of drug toxicity as the standard to compare the effect of a single drug to those of two- or three-drug combinations. This standard could vary with the therapeutic situation. For example, in developing countries where fully equipped intensive care units are in short supply, respiratory depression might be a key measure of toxicity for the safe treatment of SE, while in a well-equipped ICU, respiratory depression might not be considered a key factor, but major depression of systolic blood pressure would be the key measure of toxicity.

Our studies used a model of severe SE induced by cholinergic agents (Tetz et al 2006), and designed to mimic the effects of 1.2 x LD50 dose of nerve agent. Because this might apply to battlefield or terrorism situations where the victims' mobility is important, we selected the ability to move about and to retain consciousness as our key measures of drug toxicity. Gait ataxia, loss of the righting reflex, abolition of response to tail pinch, and loss of the corneal reflex were used to measure drug toxicity, summed up over the first hour of exposure in a "toxicity score". Outcome measures were termination of SE, measured by the number of post-treatment seizures, the time between treatment and the first sixty-second interval free of electrographic seizures, and the duration of SE. Secondary measures were the severity of hippocampal neuronal injury 24 hours after induction of SE and the frequency of spontaneous recurrent seizures recorded at least 6 weeks after SE. Our treatment was designed to counteract the loss of inhibition due to internalization of synaptic GABAA receptors, by allosterically stimulating GABAA receptors with benzodiazepines). We added a drug which enhanced inhibition at a non-GABA site, since GABA agonists can only partially restore GABA inhibition in this model. Finally, we tried to reduce glutamatergic excitation due to an increased number of synaptic NMDA receptors by treating with NMDA antagonists. We administered treatment intraperitoneally after the second convulsive seizure, since preliminary experiments showed that by that time (approximately 20 min. after injection) benzodiazepine pharmacoresistance had developed.

Benzodiazepine monotherapy reduced mortality from 52% to 7% (5 mg/kg diazepam) or less (10-20 mg/kg) but did not stop seizures even at a dose of 20 mg/kg (Dz20), which induced a deep coma. The number of post-treatment seizures was 100 ± 7 in sham-injected controls and 100±8 after 20 mg/kg DZ (N.S.). Monotherapy with ketamine 10 mg/kg, valproate 30 mg/kg, brivaracetam 10 mg/kg, diazepam (1, 5 or 10 mg/kg), and other antiepileptic drugs also failed to stop SE. Combinations of diazepam (1 mg/kg) with ketamine 10 mg/kg + valproate 30 mg/kg (DZ + K + V), reduced the number of post-treatment seizures to 8 ± 2 ($p<0.001$ compared to DZ or C) while causing mild ataxia and preserving the righting reflex (to-

xicity score 1.3), while DZ20 severely impaired locomotion and the righting reflex. Some two-drug combinations were also significantly more effective than monotherapy in this model. Synergism between drugs was strongly suggested by several methods. These results suggest that polytherapy can be more effective and less toxic than monotherapy in the treatment of cholinergic SE, and that the optimal therapy of SE and acute seizures may be based on different principles than that of chronic epilepsy.

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References

Treiman et al, (1998), New Engl. J. Med,339: 792-98; Naylor et al, (2005), J. Neurosci., 25:7724-33; Goodkin et al, (2008), J. Neurosci., 28:2527-38; Chen & Wasterlain (2006), Lancet Neurol, 5:246-56; Tetz et al. (2006), Toxicol Ind Health.22:255-66.

P01

Diagnostic value of ictal neuroimaging techniques (Spect , angioTC, MRI) in patients with non diagnostic EEG and clinical suspicion of nonconvulsive status epilepticus

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Introduction: Cerebral perfusion Spect imaging (SPECT) and other neuroimaging techniques have been used in the differential diagnosis of epileptic and psychogenic seizures and also in the differentiation between nonconvulsive status epilepticus (NCSE) and different forms of encephalopathy although the information about it diagnostic value in these situations is still scare. Our purpose is to present the utility of different neuroimage techniques in the diagnostic of NCSE when the EEG is no clear.

Methods: Seven patients with clinical suspicion of a NCSE and a non diagnostic video-EEG (normal or with periodic pattern) were included. Periodic lateralized epileptiform discharges (PLEDS) or generalized epileptiform discharges (GPEDs) were the most frequent periodic pattern. Ictal Spect or angioTC or MRI were done in these patients.

Results: In four patients an ictal Spect was done, in two and MRI and in 1 an angioTC. In three patients (2 ictal Spect,1 angioTC) a focal hyperperfusion were observed, in two (ictal Spect) a generalized patchy hypoperfusion and in the restant two focal cortical oedema or hemispheric cortical laminar necrosis (on MRI studies). Five patients were diagnosed and treated as NCSE and two patients were diagnosed and treated as encephalopathy. Interictal neuroimage techniques were done in four of the five patients diagnosed of NCSE and cortical perfusion normalization were observed in all of them.

Conclusions: 1Spect and other neuroimaging techniques maybe useful in diagnosing NCSE when video-EEG is unconclusive. 2Association of PLEDS and focal hyperperfusion on SPECT, confirm PLEDs as an ictal pattern in patients with suspicion of NCSE.

P02

Intravenous Lacosamide in clinical practice – patients to be reported to an independent registry

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Background: Most common clinical studies on antiepileptic drugs do not reflect medical everyday practice due to their strict in- and exclusion criteria and treatment regimen.

Methods: Here we present an open, prospective, non interventional registry study with the aim to collect systematically data on safety, tolerability, and administration procedures when a solution for intravenous (i.v.) infusion of Lacosamide (marketed as Vimpat) is used in routine daily clinical practice. The observed treatment period will take up to 10 days which is regarded as the critical period in which either a treatment effect can be determined and a treatment emergent adverse event can be observed. The primary efficacy variable is the incidence of treatment emergent adverse events. In a national multicenter approach from February 2011 until February 2013 Lacosamide i.v. treated patients of all ages will be reported together with their clinical data (e.g., age, seizure and epilepsy types, pre-treatment, treatment adjustments, outcome) to an independent institution.

Results: This registry is based on the results of an earlier Levetiracetam registry of the same authors, which gave insight of the i.v. use of Levetiracetam (presented at the Innsbruck Colloquium on Status Epilepticus in Innsbruck 2009). The data will help treating physicians to optimize the use of Lacosamide i.v. in clinical routine.

Conclusion: Our presentation here will give an overview of the method, expectations, and limitations concerning this kind of registry.

P03

MicroRNA expression profiles in mice with spontaneous recurrent seizures following pilocarpine-induced status epilepticus

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MicroRNAs (miRNAs) participate in the pathogenesis of various diseases by altering protein expression. In the current study, we examined the miRNA expression profile in the brains of mice with pilocarpine-induced status epilepticus (SE), a model of chronic epilepsy with spontaneous seizures. Sixty days after SE, when the mice have developed chronic epilepsy, 15 miRNAs were changed in the hippocampus and 10 in the cortex. Five miRNAs (miR-199b, miR-203, miR-223, miR-451, and miR-455) were up-regulated in both the hippocampus and cortex. At earlier time points (6 h, 7 d, and 28 d), which is during the latent phase of the disease, 5 miRNAs showed prominent changes in expression. These data should serve as a resource for further research on miRNA and may lead to targeted miRNA-based approaches in the treatment of epilepsy.

P04

Development and Characterization of Multi-Drug Resistant Epilepsy Model in Mice

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Drug resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. Even with a variety of AEDs and several non-pharmacological applications, about 30% of patients with epilepsy are refractory to drug-treatment. Patients with intractable temporal lobe epilepsy (TLE) exhibit an increased risk of psychiatric comorbidity, including depression, anxiety, and sociality. In the present study, we evaluated whether the number of spontaneous recurrent seizures (SRSs) and behavioral alterations in epileptic mice are different in AED non-responders compared to AED responders. AEDs were selected as their broad spectrums of efficacy, e.g. levetiracetam and valproate. In the chronic SRS-phase of pilocarpine-induced status epilepticus (SE) model of c57/bl6 male mice, we tested the efficacy of levetiracetam (twice daily injections for 7 days) with continuous video-EEG monitoring, and could sort out the responder group (75~100% decrease in seizure frequency) and non-responder group (0~25% decrease). Then, we treated the levetiracetam-nonresponsive group with valproate (twice daily injections for 7 days), and sorted again. After all these procedures, we obtained the responders (~70%) and multidrug-resistant nonresponders (~30%). In several anxiety- and hyperexcitability-related behavioral tasks, the non-responders showed markedly increased risk of behavioral abnormalities compared to responders and non-epileptic controls. Future study with microarray will help to uncover some genes involved in drug resistant or intractable epilepsy.

P05

Does etiology of epilepsy predispose to status epilepticus?

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Background: Some epilepsies are more prone to develop status epilepticus (SE) than others. We aimed comparing etiologies of chronic epilepsy in patients with (wSE) and without SE (w/oSE).

Methods: Large database of adult epilepsy patients (n=6899, 3198 women), registered 1975-2010, was analysed. SE (no acute symptomatic cases) was defined as a seizure lasting longer than 10 minutes (for convulsive SE) or 30 minutes (for non-convulsive SE) or seizure series without function regain between seizures.

Results: wSE group comprised of 323/6899 (4.7%) patients (132 women, median age -55 years [range 43-74]; median age at seizure onset -26 years [range 11-56]. In patients wSE, the rate of symptomatic epilepsies (211/323, 65%) was significantly higher than rates of idiopatic (55/323, 17%) or cryptogenic (57/323, 18%) epilepsies if these rates were compared to ones in patients w/oSE: symptomatic (3330/6576, 50%), idiopatic (1351/6576, 20%), cryptogenic (1895/6576, 29%). The rates of idiopatic and cryptogenic epilepsies did not differ in patients wSE vs. w/oSE. Two groups (wSE vs. w/oSE) did not differ if main etiologies of epilepsy were compared in patients with symptomatic epilepsies: vascular (80/211, 38% vs. 1031/3330, 31%), cerebral tumor (23/211, 11% vs. 400/3330, 12%), post-traumatic (23/211, 11% vs. 513/3330, 15%), perinatal injury (22/211, 10% vs. 440/3330, 13%), CNS infection (18/211, 8% vs. 205/3330, 6%) and malformations of cortical development (18/211, 8% vs. 244/3330, 7%).

Conclusions: Symptomatic epilepsies are more inclined to develop SE compared to idiopatic or cryptogenic epilepsies. In symptomatic epilepsies, specific etiologies do not play a predisposing role for development of SE.

P06

Status epilepticus in patients with malformations of cortical development

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Background: Malformations of cortical development (MCD) are increasingly recognised as a major cause for pharmacoresistant seizures, neurological deficits and cognitive disturbances. MCD occur due to disrupted neuronal proliferation, migration and/or organization. We aimed to identify MCD spectrum in patients with status epilepticus (SE) and compare clinical features of patients with MCD and SE (wSE) to those with MCD and without SE (w/oSE).

Methods: We identified 220 patients (116 women; median age 28 years, range 20-44) with MCD and chronic epilepsy in large adult and children epilepsy units. All patients were clinically examined, underwent EEG and MRI. SE (no acute symptomatic cases) was defined as a seizure lasting longer than 10 minutes (for convulsive SE) or 30 minutes (for non-convulsive SE) or seizure series without function regain between seizures.

Results: SE was observed in 15/220 (7%) of patients with MCD (10 women; median age 21 years, range 11-34). MCD spectrum included six patients with focal cortical dysplasia, three with polymicrogyria, two with microcephaly and single patients with tuberous sclerosis, hemimegalencephaly, periventricular nodular heterotopia and ganglioglioma respectively. MCD due to abnormal neuronal proliferation, migration and organization were equally distributed in patients wSE and w/oSE. Earlier seizure onset was observed in patients wSE (median age 24 months, range 12-84) compared to those w/oSE (median age 132 months, range 24-204; p=0.020). There was no difference between two groups with regard to other clinical features.

Conclusions: MCD patients with earlier seizure onset were more prone to develop SE.

P07

Description of Four Cases of Simple-Partial Status Epilepticus Presenting as Epileptic Aphasia

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Introduction: Epileptic aphasia is not uncommon as part of partial complex seizures, but it is rarely described as the solely manifestation of simple partial seizures or status epilepticus.

Methods: We describe four cases of self-awareness difficulty in elaborating language as the unique presentation of status epilepticus, diagnosed between July 2008 and December 2010. All patients were aphasic for more than 30 minutes. The diagnosis was made by neurologists and based on clinical features plus EEG findings or clear response to antiepileptic drugs, with exclusion of acute structural aetiologies on MRi.

Results: Two of the patients were women. Ages ranged between 49 and 69 years old (median of 55 years). In three cases an EEG was obtained while the patient was aphasic. One patient had a previous diagnosis of epilepsy and three cases were of acute symptomatic origin. Benzodiazepines were used as first-line AED in three cases with an excellent response. Follow-up information was obtained: three achieved an excellent control and one patient recurred despite of different schemes of AED treatment, in relation with the underlying disease.

Conclusion: Isolated epileptic aphasia is a rare and difficult to diagnose condition to be aware of, though it can be the presenting symptom of status epilepticus in non-epileptic middle-aged patients.

P08

Non-convulsive status epilepticus (NCSE): The Greek experience after introducing EEG recording in the emergency department

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Introduction: NCSE is a neurological condition that is often missed or misdiagnosed in the emergency department. Methods: From June 2010 to February 2011, more than 200 patients were referred to our emergency department due to sudden behavioral abnormalities, decreased level of consciousness or prolonged confusional state after a generalized convulsive seizure.

Results: Having the possibility of immediate EEG recording, 16 patients were diagnosed with NCSE based on EEG patterns, such as PLEDS, GPEDS and BIPEDs.

According to generalized convulsive status epilepticus' treatment protocols, aggressive treatment with benzodiazepines, phenytoin, valproate or levetiracetam was initiated.

In most of the cases there was no immediate clinical or EEG response. On the other hand, the adverse events of benzodiazepine and phenytoin administration were often evident.

The causes of NCSE proved to be brain tumor, degenerative or demyelinating disease, stroke, encephalitis, electrolyte disturbances, sudden withdrawal of antiepileptic medication, high clozapine dosage, hyponatraemia due to oxcarbazepine and lupus encephalopathy.

Treatment of the underlying disease was initiated, phenytoin, valproate or levetiracetam were administered regularly and daily EEG recordings were captured.

Clinical improvement and EEG normalization were evident in patients with reversible NCSE causes. On the other hand, patients suffering from severe viral encephalitis or brain tumors never regained consciousness, their EEG patterns remained unchanged and died weeks or months afterwards.

Conclusions: EEG recording proved to be an extremely valuable tool in emergency neurology in the diagnosis of NCSE. Furthermore, NCSE does not require aggressive treatment as the clinical outcome is mostly influenced by the underlying disease.

P09

Clinical Characteristics and Prognosis of Febrile Status Epilepticus in Korean Children

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Background: febrile status epilepticus (FSE) is not uncommon and may be a life threatening emergency. This study is aimed to evaluate the clinical manifestations of FSE and its prognosis in Korean children.

Methods: A total of 86 children were involved in the study. Forty three children with FSE from January 1, 2002 to December 31, 2010 were enrolled and 43 with simple febrile seizure (FS) at their ages were selected as control group. Clinical data obtained from each group were retrospectively analyzed for clinical features and prognostic factors.

Results: The age of subjects ranged from 3 month to 5 years (FSE 43; M;F 19:24, 24.9±16.5 months, FS 43; M:F 19:24, 25.1±16.2 months). The most common etiologies for both groups were upper respiratory infections and nonspecific viral illnesses. Temperature at the time of seizure was higher in children with FSE than in those with FS ($P<0.05$). Seizure types, family history, previous history and recurrence of FS were not different between two groups. Abnormal findings on Brain MRI (13% vs 0%) and EEG (7% vs 0%) were more common in children with FSE, but were not statistically different. The development of afebrile seizures or epilepsy was more common in children with FSE (10% vs 5%), but were not statistically significant (OR 0.48, CI 0.08-2.75, $P>0.05$). None of children with FSE was dead during the admission.

Conclusion: As compared to FS, children with FSE appear to be at higher risk for afebrile seizures or epilepsy. However, they seem to develop normally when treated appropriately at the time of event regardless of the duration of seizures.

P10

New Onset Refractory Status Epilepticus: Outcomes and role of immunotherapy

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Introduction and Background: Cryptogenic new onset refractory status epilepticus (NORSE syndrome) has been described in both adults and children, and is often associated with poor outcome. The condition may be triggered by as yet unidentified infections or immunological mechanism. We present a patient with NORSE and good functional neurological outcome with early immunotherapy. We have identified four other patients with NORSE syndrome treated at our centre.

Methods: Case notes review of the index case and four other patients at the Greater Manchester Neurosciences Centre was undertaken obtaining details of clinical presentation, imaging and CSF findings, infectious/inflammatory tests, management of seizures, immunotherapy and outcome. Description of the initial case and summary of clinical characteristics of others will be presented.

Results: Case 1 was a 26 year old male with a prodrome of headache and vomiting. He developed refractory multifocal and generalised seizures. Seizures recurred on withdrawal of barbiturate anaesthetic up until day 29. MR imaging, CSF examination and viral/autoimmune investigations were all normal other than positive anti-TPO antibodies and he had previously treated hypothyroidism. He was initially treated with aciclovir and antibacterials. IV steroids were administered day 12 and IV immunoglobulin day 18. He made a good recovery being discharged home 2 months after admission. Seizures recurred on withdrawal of steroid therapy, and required longer term immunosuppressant treatment with azathioprine.

Conclusion: In our experience immunotherapy has been associated with good outcomes in NORSE, but multicentre collaborative RCTs are required to establish the role of immunotherapies in the management of NORSE.

P11

Buccal midazolam or rectal diazepam for ongoing seizures - what is best?

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Objectives – We wanted to compare the effect and tolerability of buccal midazolam with rectal diazepam as emergency treatment in adults with convulsive or non-convulsive status epilepticus. We also wanted to find out what treatment option the patient and nursing staff preferred.

Materials and methods – 80 consecutive convulsive or non-convulsive seizures lasting more than 5 minutes were treated alternating with rectal diazepam or buccal midazolam. The dose of each study drug was tailored individually. The primary outcome was defined as termination of seizure activity within 10 minutes without seizure relapse within 2 hours.

Results – Convulsive status epilepticus was treated after a mean of 6.2 minutes, and terminated faster with buccal midazolam than with rectal diazepam; i. e. after a mean of 2.8 vs. 5.0 minutes, respectively (n=0.012). There were no significant difference between the midazolam group and the diazepam group in time to seizure cessation in the other subcategories of emergency situations (7.4 minutes vs.7.6 minutes).

The success rate was 83.3% in the diazepam group and 74.4% in the midazolam group (NS). The difference was mostly due to slightly more seizure relapses during the first 2 hours in the midazolam group. Temporary tiredness was the most frequent reported side effect. All the nursing staff and six of the seven patients who gained experience with both treatment options favoured the buccal route.

Conclusions – To ameliorate acute seizures, buccal midazolam appeared to be at least as effective as rectal diazepam with little or no side effects. The buccal administration was easy to handle and socially more acceptable than the rectal route.

P12

Investigations of neurophysiology in human health and disease: Effects of mental arithmetic and music on EEG

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Aim: A study investigating effects of mental arithmetic and classical music on EEGs using new ADI equipment.

Methods: EEG and heart rate was recorded from 17 healthy undergraduates during eye opening, mental arithmetic tasks and while listening to classical music, using closed eyes as the control. The EEG from the left frontopolar-occipital (O1-Fp1) and parietal (P8-P7) bipolar electrode positions was filtered into frequency bands delta (0.1-3.5Hz), theta (4-7.5Hz), alpha (8-13Hz), beta (14-30Hz) and gamma (30-50Hz) using LabChart7 software for analysis.

Results: Eye opening showed a significant decrease in alpha activity. The addition arithmetic task showed a significant decrease in alpha amplitude (30.6%Ø, P<0.05 in O1-Fp1 and 27.4%Ø, P<0.05 in P8-P7) and power (3.5%Ø, P<0.001 in O1-Fp1 and 2.5%Ø, P<0.001 in P8-P7). Similarly, the multiplication arithmetic task showed a significant decrease in alpha amplitude (33.9%Ø, P<0.001 in O1-Fp1 and 29%Ø, P<0.001 in P8-P7) and power (2.1%Ø, P<0.001 in O1-Fp1 and 3.1%Ø, P<0.001 in P8-P7). Furthermore, both arithmetic tasks showed increased heart rate. Listening to classical music decreased the beta power (1.5%Ø, P<0.01 in O1-Fp1). Although some significant changes in other bands were seen, the presence of artefacts makes their validity debatable.

Conclusion: Although artefacts created some discrepancies, the ADI equipment has recorded EEG data and shown a statistically significant difference between groups, in accordance with previous findings. Future EEG research using this new equipment could be simpler and more cost effective. Furthermore, it is more patient-friendly than traditional EEG machines, and may increase efficiency in terms of neuropsychiatric diagnoses.

P13

Histopathology of Resistance Generalized Convulsive Status Epilepticus

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Prolonged generalized convulsive Status Epilepticus (PGCSE) is characterized by severe disorders of all vital activity systems mainly respiratory, homeostatic and hemostatic ones. Are these disorders the consequence of functional disturbance or also of arising during PGCSE structural brain disorders? Old classics histologists described massive acute brain alterations, but did not find their presence in hypothalamus (Sommer W, 1880; Spielmayer W, 1926) or even denied them (Scholz W, Hager H, 1956).

Purpose: Study of condition of viscera organs and brain of dead connected with PGCS patients.

Methods: Macro- and microscopic investigation of brain and visceral organs of 4 dead patients. Duration of PGSE was 10 hours – 6 days. All had clinical homeostatic disorders (hyperthermia, metabolic acidosis, etc). Direct death causes were profuse gastric bleeding, thromboembolism of the pulmonary artery, acute adrenal gland insufficiency, syndrome of disseminated intravascular coagulation. The peculiarity of our investigation was the examination of frontal serial cuts of hypothalamus and hypophysis. The following basic methods of straining were used: hematoxylin-eosin, of Nissl, gold-sublimate of Cajal, methods of Snesarev, Spielmayer and Gomori. .

Result: Common finds were the plethora of viscera organs, edema, dystrophy and focal necrosis of muscles, that predominates in intercostals musculi. The main neuron alteration was severe acute dystrophic disorders: swelling, ischemic, wrinkling, karyocytolysis. Astrocytes were subjected both to degenerative (clasmatodendrosis, decomposition of bodies and processes) and proliferative (satellitosis. gliofibrosis) changes. Maximum of disturbances was revealed in hippocampus and hypothalamic regions, particularly neurosecretory nuclei, where about 30% cells were visualized as formless fragments of microvacuolar cytoplasm.

Conclusion: Arising during PGCSE disorders of the homeostatic system is the consequence of severe hypothalamic destruction.

P14

Convulsive status epilepticus as initial manifestation in tetramethylenedisulfotetramine poisoning patients

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Introduction: Tetramethylenedisulfotetramine (TETS), a banned neurotoxic rodenticide, has been shown repeatedly to cause mortality in healthy people in China. The typical symptoms include seizures, bellyache, vomiting, and headache. Convulsive status epilepticus (CSE) as initial manifestation in TETS poisoning is not common and requires timely recognition and prompt treatment. Our objective is to highlight CSE as an initial manifestation of TETS poisoning and emphasize the need for prompt diagnosis and management.

Methods: We collected demographic and clinical manifestations of CSE as the initial manifestation of TETS poisoning in 9 patients. The clinical features, treatments (combined anti-convulsant and anti-toxicity treatment), and prognosis are discussed in this descriptive case series.

Results: Eight patients lived in rural areas. All patients presented with CSE and had TETS poisoning confirmed with laboratory analyses. Because patients presented in CSE, a history of TETS poisoning was often lacking. Typical findings were structurally normal in MRI, EEG with abnormal and prominent slow background waves after control of CSE, multiple organ dysfunction syndromes (MODS), and high mortality.

Conclusion: TETS poisoning should be considered as a potential etiologic factor in those who present with CSE but have no clear history of TETS exposure. It is difficult to control CSE due to TETS. Prompt diagnosis and combined treatment including anti-convulsant treatment, elimination of TETS and supportive therapy are required. Additionally, it is important to educate the public, especially in rural areas about the risk of life-threatening toxicity of TETS.

P15

The etiology of convulsive status epilepticus: a study of 220 cases in Western China

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Introduction: To investigate the etiology and the prognostic factors for convulsive status epilepticus (CSE) in Western China.

Methods: A consecutive registration and prospective observation of 220 cases with CSE in Sichuan Epilepsy Center was performed from 1996 to 2007 to study the etiology. Logistic regression model was used to analyse the relationship between etiology and demographics, duration, outcomes or complications of CSE.

Results: The mean age was 37.5±20.31 years. Most CSE (63.2%) were acute symptomatic ones with central nervous system (CNS) infections (32.7%) as the primary cause was. 50% patients had a past history of epilepsy. 30.9% CSE in patients with pre-existing epilepsy occurred due to discontinuation and reduction of antiepileptic drug (AED). Anoxia / poisoning ($p<0.05$, OR 8.0, 95%CI 1.34-47.77) was an independent predictor of mortality. CNS infections ($p < 0.001$, OR 8.99, 95% CI 3.52-22.92), cerebrovascular diseases ($p = 0.001$, OR 6.75, 95% CI 2.11-21.61) and anoxia/poisoning ($p<0.01$, OR7.64, 95%CI1.93-30.21) were major risk factors for complications associated with CSE.

Conclusions: Compared with developed countries, CNS infections seemed to be more common in developing countries as a cause of CSE. Noncompliance with AEDs in patients with epilepsy is a prominent and avoidable trigger of CSE.

P16

Status epilepticus in the intensive care unit: frequency, management and impact on outcome

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Introduction: Refractory generalized convulsive (GCSE) and some forms of non-convulsive status epilepticus (NCSE) are treated by anaesthetising agents and managed in an intensive care unit (ICU).

The aim of our study was to examine clinical features, risk factors, management and outcome among patients admitted with GCSE and NCSE.

Methods: We retrospectively reviewed notes or electronic files of ICU patients admitted with status epilepticus (SE) over the last 10 years.

Results: 66 patients (33male, 33female) of age range 17 - 85 years (mean 38.66 years) were admitted over a ten year period (2001-2010). 94% fulfilled a diagnosis of GCSE, 4% of NCSE. The yearly prevalence of SE was of 5%. The most common identified causes of SE were infectious and autoimmune encephalitides, congenital disorders and neoplasias. Mean duration of ICU admissions was of 14 days (range 2 – 85 days) with hospital acquired pneumonia, sepsis and refractory seizures on weaning anticonvulsants as the main side effects hampering recovery. The average fatality rate per year was of 6.6% and age the main mortality risk factor. Intravenous treatment with barbiturates or propofol was titred against a burst suppression pattern and followed, in refractory cases, by administration of Levetiracetam or Topiramate. In some cases, the intravenous route was superior to the nasogastric route to prevent breakthrough seizures. A subgroup of patients was successfully treated with intravenous immunoglobulins and steroids.

Conclusions: Timely treatment of GCSE and NCSE with anaesthetising agents, prevention and management of side effects and expert opinion contribute to a better neurological outcome.

P17

Treatment of status epilepticus in a large community hospital

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Background: Status epilepticus (SE) is a neurological emergency usually requiring instant medical treatment. Due to the lack of adequate studies, treatment guidelines and their application vary between countries and institutions.

Methods: We retrospectively identified patients from a large community hospital in northern Germany who had been diagnosed with SE between August 2008 and Juli 2010. Their charts were reviewed regarding sociodemographic variables, treatment and outcome.

Results: We identified 170 episodes in 141 patients with a median age of 71 years (range 18-90 years). The etiology was acute symptomatic in 28 episodes, progressive symptomatic in 25 episodes and remote symptomatic in 117 episodes. Presentation was generalized convulsive in 58 episodes, non-convulsive in 74 episodes and simple motor in 38 episodes. Median latency from onset to treatment start was 0.5hours (range 0.1 – 336 h). In 161 episodes (96%), SE could be terminated. Initial treatment consisted of benzodiazepines in 166 episodes (success rate (SR) 41%). For second line therapy, levetiracetam (81 episodes, SR 47%), phenytoin (36 episodes, SR 47%), lacosamide (32 patients, SR 41%) and valproate (17 episodes, SR 41%) were used, usually levetiracetam preceding phenytoin, valproate and/or lacosamide. Further therapy included a large variety of anticonvulsant and/or anesthetic drugs. Relevant side effects occurred with benzodiazepines and phenytoin. No relevant adverse events were documented that could be related to levetiracetam or lacosamide.

Conclusion: Status epilepticus can be terminated successfully in the vast majority of the patients treated in a large community hospital. The success rate of the most commonly used agents seems to be between 40% and 50% for each treatment escalation step.

P18

Successful outcome of episodes of status epilepticus after implementation of vagus nerve stimulator: A multicenter study

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Introduction: Vagus nerve stimulation (VNS) has been reported as an effective treatment for refractory epilepsy in patients who are not good surgical candidates; it has also been implanted acutely to treat refractory status epilepticus. The aim of this study is to describe the effect of VNS in patients with a history of episodes of status epilepticus before implantation.

Methods: From a series of 60 total adult patients with refractory epilepsy who had VNS implanted in three tertiary centers of Spain between 2000 and 2010, 11 patients had a previous history of repeated episodes of status epilepticus. We analyzed the seizure and status epilepticus outcome after implantation. Stimulation was started at the usual settings and intensity increased according to clinical response.

Results: Mean age at VNS implantation was 29.82[14-51] years. Epilepsy duration until the implantation was 21.55[5-39.5] years and the mean follow-up since the implantation was 42[12-72] months. Mean seizure frequency decreased from 36.91 to 7.82 per month, including secondarily generalized seizures and those occurring in clusters. Interestingly, 6 out of 11 patients with a previous history of status epilepticus remained free of new episodes of status epilepticus after implantation, and 2 of them had the frequency of status decreased by ≥50%. Adverse effects were mild or moderate in intensity and included dysphonia and cough.

Conclusion: In those patients with refractory epilepsy who are not surgical candidates, VNS is a safe and effective method to reduce seizure frequency. In those patients with repeated status epilepticus, it may also help to control these life threatening events.

P19

Rapid cell-specific plasticity of AMPA receptors on the principal hippocampal neurons during experimental status epilepticus

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Introduction: Plasticity of AMPA receptor mediated transmission during status epilepticus has not been investigated in detail.

Methods: AMPA receptor (AMPAR) properties in hippocampal principal cells: CA1 Pyramidal neurons and dentate granule cells were studied following in vivo or in vitro SE using electrophysiological, biochemical, immunochemical and imaging studies.

Results: AMPAR currents recorded from CA1 neurons obtained from animals that experienced pilocarpine-induced SE for either 10 or 60 min exhibited inward rectification and sensitivity to block by philanthotoxin-433, whereas in the dentate granule cells, these changes were observed only in animals that experienced SE for 10 min. Biotinylation studies using hippocampal slices revealed an associated decrease in the surface expression of the GluR2 subunit. Similarly, in vitro SE in cultured pyramidal neurons resulted in a time dependent reduction in the surface expression of GluR2 subunit that was in part due to an enhanced rate of internalization of the subunit. Application of IEM-1460, a selective blocker of GluR2-lacking AMPARs, reduced but did not terminate bursting in vitro. Further, IEM-1460 attenuated bursting induced increase in total intracellular calcium ([Ca]i) and the rate of [Ca]i accumulation. Finally, treatment with AMPAR antagonist, GYKI 52466 after the development of SE terminated pilocarpine-induced SE in a dose-dependent manner suggesting the utility of AMPA antagonists in the treatment of SE.

Conclusion: Together these studies demonstrate dynamic, cell-specific expression of calcium-permeable, GluR2-lacking AMPARs during SE. AMPA receptors could be targeted to terminate SE.

P20

Pathophysiology and antiepileptic drug therapy in Tumour associated epilepsy and its implications in Status Epilepticus

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Introduction: Seizures occur in 20-45% of patients with brain tumours. They are also at risk of developing Status Epilepticus (SE). This reinforces the importance of adequate therapeutic management of Tumour associated epilepsy (TAE).

Method:

A retrospective chart review was done, of twenty patients who presented with TAE from 2006-2009. The type and location of the tumour, type of seizure experienced, choice of antiepileptic drugs (AEDs) were noted. A literature review was undertaken. MEDLINE was searched for systematic reviews from 1950 to 2010, twenty eight journal articles were selected. Comparisons were made between the retrospective chart review and the literature review. Treatment complications and implications in SE were investigated.

Results: Multi-factorial pathophysiological mechanisms involving a complex interplay between histological, anatomical, biochemical, physiological and genetic factors have been suggested. Contrary to literature, complex partial seizures (30%) were more common compared to simple partial seizures (10%). Similar to literature, lesions in the frontal (35%) and temporal (50%) lobes had the highest epileptogenecity compared to the occipital (5%) lobe. SE occurred in 15% of the patients. Even though Valproate and Levetiracetam was the best combination of AEDs suggested, it was only used in 10% of patients. Instead Valproate and Phenytoin were used (20%). Phenytoin was preferred in SE (66%) and in monotherapy (25%) instead of Levetiracetam. However treatment complications exist.

Conclusion: The best choice of AEDs remains controversial due to the underlying pathophysiological complexity. Type of seizure, treatment complications and individual patient factors therefore need to be considered. Development of novel therapies targeting multiple pathophysiological mechanisms coupled with intrinsic antineoplastic activity would be desirable.

P21

Refractory Status Epilepticus: response to combo anaesthetic therapy

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Introduction/Background: Refractory Status Epilepticus (RSE) occurs in upto 30% of status epilepticus with higher mortality. These are usually treated with "an" IV anaesthetic agent. We describe a patient with RSE that responded to combination of anaesthetic agents.

Methods: We present a 19yr old male with prior HSV encephalitis and intractable epilepsy, who was treated for RSE with IV Propofol and Thiopental together.

Results: The patient (50 kg) presented with multiple seizures and encephalopathy over 24 hours. Following IV Lorazepam and Phenytoin load, he continued to have clinical seizures. He was intubated and, started on Midazolam and Fentanyl infusions that helped initially, however breakthrough seizures occurred inspite of AED maintenance. EEG confirmed status epilepticus. Then, Propofol infusion was started (after bolus of 1mg/kg) and increased until 5mg/kg /hour. Despite this seizures persisted, so additional Thiopental was given at 3mg/kg bolus followed by 1mg/kg/hour maintenance, which was cautiously titrated up keeping systolic blood pressure (SBP) above 90mmHg. Burst-suppression occurred in 2 hours and near-complete suppression by 5 hours of therapy (both Thiopental and Propofol at 5mg/kg/hr). Propofol was stopped after 2 hours due to concerns of adverse effects that caused electrographic seizure recurrence. The Propofol was restarted and both infusions continued for another 48 hours. The Propofol was then weaned off by 1mg/kg/hr due to drop in SBP followed by Thiopental after 24 hours at 0.5mg/kg/hr. No seizure occurred, however patient's recovery was prolonged.

Conclusion: Combined treatment with Propofol and Thiopental may be cautiously used to abort RSE in select patients.

P22

Psychogenic Status Epilepticus

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Introduction/Background: Psychogenic status epilepticus (PSE) can be seen in upto 78% of patients with Psychogenic Non-Epileptiform Seizures (PNES). It's imperative to recognize such patients to avoid unnecessary investigations, admissions and mistreatment. Clinical semiology of patients with PSE is under recognized. Objective of our study was to define clinical features of patients with PSE

Methods: We included all patients diagnosed with PNES on the basis of VEEG monitoring, who had event lasting > 5 minutes in duration. We reviewed their demographics, history, event semiology, EEG, EKG and MRI brain.

Results: Seven patients (2 Male, 5 Female) met the criteria for PSE. Average age was 24.7 years (range16-37), with mean (+ SD) history of events was since 27.9(+32.5) months. PSE lasted average of 14.3 minutes (range 5-42 minutes). All patients had abrupt onset of the event and a post ictus slowed recovery. Semiological features that were common to all patients were eye closure at the onset, unresponsiveness to verbal and painful stimuli and low intensity motor manifestations. The motor activity exhibited by the patients included intermittent variable tremors, arching of the neck and back, facial grimacing, lip smacking, tightening of fists, unilateral head turning and posturing of limbs. Hyperventilation was seen in 5 and groaning was in 3 out of 7 patients. No abnormal EEG and EKG correlate was present. MRI was normal in all patients.

Conclusion:PSE was seen in young, majority females. Eye closure at onset, unresponsiveness and low intensity motor manifestations may help in earlier recognition of such patients.

P23

A malignant variant of nonconvulsive status epilepticus

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Background: We propose the term malignant nonconvulsive status epilepticus (mNCSE) for those cases of ambulatory partial or generalized refractory NCSE (rNCSE) where clinical and EEG NCSE remain uncontrolled even after standard parenteral benzodiazepines (e.g. lorazepam); parenteral second line agents (e.g. phenytoin, valproate or levetiracetam); and at least an initial anesthetic agent (e.g. propofol, midazolam, pentobarbital) while the patient is monitored for at least five days.

Methods: We retrospectively analyzed the clinical characteristics, EEG records, brain MRI scans, antiepileptic therapy and prognosis of six subjects fulfilling the criteria for mNCSE.

Results: Four women and two men, were studied; mean age =42.8 years (range 19-63 years; SD, 19.1). Two out six had a previous diagnosis of epilepsy. Four patients died during mNCSE. Two patients had a good outcome with return to consciousness and activities of daily living. One subject developed temporal lobe epilepsy after mNCSE. In four patients, the cause of mNCSE was encephalitis. In three subjects, the clinical presentation was an alteration of the mental state as consequence of complex partial status epilepticus (CPSE). One patient had refractory atypical absence status epilepticus (ASE). The mean duration of the NCSE episode was 47.5 days (range 9-139 days, SD 53.1). Antiepileptic treatment was heterogeneous, and patients were treated with an average of 6.0 AED (range 3-10; SD, 3.0).

Conclusions: Malignant NCSE, resisting even anesthetic agents, is a severe epileptic condition that occurs most frequently in the context of encephalitis. Although a high mortality is frequent, a few patients may survive with normal recovery.

P24

A multicenter, open-label trial to assess the safety and tolerability of a single intravenous loading dose of lacosamide followed by oral maintenance as adjunctive therapy in patients with partial-onset seizures

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Introduction/Background: An IV loading dose of lacosamide is desirable when rapid titration is necessary but current dosing instructions recommend weekly titration. This trial examined safety and tolerability of a 15-minute lacosamide intravenous (IV) loading dose, followed by oral maintenance treatment at common target doses, in patients with partial-onset seizures (POS).

Methods: Subjects were 16-60 years old and taking 1-2 AEDs. Consecutive 25-subject cohorts were given three progressively increasing doses of lacosamide (200, 300, 400mg) administered IV over 15 minutes. A fourth cohort of 25 subjects repeated the 300mg dose to provide safety data on 50 subjects at the highest well-tolerated dose at this infusion duration. Subjects received the loading dose followed 12hrs later by the equivalent daily dose administered orally twice daily for 6.5 days. Safety evaluations

included adverse events, 12-lead ECGs, vital signs and laboratory parameters. Lacosamide and AED plasma concentrations were measured.

Results: Overall, adverse events were dose-dependent. Within the first 4 hours following infusion, dizziness, somnolence, nausea, and diplopia were common in subjects receiving 400mg (44%, 26%, 19%, and 1% respectively); less common for 300mg subjects (19%, 17%, 4%, and 0%); and infrequent for 200mg subjects (4%, 0%, 0%, and 4%). Seven patients withdrew from the trial, all due to adverse events; 3(6%) from the 300mg cohorts, and 4(16%) from the 400mg cohort.

Conclusions: IV loading doses of 200mg and 300mg lacosamide administered over 15 minutes were best tolerated. The 400mg loading dose was less well tolerated, due to a higher frequency of dose-related adverse events.

P25

A Case of Epilepsy Presenting as Insomnia Only; Insomnia Symptom may be related to Rhythmic Discharges

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Introduction: There is no reported case of a patient with frontal lobe epilepsy presenting as insomnia only, to my knowledge. We are reporting a patient who had complained of only insomnia, but will likely be ascertained as epilepsy.

Methods: A 55 year old male visited our sleep disorder clinic to evaluate his insomnia. Since last year, he complained he only sleeps 2-3 hours without sleeping pills. He denied having any previous seizure history or sleep problems before that time. He denied having any subjective symptoms, even during the period of rhythmic discharge, except sleep disturbance.

Results: His EEG showed rhythmic evaluation patterns during his waking state. His EEG showed a build up of rhythmic sharp discharges that poorly lateralize and localize to the right and fronto-central areas; if he were awake throughout that would make it more likely frontal. During all of the rhythmic evaluation periods, the patient was fully awake, had no abnormal behavior, and was talking normally. His MRI showed abnormally high signals on the left frontal gyrus in FLAIR. And his SPECT study (SISCOM) shows focal hyperperfusion in the same areas. When we tried Keppra 1000mg and Lyrica 150mg, there was mild improvement in his rhythmic discharges. However, his insomnia was much improved.

Conclusion: Our patient's symptom presenting as only insomnia is related with his rhythmic discharges. His rhythmic discharges may be from a frontal lesion based on his MRI and SPECT findings. Perhaps insomnia only, can be the main presenting symptom of frontal lobe epilepsy.

P26

Mood change and mutism in the elderly and status epilepticus

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Introduction: The incidence of status epilepticus is higher in the elderly and their prodromal symptoms could be unspecific and subtle. Here we report three cases whose prodromal symptoms of status epilepticus were mood changes and mutism. Convulsive status epilepticus followed in the case presented with mood change, and non-convulsive status epilepticus was found via EEG in the other 2 that had mutism.

Method: We identified three cases who were admitted to our hospital during October 2010. The disease courses, past medical history, in-hospital investigations and treatments, and the conditions upon discharge were reviewed.

Result: All three cases had status epilepticus following subtle and unspecific changes of cognitive function. One had convulsive status epilepticus, one had epilepsia partialis continua, and the third one had non-convulsive status epilepticus with unidentifiable jerks. They all had complicated medical history but epilepsy: two had old ischemic stroke, and one of them also had liver cirrhosis and co-

lon cancer. The third had DM with impaired renal function and DM polyneuropathy. Each of them received at least 2 EEGs during hospital days and showed marked epileptiform discharges: one had generalized epileptiform discharges, and all of them had PLEDs. Two cases expired, and the survived has not regained his usual cognitive function.
Conclusion: Although subtle, prodromal symptoms can be identified in the elderly before status epilepticus happened. EEG is a useful tool in diagnosing non-convulsive status epilepticus particularly in the elderly who exhibit subtle changes of cognitive function.

P27

Efficacy of intravenous lacosamide in refractory nonconvulsive status epilepticus and simple partial status epilepticus

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Introduction: Nonconvulsive status epilepticus and epilepsia partialis continua are common epileptic conditions for which straightforward recommendations based on controlled randomized trials for treatment in therapy refractory courses are still lacking.
Methods: In a large retrospective study on drug efficacy in status epilepticus we identified patients treated in our department by searching for the term "status epilepticus" in the electronic archive of medical reports of our clinic. Here we present the subset of data concerning those patients treated with Lacosamide. To control for age dependency of results we calculated a Pearson correlation coefficient with age as independent variable and return to baseline = 1, worsening of condition = 2 and death in hospital = 3 as dependent variables.
Results: Ten episodes of status epilepticus (two epilepsia partialis continua, nine nonconvulsive status epilepticus) in nine patients could be analyzed. Lacosamide was given in dosages of 50 mg to 100 mg. It was not earlier administered than as fourth drug. Nevertheless it seemed to be effective in 20% of the episodes. The outcome seemed mainly to depend on age of patients ($r = 0.94$, explaining 89% of variance!).
Conclusion: Lacosamide may be a useful therapeutical approach in refractory nonconvulsive status epilepticus. But after all it seems hard to evaluate the efficacy of a drug in a medical condition, where outcome seems mainly to depend on age of patients.

P28

Role of Mg-RBC and temporal-parietal-occipital EEG epileptiform activity in FSS and Complex partial epilepsy

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Background: Magnesium is a potential modulator of seizure activity because of its ability to antagonize the excitatory calcium influx through the N-methly-D-aspartate (NMDA) receptor.
Aim of this Study: Influence of Magnesium deficiency on epileptic discharge in FSS and Complex partial epilepsy
Methods: Thirty patients with focal sensory seizure (FSS) and Complex Partial epilepsy (15 females and 5 males, mean age: 30,9) were diagnosed according to the classification of ILAE. FSSs were subdivided according to the type of sensation in somatosensory, simple visual or oculosensory, viscerosensory, and experiential sensations,who have definitive epileptogenic EEG activity in the temporal-parietal-occipital area.
10 ml of venous blood sample was collected and measured red blood cells magnesium concentrations by atomic absorption spectrometry (850nm, Perkin-Elmer 3030).
Results: We determined lower RBC magnesium concentrations (<1.80-/+0.24) are associated with focal spike and waves complexes in 55% of FSS and complex partial epilepsy patients during seizures.
Conclusions: low RBC-Mg could be a peripheral expression of the reduced brain magnesium concentration observed in FSS and complex partial epilepsy patients

P29

Topiramate and Status Epilepticus: Outcome of 8 Cases

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Background: Status epilepticus (SE) is an emergency condition that requires prompt and proper management. Topiramate is a new anti-epileptic medication but experience with topiramate in the treatment of SE is limited.

Methods: We reported clinical features and outcomes of eight patients with SE who treated with oral topiramate.

Results: Five patients were convulsive SE and three patients were non-convulsive SE. The first three common causes of SE were post-stroke, encephalitis and uremic encephalopathy. Oral topiramate was used as first, second, third, and fourth line therapy in one, three, three, and one patient, respectively. Loading dose of topiramate was 400 mg with the maintenance dose of 200 mg/day. Outcome of seizure controlled were complete controlled (25%), stopped seizure, but recurrent seizure (62.5%) and partially controlled (12.5%). No adverse event was recorded.

Conclusion: Topiramate has a potential effect in the treatment of SE; particularly in situations where other anti-epileptic medications cannot be used.

P30

Outcome of Status Epilepticus in North-East of Thailand

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Introduction: Status epilepticus (SE) is one of the common neurological emergencies in adult and for which morbidity and mortality are high and associated with an appropriate management or underlying diseases. In Thailand, the healthcare system is comprised of primary care hospitals, secondary care hospitals, and tertiary care hospitals. Medical personnel and facilities are different among each level of hospitals. This study aims to compare clinical presentations and treatment outcome of SE between university hospital (Srinagarind hospital) and secondary care hospital (Nong Khai hospital).

Materials and Methods: We retrospectively reviewed medical records of patients diagnosed as SE at Srinagarind hospital (January 1, 1995 to December 31, 2005) and Nong Khai hospital (January 1, 2006 to December 31, 2009). Clinical manifestations and outcomes were compared by descriptive statistics.

Results: We enrolled 40 and 80 patients with SE from Srinagarind hospital and Nong Khai hospital, respectively. Most patients were male (57% & 69%; the first number representing data from Srinagarind hospital). Generalized tonic clonic were found in 85% and 94%, respectively. The first three common causes of both sites were acute symptomatic (53% & 42%), previous epilepsy (28% &23%), and post-stroke (15% & 23%). Regarding outcomes, Srinagarind hospital site had higher number of patients with dependent status (35% vs 10%, p value 0.002) and lower number of patients with complete recovery (30% vs 59%, p value 0.005). The mortality rate was not different between both sites (34% & 31%, p value 0.836).

Conclusion: The outcomes of SE may be different between healthcare facilities and better in time.

P31

Intravenous Lacosamide as Treatment of Status epilepticus in Children – A Small Case Series

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Background: Lacosamide (LCM) is a new antiepileptic drug (AED) which enhances slow inactivation of the sodium channel. In adults, the intravenous application seems to be an effective alternative in the acute treatment of status epilepticus. In children, however, use of LCM still remains off-label and only few case reports exist.

Methods: 4 children clinically presenting a status epilepticus were successfully treated with intravenous LCM in our hospital between November 2008 and April 2010. Baseline demographic data, etiology and type of status epilepticus, first-line antikonvulsants, dosage of LCM, effects and tolerability were reported.

Results: Two patients presented a generalized convulsive SE, one a non-convulsive status and one a complex-partial status. Diagnoses included encephalitis, shaken baby syndrome, cerebral palsy and an unclear syndrome with multiple contractures. The age range was 2;5 months to 14;5 years.

LCM was introduced after other typical first- and second-line antikonvulsants as benzodiazepines, phenytoin, levetiracetam and propofol had failed. LCM was administered in an iv. bolus from 8,5 to 18 mg/kg/d. After addition of LCM seizure activity stopped promptly. No relevant adverse effects or interaction with other AEDs were seen during the course of treatment. Two patients maintained LCM as monotherapy, two patients received a combination with valproate and levetiracetam respectively.

Conclusion: Despite our limited experience, we believe that Lacosamide should be taken into consideration for the treatment of status epilepticus in children after failure of standard approaches. Moreover, long-term effects seem to be favourable. Controlled clinical studies of lacosamide in pediatric patients are needed.

P32

Sequencing of the ACCN2 gene in status epilepticus does not identify pathogenic mutations

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Background: Animal studies suggest that the acid-sensing ion channel 1a (ASIC1a) plays a role in seizure termination and severity. Specifically, disruption of ASIC1a in mice increases seizure duration and progression 1. We postulated that mutations in ACCN2, the gene encoding human ASIC1a, play a role in status epilepticus (SE).

Methods: We retrospectively identified 33 patients with refractory SE (defined as seizure duration > 30 minutes). We sequenced all coding exons and splice sites of the ACCN2 gene. Novel variants were genotyped in 229 ethnically matched controls and 56 further SE patients using TaqMan technology.

Results: Sequencing of all 11 coding exons identified four known polymorphisms and two novel intronic variants (c.837+58T>G, present in 6/33 patients and c.1435+208G>A, present in one patient). Genotyping of the two novel variants in 229 control samples showed no statistically significant difference between patients and controls for c.837+58T>G. For c.1435+208G>A, we observed a trend for overrepresentation of GA heterozygotes in patients compared to controls. However, genotyping of c.1435+208G>A in another 55 SE samples failed to confirm this trend.

Conclusions: Exonic mutations in the ACCN2 gene do not seem to contribute to SE in this population. Our study does not exclude a role for deep intronic variants or large deletions in ACCN2.

References: 1. Ziemann AE, Schnizler MK, Albert GW, et al. Seizure termination by acidosis depends on ASIC1a. Nat Neurosci 2008;11(7):816-22.

P33

Preliminary experience in the use of IV lacosamide in the treatment of refractory status epilepticus and seizure clusters

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Introduction: Status epilepticus (SE) and seizure clusters (SC) are life-threatening conditions for which few evidence-based guidelines exist. In particular, there are little data available regarding the use of novel AEDs. Recent case series suggest that lacosamide (LCM) might be an efficient and safe drug in SE. We report our preliminary ex-

perience with IV LCM as an adjunctive therapy in patients with refractory SE and SC.

Methods: We retrospectively identified patients with either SE or SC who received IV LCM between October 2010 and February 2011. Continuous video-EEG monitoring was performed in every patients.

Results: Ten patients (7 non convulsive SE and 3 partial SC) were identified. LCM was used as third-line agent in 5 patients and as fourth-line agent or more in 5 patients. SC stopped in one patient within one day after onset of LCM administration. Six patients required further drugs before seizure cessation. Two patients died before SE could be controlled. Seizures worsened in one patient on LCM, which led to treatment discontinuation. No other serious adverse events occurred but doses had to be decreased after SE termination in two patient due to side effects.

Conclusions: In our small series, LCM is a relatively well-tolerated IV agent in the treatment of SE and SC. In particular, no cardiac adverse events were noted.

When given late in the course of refractory SE or SC, its efficacy is low.

Randomized controlled trials are needed to assess its efficacy as a second-line drug.

P34

Autoimmune limbic encephalitis with antibodies to leucine-rich glioma inactivated 1 protein and N-type-voltage-gated-calcium-channels presenting as pilomotor status epilepticus

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Limbic encephalitis (LE) is characterised by amnesia, confusion, seizures, personality changes or psychosis with hippocampal abnormalities. Onset is typically subacute over few weeks or months but may evolve over days.

We present a 71-year-old woman with a LE with antibodies to leucine-rich glioma inactivated 1 protein (LGI1) and N-type voltage-gated-calcium-channels (VGCC). The patient presented with simple focal seizures with unilateral piloarrection and secondarily generalised tonic clonic seizures. This unusual seizure semiology was misdiagnosed as somatoform disorder and panic attacks, therefore she was treated with SSRIs and Benzodiazepines. Additionally she complained memory problems and behavioural change with obsessive-compulsive features. Her pilomotor seizures repeated frequently forming continuous seizure activity for six hours. Ictal EEG revealed right temporal rhythmic theta. IV-Lorazepam (4mg) and IV-Levetiracetam (1000mg) did not control seizures. Further loading dose of IV-Lacosamide (400mg) controlled status completely. 3T-MRI of the brain and CSF were normal, serum sodium 128 mmol/L. After a course of IV-immunoglobulins followed by Methylprednisolone (10mg/kg) the seizures remained controlled over 3 months and the behavioural changes improved.

LGI1 gene is mainly expressed in the hippocampus and responsible for autosomal-dominant partial epilepsy with auditory features. Typical clinical features of LE with antibodies to LGI-1 are seizures, confusion, hyponatraemia and sleep disorders. Antibodies to N-types-VGCC have been described in a patient with LE with epilepsy in a patient with small cell carcinoma of the lung. However screening with FDG-PET-CT-scan of the whole body did not reveal any malignancy and the clinical significance of these antibodies in our patient remain undetermined.

P35

Variations in susceptibility to electroshock-induced seizures in rats with different degrees of brain dysplasia

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Brain dysplasias of different genesis show variations in their susceptibility to seizures depending on the neurochemical specificity of pharmacological agents used to evoke seizures. To verify a discrepancy between the data obtained using different pharmacological models, repeated electrical stimulation was applied here. Pregnant Wistar rats were exposed to a single 1.0 Gy dose of gamma rays on gestation days 13, 15, 17 or 19 (E13, E15, E17

and E19, respectively). From the postnatal day 60, their male offsprings were subjected to 21 daily electrical stimulations to evoke seizures. Tonic and clonic reactivity to electrical stimulation showed opposite profiles of changes and significantly differed from those previously observed following pilocarpine or kainic acid administration in rats irradiated at the same developmental stages. Generally, the rats irradiated on E17 showed minimal intensity of tonic and maximal of clonic seizures. On the contrary, very high tonic and low clonic reactivity was observed in rats irradiated on E13 or E15. Rats irradiated on E19 showed intermediate features. Interruption of neurogenesis on different stages of prenatal development evoked functionally critical but still poorly defined various structural modifications that could switch the rat brain from the tonic to clonic reactivity or vice versa. Those intergroup differences revealed using neurochemically non-specific electrical stimulation proved that susceptibility to seizures did not depend on the absolute degree of neuronal deficit but on the developmental stage at which the dysplasia was produced. The differences indicated to what extent the observed phenomena could be modified by different pharmacological models of epilepsy.

P36

Specific features of status epilepticus caused by metabolic diseases in children

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Purpose of the study was evaluation of clinical features and response to treatment in children with status epilepticus (SE) caused by different metabolic diseases (MD).

Method: Investigation included children 2-16 years aged with first and recurrent SE caused by different MD. SE was defined as an acute epileptic condition characterized by continuous seizures for at least 30 minutes, or by 30 minutes of intermittent seizures without full recovery of consciousness between seizures. The same protocol for SE treatment was used initially, while in further episodes approach was changed according previous response to the drug and side effects.

Results: Thirty one SE episodes in 12 patients mean aged 6.67 years were enrolled. Etiology was heterogeneous: mitochondrial disease (4), ceroidlipofuscinoses (3), M. Sanfilippo (1), M. Krabbe (1), M. Nieman-Pick (1), M. Lafora (2). Dominate SE types were: complex partial (20) and secondary generalized (11). Six cases experienced epilepsia partialis continua during disease course. Mean SE duration was 169.2 minutes. For SE treatment was given: midazolam (14) in combination with dexamethason (4), phenobarbital (10), diazepam (6), thiopental (3), levetiracetam (3), propofol (1). Adverse events were observed: respiratory depression due to diazepam (2) and phenobarbital (2), while prolonged comma due to prolonged infusion of midazolam (6), diazepam (2), phenobarbital (2) and thiopental (1). Two cases continued seizing till death.

Conclusion: Specific features of SE caused by MD were long duration and complex partial as dominate SE type. Frequent adverse effects contributed changing in therapeutically approach in SE caused by MD.

P37

Status epilepticus in 12 day old rats leads to progressive hippocampal atrophy and epileptogenesis

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Effects of status epilepticus on hippocampal morphology and functions in rats younger than 2 weeks are still unclear.

SE was induced by pilocarpine (40 mg/kg) in P12 rats pretreated with LiCl 24 h earlier. Acute hippocampal damage was assessed with FluoroJade B up to 1w after SE. To determine impairment of hippocampus-related functions, development of habituation was assessed using repeated exposure to the open field; three mo after SE animals were tested in Morris water maze. To diagnose epilepsy, animals were video/EEG monitored for 5 days 5 or 7 mo after SE, and then the hippocampus was morphologically examined. The number of hilar neurons was stereologically estimated and the volume of the hippocampus was assessed.

In acute phase, degenerating neurons were detected in all hippocampal fields. Severity and distribution of damage among hippocampal subfields were highly related to the interval after SE. Functional tests revealed developmental delay of habituation and cognitive impairment expressed as a worse performance in Morris water maze. Epilepsy was diagnosed in 50% and 87.5% of animals 5 and 7 mo after SE, respectively. Morphometric analysis revealed progressive hippocampal atrophy. Hippocampal volume was reduced by 6.9% and 18.8% 5 and/or 7 mo after SE, respectively. The density of neurons in the septal hilus was reduced by 20% and 35.5% compared to controls.
Early SE leads to impairment of hippocampus-dependent functions, development of epilepsy and hippocampal atrophy in adulthood.

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P38

Does status epilepticus modify the effect of ifenprodil on cortical epileptic afterdischarges in immature rats?

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Ifenprodil is a subunit-specific antagonist of NMDA receptors, it binds only to receptors containing NR2B subunit markedly expressed in immature rat brain. NR2A subunit increases during the postnatal development and NR2B becomes less important. Previously we found that anticonvulsant action of ifenprodil against cortical epileptic afterdischarges (ADs) decreases during the third postnatal week in rats. The aim of the present experiment was to check if status epilepticus (SE) induced in rat pups at postnatal day 12 affects the developmental change in ifenprodil action.
Lithium-pilocarpine model of se was used. Epileptic activity in 12-day-old rat was after 2 hours interrupted by paraldehyde and pups were returned to mothers. Control animals received saline instead of pilocarpine, other treatment was identical. Cortical stimulation and recording electrodes were implanted to 15-, 18-, 21- and 25-day-old rats; one hour after surgery low-frequency stimulation was repeated with increasing intensities. Ifenprodil (20 mg/kg i.p.) was administered after the ninth stimulation (current intensity in this stimulation was 3.5 mA) and stimulation continued up to 15 mA. Duration and pattern of ADs was evaluated.
There were only moderate differences between SE and control rats at postnatal days 15 and 18. Even these small changes disappeared with further development - 21- and 25-day-old rats did not exhibit any difference.
The moderate changes at a short time after SE may be interpreted as developmental delay rather than as a sign of brain damage.

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P39

Stiripentol Is Anticonvulsant In Benzodiazepine-Resistant Status Epilepticus

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Introduction: Benzodiazepines (BZDs) are first-line therapy for treatment of status epilepticus (SE). However, BZD treatment is negatively affected by seizure duration due to a decrease in BZD-sensitive GABAA receptors during prolonged SE. Stiripentol (STP) is a novel anticonvulsant that is a positive allosteric modulator of GABAA receptors. The subunit selectivity of STP at GABAA receptors suggests that it could continue to potentiate GABAergic inhibition during prolonged SE when GABAA receptors have become BZD-resistant. The goal of these studies was to determine whether STP is anticonvulsant in BZD-resistant rats.
Methods: SE was induced using lithium-pilocarpine in

male rats (5-65 days). After brief (first S3 seizure) or prolonged SE (45 min after first S3 seizure), STP or diazepam (DZP) was administered and the seizure score assessed. Whole-cell brain slice electrophysiology was used to study STP and DZP modulation of GABAergic currents in dentate granule cells during SE.

Results: STP was anticonvulsant and displayed substantially less pharmacoresistance than DZP during prolonged SE (2.7 fold increase in STP ED50 vs 12.5 fold increase in DZP ED50). In vitro STP potentiated GABAergic IPSCs, as well as tonic GABAergic current and this potentiation remained intact during prolonged SE. In contrast, potentiation of GABAergic currents by DZP was lost. Both IPSC potentiation and anticonvulsant activity of STP were greater in younger animals.

Conclusion: We suggest that STP is anticonvulsant by potentiating GABAergic inhibition and that the subunit selectivity profile of STP enables it to remain effective despite GABA receptor subunit changes during prolonged SE.

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P40

A Case of Prolonged Status Epilepticus with a good outcome: The Importance of Aetiology in determining prognosis

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Introduction: It is generally accepted that the longer the duration of an episode of status epilepticus the worse the prognosis. Indeed persistent seizure activity despite full anaesthesia after 24 hours is usually fatal. We present a case of NMDA receptor encephalitis with persistent status epilepticus lasting over 60 days with a good outcome and review the literature concerning NMDA receptor associated status epilepticus.

Methods: We present the case of a 33 year old woman, with no prior history of epilepsy, who presented to hospital with refractory status epilepticus.

Results: Seizures continued despite full anaesthesia, treatment with combinations of multiple AEDs (Sodium Valproate, Phenytoin, Phenobarbital, Topiramate, Clonazepam and Levetiracetam). NMDA receptor antibodies were detected in the serum with subsequent treatment with IV immunoglobulins, Rituximab and IV Magnesium. Seizures stopped after 63 days of persistent status epilepticus. The patient is still an inpatient 4 months after presentation (GSS 15) but is slowly recovering.

Conclusions

This case underlines the importance of aetiology in determining outcome even in cases of status epilepticus lasting many days. Indeed in cases of persistent refractory status epilepticus, a diagnosis of anti-NMDA receptor encephalitis should be considered. Subsequent treatment with immuno-suppression may result in seizure cessation with a good prognosis irrespective of seizure duration.

P41

Uncommon Causes of Status Epilepticus: A Systematic Review

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Introduction: The prognosis of status epilepticus is largely determined by the underlying aetiology. In many instances treatment of status epilepticus is ineffective unless the underlying cause is addressed.

Methods: We carried out a systematic review of the literature for uncommon causes of status epilepticus, defined as 'a cause not reported (or not included in a separate category because they were so rare, typically <1% of causes) in the major epidemiological studies of status epilepticus.

Results: 181 different causes were identified. These were easily categorised into 5 specific aetiological categories: immunological disorders, mitochondrial disorders, infectious diseases, genetic disorders and drugs/toxins. A sixth category of 'other causes' has also been included.

Conclusions: Knowledge of these causes is important for clinical management and treatment, and also for a better understanding of the pathophysiology of status epilepticus.

P42

Semiautomatic quantification of spiking in the evaluation of continuous spikes and waves (CSWS): sensitivity to settings and correspondence to visual assessment

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Introduction: Spike index (SI) indicates the proportion of the NREM sleep covered by CSWS. The aim of this study was to characterize the dependency of the semiautomatic quantification of SI on the a priori defined maximal inter-spike intervals (max ISI) and, to assess the validity of this method against the gold standard.

Methods: SI was analysed with a previously described semiautomatic method from ten overnight EEGs with abundant spiking during sleep. The analysis started with an automated spike search of manually selected spikes with BESA software. Spike detections were processed with a MATLAB -based script to obtain SI from both the whole night sleep as well as for all consecutive 20 min epochs. We analysed the dependency of SI on max ISI, the stability of SI over time and for variation in the spike search procedure. Finally, the semiautomatic method was compared with the quantification based on visual scoring by two neurophysiologists.

Results: Using max ISI of 3 seconds appeared to yield the best combination of sensitivity and stability in SI quantification. The SI of the first hour of sleep did not differ significantly from the SI of the whole night. Notably, the relative mean error of the semiautomatic method compared to the gold standard generated by expert markings was only 8%.

Conclusion: Semiautomatic quantification of SI is a robust and a clinically promising tool for assessing the quantity of spiking during sleep in the evaluation of CSWS. Max ISI of 3 seconds is recommended for the best stability and sensitivity.

P43

Posterior reversible encephalopathy manifested by refractory non-convulsive status epilepticus

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Introduction: Posterior reversible encephalopathy (PRES) is now a well recognized syndrome and epileptic seizures one of the most frequent symptoms. However, status epilepticus (SE) as initial manifestation is seldom reported. Chemotherapy is a possible trigger for PRES.

Material: Two cases are presented: a 19 years-old man with Hodgkin lymphoma under ABVD (Adriamicin, Vinblastine, Bleomicine, Dacarbazin), and a 44 years-old woman under Docetaxel and Gemcitabine for treatment of a femoral sarcoma developed refractory non-convulsive SE. Brain MRI allowed the diagnostic of PRES: both patients showed bilateral predominantly parieto-occipital lesions with restriction on diffusion weighted imaging. The first EEG recorded in the first patient showed two seizures in posterior right leads, associated with increased eye movements, when he was already on propofol; in the second patient, the first EEG disclosed multifocal periodic discharges at 3.5 Hz with a posterior predominance, and five nonconvulsive seizures in central leads. Both patients were successfully treated for the SE plus blood pressure control and nimodipine. The first patient repeated ABVD afterwards without recurrence of PRES. In the second patient, no further chemotherapy regimens where performed due to neoplasm refractoriness. Furthermore, both showed complete resolution of citotoxic edema on repeated MRI.

Conclusions: It is important to recognize PRES as a potential cause of SE because the appropriate management of SE includes the treatment of the underlying cause. Hence, the recognition of chemotherapy as a PRES trigger factor is determinant in order to perform an urgent MRI. PRES also requires early treatment to avoid irreversible parenchyma damage.

P44

A comparison of topographic and quantitative changes in the elemental composition of rat hippocampal formation during the acute and latent periods in the pilocarpine model of epileptic seizures

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Changes in elemental composition, especially in the contents of metals, are closely related with seizure-induced neurodegenerative processes observed in humans and in animal models of epilepsy. The present paper focuses on these changes in the rat brain following pilocarpine-induced seizures. Sixty-day-old rats received pilocarpine injections and were observed continuously for 6 hours following the injection. Six hours or three days after pilocarpine injection (acute and latent stages of seizure response), the animals were perfused and sections of their unfixed brains were mounted on the Ultralene foil and analysed using X-ray fluorescence microscopy. The multilayer monochromator was applied and the primary photon energy was set to 17 keV. The polycapillary optics was used for the focusing of the beam and the beam spot had the diameter of 15 micrometers. The X-ray fluorescence spectra were measured using the Vortex SDD detector and the time of single spectrum acquisition was 10 s. The analysis was performed within CA1 and CA3 sectors of the Ammon's horn, the dentate gyrus, its hilus and the neocortex. For these areas the mean masses per unit area of phosphorus, sulflur, potassium, calcium, iron, copper and zinc were calculated. When compared to the initial acute stage, the latent stage of seizure response to pilocarpine action was characterised by more numerous and significant variations. Ammong them, the most important changes were detected in the accumulation of copper and potassium in all the analyzed brain areas. The results indicate important involvements of the elements in post-seizure neurodegenerative but also neurorestorative processes.

P45

Safety and Efficacy of IV Lacosamide in Status Epilepticus and Seizure Cluster

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Background: Status epilepticus (SE) and seizure clusters represent neurological emergencies. Treatment requires immediate anticonvulsant therapy. The aim of our study was to assess safety and efficacy of IV lacosamide (LCM) in treatment of SE and seizure clusters. All patients were treated with Benzodiazepines as a first line treatment.

Methods: Patients with SE (convulsive or non-convulsive) as well as seizure clusters who were treated with IV LCM between December 2009 and November 2010 in two large Austrian Centers (Innsbruck 24 patients, Salzburg 12 patients) were retrospectively enrolled. Clinical data was extracted from patients' charts.

Results: 36 patients (18m/18f) aged 19-95 years (median 59) were enrolled. Seizure clusters occured in 13 patiens (4m/9f), SE emerged in 23 patients (14m/9f). SE could be further classified in convulsive SE (n=8), non-convulsive SE (n= 9) and simple focal SE (n=6). The following underlying etiologies could be detected: tumour – 9/36 (25%), brain trauma - 4/36 (11%), malformations of cortical development – 5/36 (14%), vascular – 4/36 (11%), encephalitis – 1/36 (3%), and others – 13/36 (36%). First dose mean of IV lacosamide was 226 mg (SD 65) and median 200 mg (range 200-400mg). IV LCM was used as second and third drug in most of the patients – 28/36 (78%). Side effects occured in 2 patients with pruritus and diplopia and nausea, respectively. IV LCM terminated seizure clusters in 11/13 (85%) patients and SE in 18/23 (78%) patients.

Conclusion: LCM is currently NOT approved for treatment of SE. However, our data show that IV LCM is safe and effective and may be an alternative to standard AED. Further RCT are needed to ascertain optimal treatment of seizure emergencies.

P46

Sporadic Creutzfeldt-Jakob disease presenting as refractory status epilepticus: two case report

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Background: Creutzfeldt-Jakob disease (CJD) is the most common transmissible human spongiform encephalopathy. Seizures and status epilepticus (SE) are an occasionally finding as presenting in CJD and create a diagnostic dilemma.

Methods: We report on two patients with a rapidly declining of consciousness and clinical picture and EEG suggestive of SE.

Results: The first patient was 67-year-old woman with two weeks of progressive cognitive declining, tremor involved the left upper extremity and "staring" spells in which she would be unresponsive. Who had EEG changes suggestive of non convulsive SE (NCSE): bilateral synchronous high amplitude, periodic sharp wave discharges (PSWD). Phenitoin, midazolam and propofol was used in Intensive Care unit. Brain MRI showed abnormal increased T2, FLAIR and diffusion signal involving the head of the right and left caudate and the right temporo-occipital cortex. She was later diagnosed with sporadic CJD. The second patient was a 62-year-old man with three weeks of episodic visual hallucinations and tremor on the left upper extremity that in last day onset myoclonic seizures involved left extremities. The EEG showed generalised high amplitude PSWD, and was refractory to several anti-epileptic drugs, adding to anesthesic. Brain MRI showed abnormal increased T2, FLAIR and diffusion signal involving the head of the right caudate and bilateral occipital cortex. He was later diagnosed with sporadic CJD.

Conclusions: Sporadic CJD should be considered as a differential diagnosis of apparent refractory SE, in patients who presents with rapid cognitive declining. EEG features and previous clinical events must to be considerer to harmful and unnecessary treatments can be avoided.

P47

Neurofilament heavy chain and HSP-70 as markers of seizure related brain injury

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Objective: Status epilepticus (SE) has deleterious effects on brain tissue, but whether brief recurrent seizures are also destructive to neurons is discussed controversial. The study aimed to analyze the levels of heat shock protein 70 (HSP-70) and neurofilament heavy chain protein (NfHSMI35) in cerebrospinal fluid (CSF) of patients suffering from seizures of different severity.

Methods: 42 patients were included, of whom 21 patients had a single seizure episode (SS), 11 with repetitive generalized tonic-clonic seizures (RS) and 10 with convulsive SE. Control group included 18 subjects. HSP-70 levels were measured using ELISA assay while NfHSMI35 protein with electrochemiluminescence immunoassay.

Results: Patients with SE ($p<0.001$) and RS ($p<0.05$) had higher CSF NfHSMI35 levels than controls, and SE had increased concentrations compared with SS ($p<0.001$). NfHSMI35 levels in SS did not differ from controls ($p>0.05$). SE patients had raised HSP-70 levels compared to RS ($p<0.05$), SS ($p<0.05$) and controls ($p<0.001$). SS and RS patients did not differ from controls ($p>0.05$). There was a significant correlation between CSF NfHSMI35 and HSP-70 levels ($r=0.4$; $p=0.005$), while the correlation disappeared when calculated among controls ($r=0.3$; $p>0.05$) or seizure patients ($r= 0.3$; $p=0.09$). In the subgroup of SE patients the correlation between NfHSMI35 and HSP-70 tended to be inverse but did not reach statistical significance ($r=-0.2$; $p>0.05$).

Interpretation: NfHSMI35 and HSP-70 might be potential biomarkers to identify subjects at risk of accumulating neuronal damage as the consequence of uncontrolled seizures.

P48

Prolonged seizure activity impairs mitochondrial bioenergetics and induces cell death

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Prolonged seizures are associated with cell death. The sequence of events leading to cell death and the differential impact of these events on neurons and astrocytes are, however, not fully understood. To determine cellular mechanisms of seizure-induced cell death, we have applied fluorescence imaging techniques to in vitro epilepsy models of rat neocortical co-cultures of neurons and astrocytes. Reducing magnesium or adding 4-AP to the bath medium induced glutamate driven calcium oscillations in neurons and, to a lesser extent, astrocytes. Under low magnesium conditions, neurons responded with a sustained depolarization of the mitochondrial membrane potential ($p<0.001$), that was dependent on glutamate release and NMDA receptor activation, as it was not observed after depleting vesicular glutamate with vacuolar-type H+ ATPase concanamycin A or blocking NMDA receptors with APV. Mitochondrial depolarization was cyclosporin A sensitive suggesting mitochondrial permeability transition pore opening. Neuronal ATP levels, measured as a change in [Mg(2+)](c), decreased significantly during prolonged seizures and correlated with the frequency of the oscillatory calcium signal, indicating activity-dependent ATP consumption. Astrocytes showed no changes in [Mg(2+)](c) after low magnesium treatment but exhibited a significant sustained hyperpolarization of mitochondrial membrane potential. Neuronal death was increased after two and twenty-four hours of low magnesium, compared to control treatment. Both neuronal and astrocytic cell death were reduced if the mitochondrial substrate pyruvate was supplemented. Our data highlight an important role of mitochondria in neuronal and astrocytic cell death after prolonged seizures and indicate that therapies aimed at rescuing mitochondrial function can prevent seizure-induced cell death.

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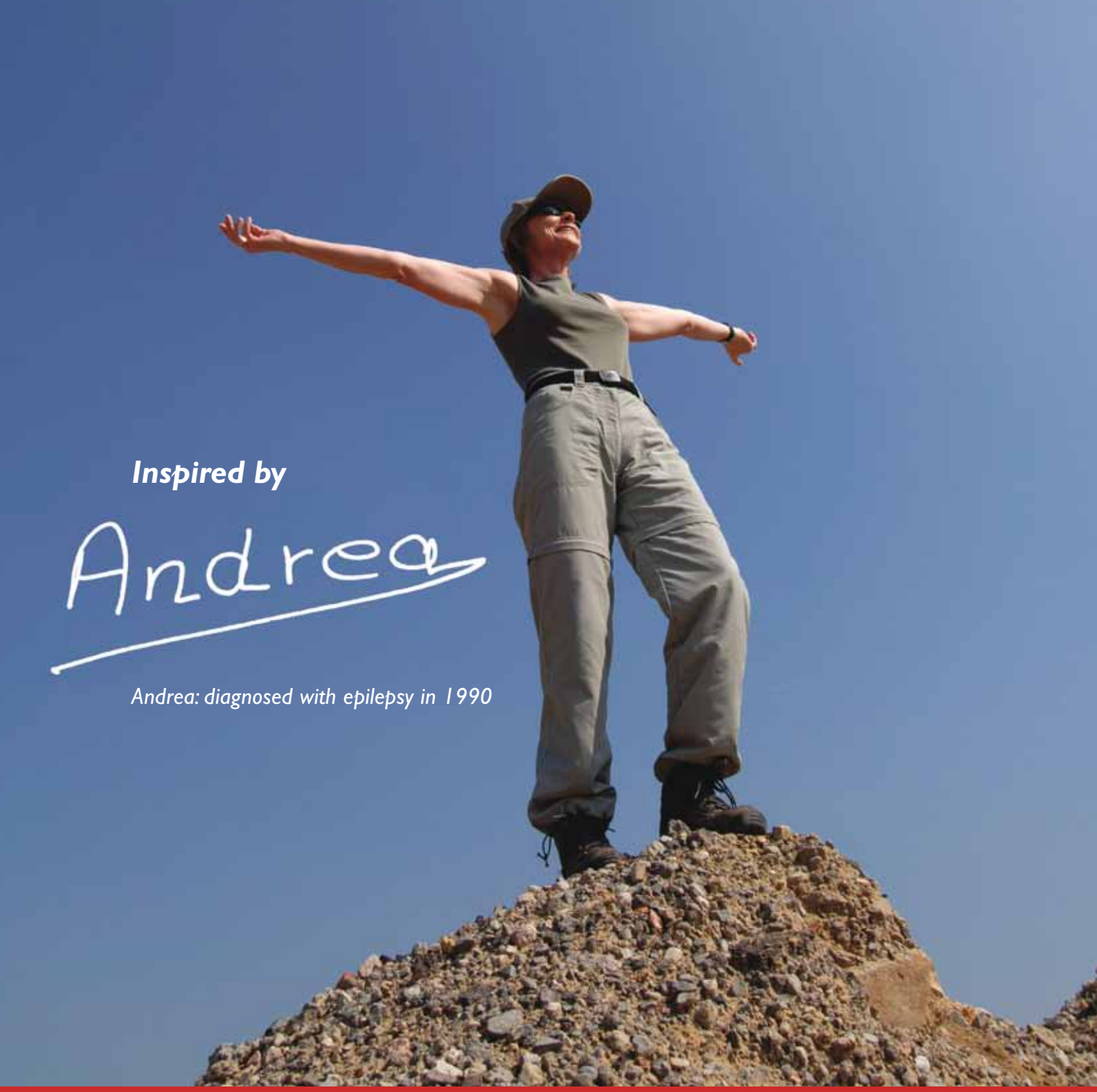

With her fear and denial of epilepsy behind her, Andrea looks forward to the possibilities ahead.

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