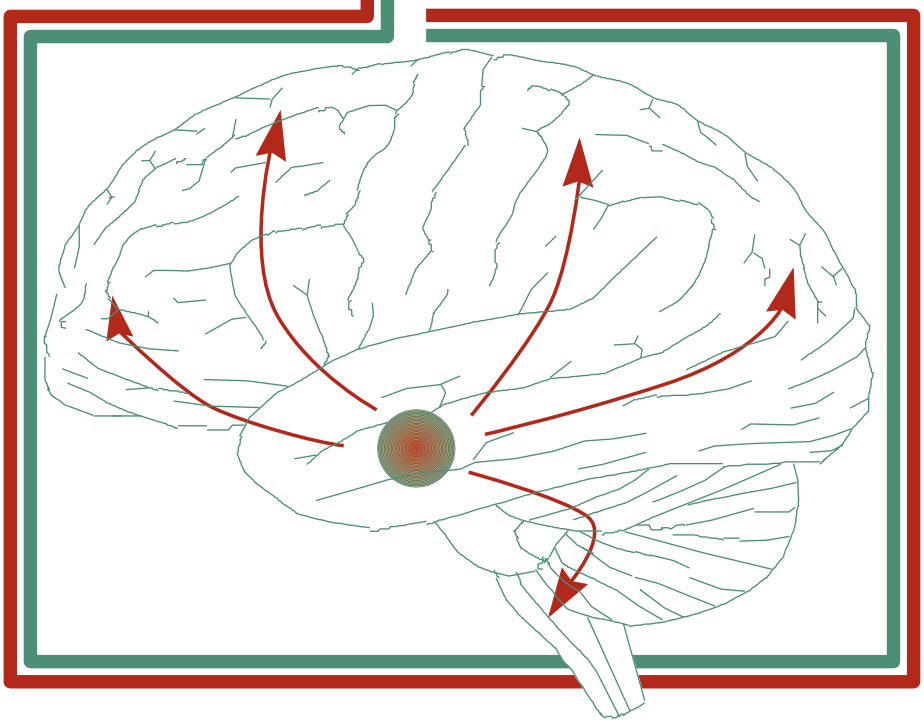
2008



THE 5th KUOPIO EPILEPSY SYMPOSIUM

Final Programme

March 28-29, 2008

Kuopio Music Centre, Kuopio, Finland

Welcome to Kuopio

On behalf of the Finnish Epilepsy Society and the Finnish Epilepsy Association, we cordially welcome you to participate in "The 5th Kuopio Epilepsy Symposium" in Kuopio, March 28-29, 2008.

The meeting will be the fifth in a series of epilepsy meetings that are organized jointly by the A.I.Virtanen Institute for Molecular Sciences and the Department of Neurology, University of Kuopio. The objective of the meeting is to present up-to-date knowledge of selected topics related to epilepsy. Both experimental and clinical data will be presented. We hope to bring together people working in the different fields of epileptology to facilitate the exchange of information and ideas, and to update our understanding of basic mechanisms, diagnostics and treatment of epilepsy.

Reetta Kälviäinen, Docent
Program Co-Chair of the Organizing Committee

Asla Pitkänen, Professor
Program Co-Chair of the Organizing Committee

The abstract book was edited by Dr. Anne-Mari Kantanen.

Friday, March 28, 2008

7:30 - Registration

Opening of the Symposium

08.30 - 08.45 Rector of the University of Kuopio: Matti Uusitupa

Program Co-Chair Dr. R. Kälviäinen

08.45 - 09.30 **Key note address:** Cortical Development and Cortical Malformations - An Overview
Speaker: Prof. Charles Raybaud (Canada)

Cortical Dysplasias

Chair: Prof. Asla Pitkänen (Finland)

09.30 - 10.30 Classification of Cortical Dysplasias for Clinical Practice
Speaker: Prof. Roberto Spreafico (Italy)

Coffee

11.00 - 12.00 Presurgical work-up and surgical treatment of cortical dysplasias
Speaker: Prof. Gary Mathern (USA)

Lunch

Hot Topics

Chair: Dr. Tapani Keränen (Finland)

13.00 - 13.30 Can we predict the outcome of combination therapy in localisation related epilepsy?
Speaker: Dr. Tapani Keränen (Finland)

13.30 - 14.00 Epilepsy Partialis Continua - What Are the Causes and How Is It Treated?
Speaker: Prof. Simon Shorvon (UK)

14.00 - 14.30 Early Development of Brain Activity: Structure vs. Function
Dr. Sampsa Vanhatalo (Finland)

Coffee

15.00 - 15.30 Seizure Prediction - How close are we?
Speaker: Dr. Brian Litt (USA)

15.30 - 16.00 Can Post-Surgical Memory Impairment be Predicted?
Speaker: Prof. Christoph Helmstaedter (Germany)

16.00 - 16.30 Deep Brain Stimulation - Is It a Real treatment Option in Epilepsy?
Speaker: Prof. Paul Boon (Belgium)

Prebanquet Session: Interactive epileptology through challenging case studies

Chair: Dr. Leena Jutila and Prof. Esa Mervaala

18.15 - 18.35	The History and Future of Epilepsy Surgery Speaker: Prof. Frederick Andermann (Canada)
18.35 - 20.00	Interesting cases from Kuopio Epilepsy Center Interactively voted and discussed with the audience Commentators: Dr. Eija Gaily, Dr. Kai Eriksson, Dr. Björn Falck

Banquet

20.00 - 22.00	Kuopio Music Centre

Saturday, March 29, 2008

Satellite Symposium of the Kuopio University Neuroscience Centre

Genetics and Pharmacogenomics: Hype, hope, and reality

Chair: Prof. Anna-Elina Lehesjoki (Finland)

08.00 - 08.45	**Key note address:** How Has Genetics Helped Us to Understand the Neurobiology of Epilepsy Speaker: Prof. Ingrid Scheffer (Australia)
08.45- 09.15	CNS Channelopathies with Epilepsy - Is There a Common Link between Co-morbidities? Speaker: Dr. Mikko Kallela (Finland)
09:15 - 09:35	Can Genetic Abnormality be Neutralized by Modulating Down-Stream Cascades - Update on Tuberous Sclerosis Speaker: Prof. David N. Franz (USA)
09.35 - 10.05	Pharmacogenomics - what has it added to our understanding about drug treatment Speaker: Prof. Sanjay Sisodiya (UK)
	Coffee Posters in the Hall of Light - Authors Present

Update of epilepsy research in Finland: selected abstracts

Chair: Prof. Hilkka Soininen and
Prof. Matti Vapalahti

Oral presentations I - V

10.35 – 10.50	Fibrillar β-amyloid associates with epileptic seizures in appswe/ps1de9 mice and changes excitability in cortical and hippocampal neurons Rimante Minkeviciene, Kuopio, Finland
10.50 – 11.05	Whole brain diffusion tensor image (DTI) analysis by tract-based spatial statistics (TBSS) in a kainic acid model of epilepsy. Alejandra Sierra Lopez, Kuopio, Finland
11.05 – 11.20	Myelinization in the *Cln8*^{mnd} central nervous system Mervi Kuronen, Helsinki, Finland
11.20 – 11.35	Use of navigated TMS and MEG for detailed functional localization before epilepsy surgery Anne-Mari Vitikainen, Helsinki, Finland
11.35 – 11.50	Unverricht – Lundborg disease (ULD): Magnetic resorance imaging with voxel-based morphometry in thirty patients and thirty matched controls Päivi Koskenkorva, Kuopio Finland

Lunch

Plenary lecture

13.00 - 13.45	Mechanisms of Drug-Refractoriness - How to Conquer the Problem in Clinical Practice Speaker: Prof. Wolfgang Löscher (Germany)

Syndrome identification as a basis for treatment decision

Chair: Prof. Heikki Rantala (Finland)

13.45 - 14.00	What is the Problem: How common is "Common Epilepsy"? Speaker: Dr. Reetta Kälviäinen (Finland)
14.00 - 14.30	Will Genetics Solve the Problem? Speaker: Prof. Jose Serratosa (Spain)
14.30 - 15.00	Role of Imaging in Practical Treatment Decision Speaker: Dr. Franck Semah (France)
15.00 - 15.30	Roundtable Discussion: Implications for Treatment Practice and Clinical Trials Participants: Speakers

Chair: Prof. Asla Pitkänen

15.30 - 15.45	Awards Ceremony Vaajasalo Foundation Young Investigator Award Epilepsy Research Foundation Awards Kuopio University Neuroscience Centre Award: Best neuroscience publication at the University of Kuopio in 2007
15.45 - 15.50	**Closing of The 5th Kuopio Epilepsy Symposium**

The congress website

www.uku.fi/epi2008.

Organizers

A.I.Virtanen Institute, University of Kuopio
Finnish Epilepsy Society
Department of Neurology, University of Kuopio
Finnish Epilepsy Association
Finnish Graduate School of Neuroscience
The Graduate School of Molecular Medicine, University of Kuopio
Kuopio Epilepsy Centre
Kuopio University Neuroscience Centre

Program Committee

Program Co-Chair: Docent Reetta Kälviäinen
Program Co-Chair: Professor Asla Pitkänen
Docent Tapani Keränen
Mrs. Pirkko Sormunen
Dr. Leena Jutila
Scientific Secretary: Dr. Anne-Mari Kantanen
Secretary: Ms. Tuija Parsons

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KEY NOTE ADDRESS:
CORTICAL DEVELOPEMENT AND CORTICAL MALFORMATIONS - AN OVERVIEW

Prof. Charles Raybaud, Canada

CORTICAL DYSPLASIAS

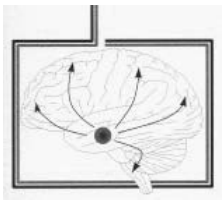
CLASSIFICATION OF CORTICAL DYSPLASIA FOR CLINICAL PRACTICE

Roberto Spreafico, MD, PhD
IRCCS Foundation Istituto Neurologico “C. Besta” , Milano, Italy

Classification is a creative activity that helps us to understand relationships and in no categories of disorders is classification more complex than in the field of epilepsy and of diverse malformations of the nervous system. (B. Sarnat). Malformations of cortical development (MCD) represent a heterogeneous group of focal and diffuse alterations of the cortical mantle resulting from a perturbation of developmental processes and they are increasingly recognized as the most frequent neuropathological substrate of focal epilepsies. The available imaging techniques has facilitated the in vivo diagnosis of MCD and basic research provided further informations in the understanding of different pathogenetic mechanisms.

Despite these advances there is still a lack of uniform, classification for these disorders helpful in clinical practice. In fact most of the current classifications are based on imaging identification of different malformative disorders visible at MRI frequently associated with genetically identified forms. However it should be noticed that despite the technological improvements, MRI is still failing in detecting some of the cortical malformations, particularly Focal Cortical dysplasia (FCD), in about 10-20% of the cases recognized by neuropathological studies after epilepsy surgery. While some forms of MCD are clearly defined, since the original observation of Taylor et al. (1971) FCD are variously grouped using disparate terminology and numerous attempts have been made in the last ten years for their classification.

The present report will be addressed at reviewing critically the available classifications reported in the literature on FCD and to correlate the findings based on imaging and electroclinical data with neuropathological diagnosis on post-surgical specimens with the aim to recognize clinical homogeneous groups allowing a presumptive diagnosis and prognosis.

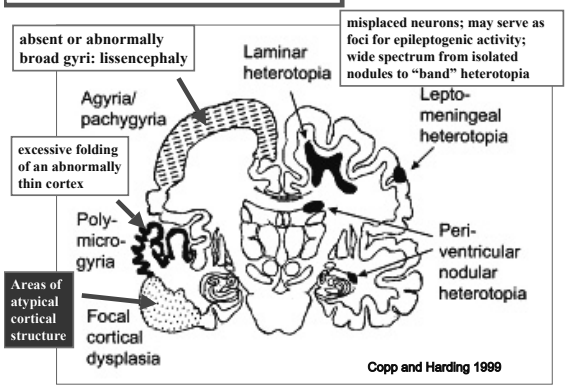


The 5th Kuopio Epilepsy Symposium
March 28 - 29, 2008

Classification of Cortical Dysplasia for Clinical Practice

Roberto Spreafico (Italy)

Malformations of Cortical Development



Classification system for malformation of cortical development

(A.J. Barkovich; R.I.Kuzniecky; G.D.Jackson; R. Guerrini; W.B.Dobyns- Neurology 2005)

I Malformations due to abnormal neuronal and glial proliferation or apoptosis
- A) Decreased proliferation/increased apoptosis or increased proliferation/apoptosis-abnormalities of brain size
- B) Abnormal proliferation (abnormal cell types)

II Malformations due to abnormal neuronal migration
- A) Lissencephaly/Subcortical Band Heterotopia spectrum
- B) Cobblestone complex/congenital muscular dystrophy syndromes
- C) Heterotopia

III Malformations due to abnormal cortical organization (including late neuronal migration)
- A) Polymicrogyria and Schizencephaly
- B) Cortical dysplasia without balloon cells
- C) Microdisgenesis

IV Malformations of cortical development, not otherwise classified
- A) Malformations secondary to inborn errors of metabolism
- B) Other unclassified malformations

Terminology and classification of the cortical dysplasias

A. Palmini, MD, PhD; I. Najm, MD; G. Avanzini, MD; T. Babb, PhD; R. Guerrini, MD; N. Foldvary-Schaefer, DO; G. Jackson, MD; H.O. Lüders, MD, PhD; R. Prayson, MD, PhD; R. Spreafico, MD, PhD; and H.V. Vinters, MD

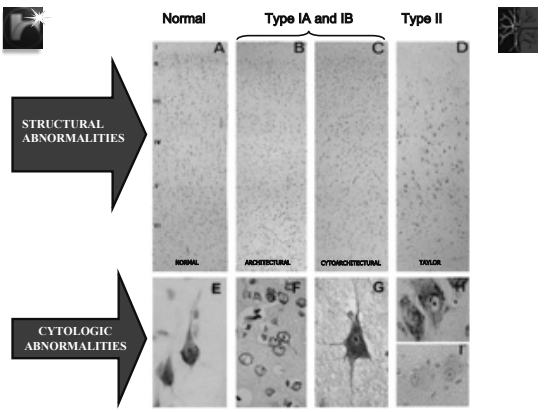
1. Mild MCD
- **Type I :** with ectopically placed neurons in or adjacent to Layer I
- **Type II :** with microscopic neuronal heterotopias outside Layer I

Structural Imaging: both types probably are not detectable by current MRI
Clinical relevance : no specific data delineating clinical or epileptic profile

2. FCD
- **Type IA :** isolated architectural abnormalities (dyslamination)
- **Type IB :** architectural abnormalities and giant or immature neurons

Structural Imaging : unclear in type I B
Clinical relevance : no specific data delineating clinical or epileptic profile
- **Type IIA :** architectural abnormalities with dysmorphic neurons without balloon cells
- **Type IIB :** architectural abnormalities with dysmorphic neurons with balloon cells

Structural imaging : increased cortical thickness, blurring grey/white matter, increased T2-weighted signal, mainly extra temporal
Clinical relevance : highly intrinsic epileptogenetic, high seizure frequency,



PRESURGICAL WORK-UP AND SURGICAL TREATMENT OF CORTICAL DYSPLASIAS

Prof. Gary Mathern, USA

CAN WE PREDICT THE OUTCOME OF COMBINATION THERAPY IN LOCALISATION RELATED EPILEPSY?

Dr. Tapani Keränen, Finland

EPILEPSIA PARTIALIS CONTINUA (EPC) - WHAT ARE THE CAUSES AND HOW CAN IT BE TREATED ?

Professor Simon Shorvon
UCL Institute of Neurology

Epilepsia partialis continua (EPC) is defined as ëspontaneous regular or irregular clonic twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body and continuing for hours, days or weeksí. The concept has an interesting history. The pathogenesis is controversial and different authorities have pointed to the possibility of a subcortical as well as cortical origin in some cases, and there is no doubt that an identical clinical condition can be produced by both cortical and subcortical pathology. Although many cortical conditions can result in EPC, in modern practice there is a relatively narrow range of causes.

Diagnoses which can be challenging and which need to be considered when evaluating a patient with EPC without obvious cause: (a) mitochondrial disease and especially mutations of the nuclear mitochondrial gene POLG1; (b) para-neoplastic encephalopathies; (c) autoimmune encephalopathies ñ and especially due to SLE or to variants of autoimmune limbic encephalitis; (d) Rasmussenís encephalitis ñ and especially the increasingly recognosed mild forms of this condition; (e) focal cortical encephalitis. Examples of some of these cases will be described.

The treatment of EPC depends fundamentally on the cause. Acute EPC may resolve spontaneously, but the chronic condition is often refractory to antiepileptic therapy and therapy should be directed at the underlying cause and include IVIg, plasma exchange, steroid therapy, TMS, surgical resection. The condition is too rare and heterogenous for controlled studies of therapy, and at the 1st London Colloquium on Status Epilepticus, it was proposed that a European registry of cases be gathered, to allow therapeutic experience to be pooled.

UCL

EPILEPSIA PARTIALIS CONTINUA (EPC) – what are the causes and how can it be treated ?

Kuopio - 28th March 2008

Simon Shorvon
Institute of Neurology,
University College London

UCL

Epilepsia Partialis continua – pathogenesis

Cortical .v. subcortical
- Juul-Jensen, Denny Brown (1966): 9 cases with jerking arising from subcortical regions (physiology/pathology) and EPC considered as - a *disequilibrium of subcortical reflex activity, of the same type which determines myoclonus*
- Wieser et al (1977): 14 yr old child with EPC and cortical epileptic activity on intracranial recording
- Marsden et al (1982) distinguished cortical myoclonus from other forms of myoclonus

Cockerell, Shorvon, Marsden (1996): 16 cases of EPC examined by MRI, SSEP, back averaging of jerks
- 6 definitely cortical, 5 probably cortical, 2 definitely subcortical, 3 not certain

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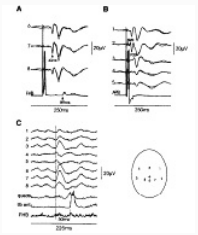
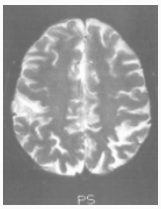
Epilepsia Partialis continua – pathogenesis

Conclusions from 1996 study
- EPC is a form of cortical myoclonus
- EPC is a form of epilepsy (physiologically a 'fragment of epilepsy)
- The term should be restricted to conditions in which there is continuous muscle jerking of cortical origin
- Subcortical forms of 'EPC' should be excluded from the definition and referred to as 'myoclonia continua'

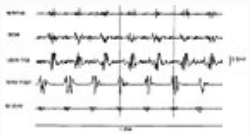
(Cockerell, Shorvon, Marsden *Brain 1996: 119, 393-407*)

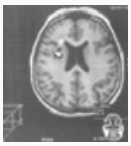
Cortical EPC
- **Short duration EMG activity**
- **Jerk preceded by positive spike on EEG on back averaging**
- **Latency compatible with cortico-spinal conduction time**
- **Assocation with epilepsy**
- **Cortical aetiology**





Sub-cortical EPC





Causes of EPC – results from in three series

	US (1) (n=85)	UK (2) (n=40)	India (3) (n= 76)
Vascular disease	18%	25%	24%
Rasmussen's	-	19%	9%
Neoplasm	15%	11%	5%
Mitochondrial disease	-	11%	1%
Other multisystem	7%	8%	1%
Perinatal	-	5%	5%
Hyperglycaemia (NKH)	-	5%	8%
Trauma	18%	3%	0%
Infection (incl. CJD)	43%	3%	24%
Unknown	n/a	19%	23%

1 – Lohler and Peters (1974)
2 - Cockerell, Shorvon, Marsden *Brain 1996: 119, 393-407*)
3 – Sinha S Satishchandra P *Ep Res 2007 74: 55-9*

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Example case

- **43 yr female**
  - **2 GTCS followed by EPC within 2 weeks**
  - **EPC affected face and right hand, with palatal myoclonus and anarthria with dyslexia/dysphasia**
  - **MRI scan showed last high T2 signal in left frontal area which resolved after a few weeks**
  - **Other investigations normal**
  - **Ductal breast carcinoma diagnosed and treated (with surgical resection, DXR and chemotherapy)**
  - **2 years later discoid lupus diagnosed and SLE serology became positive**
  - **Partial response of EPC to intensive immunotherapy**

Diagnosis - intractable EPC due to SLE

EARLY DEVELOPMENT OF BRAIN ACTIVITY: STRUCTURE VS. FUNCTION.

Sampsa Vanhatalo, Dept. Clin. Neurophys, University Hospital of Helsinki, Finland

For the past half a century, preterm and neonatal EEG has relied on recordings with only few electrodes and a limited frequency range. The EEG analysis has remained phenomenological, where EEG graphoelements are compared to the clinical correlates without insight or attempt to understand the underlying physiological mechanisms. Development of EEG recording and analysis techniques have made it recently possible to record with a much higher spatial accuracy, and without predefined limitations in the recording frequencies. Such high fidelity EEG recordings (ie. Full-band EEG (FbEEG) with high-density caps) have opened new vistas to what has been as yet lost in the conventional EEG. Moreover, this novel information has opened possibilities to design genuine translational studies, ie. animal and human experiments can be run in parallel so that physiologically sensible comparisons can be made.

The main observation in recent studies is that there is a striking amount of infraslow, spontaneous activity transients (SAT), which are unique to the preterm and neonatal period. During the development, these brain activities undergo a distinct transformation from focal to global activity, and this corresponds very closely to the development of major brain connections (thalamo-cortical and cortico-cortical pathways). At the same time, there is also a gradual build-up of an ongoing cortical activity that continues for the rest of the life. Intriguingly, latest research has shown that the growing thalamo-cortical fibers from the sensory systems (vision and touch) may exert very powerful interaction with the cortical activity. This interaction does also open a bedside opportunity to examine the functions of sensory pathways that are still in the growth phase during early prematurity.

In conclusion, recent findings demonstrate that our conventional recording practise in preterm babies leads to an ignorance of important brain activity. Correlative animal studies show that the mechanisms underlying human preterm brain activity (EEG and activity evoked by sensory input) can be explained at a detailed level. Most importantly, current views in developmental neuroscience suggest that SATs are likely the most important type of activity in the developing brain, believed to drive brain wiring at this stage. Detection of SATs may give a straightforward, and neurophysiologically reasoned method for monitoring and assessing brain during prematurity.

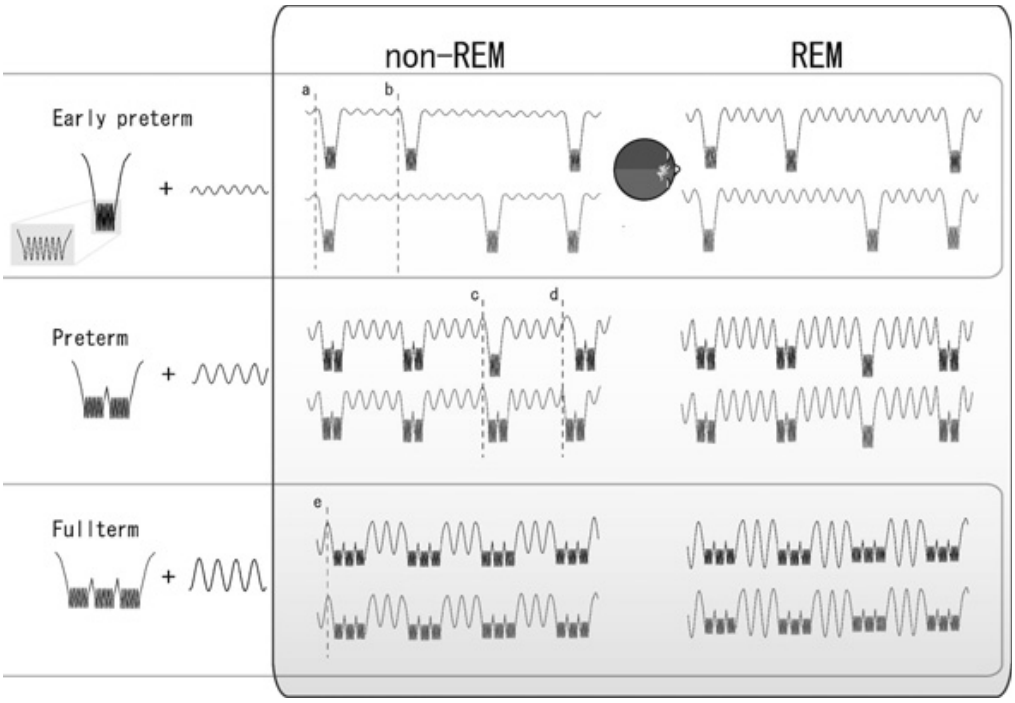


Figure. A proposed physiological framework for the EEG interpretation demonstrates how two components, SAT and the ongoing cortical activity, can readily explain major aspects in the preterm EEG development. For details, see Vanhatalo and Kaila, Seminars in Fetal and Neonatal Medicine, 2006; 11:471-8.

Notes:

DETECTION, PREDICTION AND CONTROL OF EPILEPTIC SEIZURES

Brian Litt, M.D.
Neurology and BioEngineering, University of Pennsylvania, Philadelphia,

Spurred on by the success of similar devices to treat cardiac arrhythmias, there has been tremendous interest in devices to detect, predict and control epileptic seizures. Approaches range from open loop devices that stimulate in regular duty cycles, independent of cerebral activity, to closed-loop, feedback-control systems that interpret the intracranial EEG ìon the fly. Different methods for detecting seizures are being employed to control these closed loop systems, though more promise may rest in understanding seizure generation and identifying periods of increased periods of seizure onset. New understanding of the networks involved in seizure generation, particularly at high spatial and temporal resolutions, may hold the key to the success of antiepileptic devices.

Objectives:
* Convey the spatial and temporal complexity of seizure generation in epileptic networks on multiple scales
* Explain the different systems currently being considered for antiepileptic devices, and how targets for intervention are picked
* To consider other solutions not currently embodied in antiepileptic devices
* To relate developments in this area to Translational Neuroengineering, and similar devices under development for other neurological conditions.

Detecting, Predicting and Controlling Epileptic Seizures

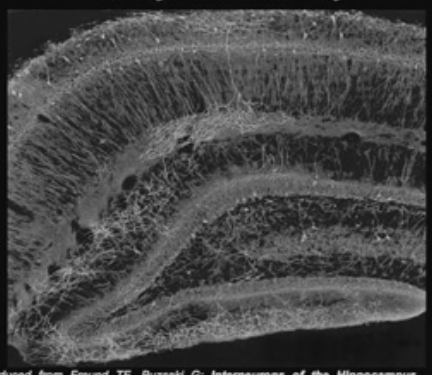
Brian Litt, MD

Associate Professor of Neurology and Bioengineering
University of Pennsylvania

Disclosures: *BioQuantix, NeuroVista, Medtronic, NeuroPace, KCI*

Hippocampal Interneurons

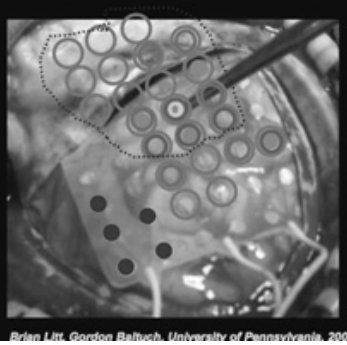
Diversity & characteristic anatomy



Images reproduced from Freund TF, Buzsaki G: **Interneurons of the Hippocampus.** *Hippocampus 1996, 6(4):345-470.*

Ictal Recording/ Mapping

Defining the Network



- Dysplasia (stealth)
- Ictal onset zone
- Rapid Sz spread
- Epileptogenic Zone
- Broca's area
- HFEOs

Brian Litt, Gordon Baltuch, University of Pennsylvania, 2004

Other Interventions

- Fisher, Stein: local drug infusion
- Rothman: focal cooling
- Gluckman, Schiff: Magnetic fields
- Durand: electric fields

15 Years of Seizure Prediction: What Have We Learned?

- Physiology > abstract functions
- Statistical rigor
- Probabilistic
- Continuous data
- Multi-scale: models, arrays, slices, in-vivo, humans

Conclusions

- Vertical, multi-scale collaboration
- Computation: Massive need
- Models: Networks, Sz generation
- *In-vivo* recording: animals, humans
- Bring basic science to patients: Broad-band
- Iterative, multidisciplinary process

CAN POSTSURGICAL MEMORY IMPAIRMENT BE PREDICTED?

C. Helmstaedter
Germany

The question of the cognitive costs is a major concern in epilepsy surgery and temporal lobe surgery in particular. Temporal lobe surgery frequently leads to memory decline in addition to preexisting cognitive problems, and the cognitive costs may weight double if patients do not become seizure free. Thus, reliable predictors of the memory outcome would be greatly appreciated.

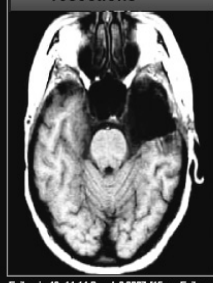
What can be taken for sure is that bilateral hippocampal resection leads to global amnesia. Since this has been taken into consideration catastrophic memory outcomes apart from surgical complications have become very rare. Current approaches to predict memory outcome at best allow a gross estimation as to whether a loss will be more likely or not, and they have in common that they consider the functional adequacy of the resected tissues and the patients mental reserve capacities for compensation and restitution as predictor variables. Seizure control, i.e. postoperative release of secondarily affected functions can be taken as a third determining factor.

Indicators for functionality and reserve capacity can be extracted from neuropsychological baseline performance (memory & IQ), patient characteristics (age, onset/duration/lateralization of epilepsy), language/memory WADA testing, from intra-cranial electro-physiologic recordings (e.g. event related potentials), and more recently also from language/memory functional imaging (fMRI). These methods are more (WADA, intracranial ERP¥S) or less (neuropsychological testing, fMRI) invasive, and they are overlapping and complementary as well in that they have a different emphasis on the assessment of the functional adequacy or reserve capacity.

Regression based prediction models at best reach a 70% to 80% accuracy in predicting individual losers. However, use of different WADA- fMRI- and neuropsychological- test-protocols prevents a generalization of findings from individual epilepsy centers. Taking additionally into account the variations of surgeries (tailored vs. standard resections) plus optional approaches in selective surgery (transsylvian, transcortical, subtemporal), at present none of the above mentioned procedures appears to have a resolution which can meet all these conditions. Thus final risks cannot be excluded but we should keep in mind with this that epilepsy surgery aims at seizures is not meant to by psychosurgery.

Temporal Lobe Epilepsy Surgery

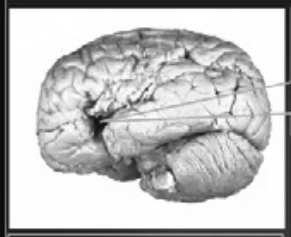
- 65% seizure free: 12 months cognitive outcome [N=732] -



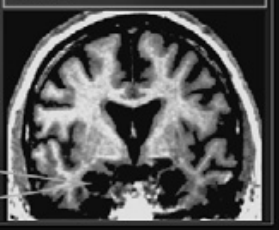
temporal lobe resections	cognitive domain	N	deterioration right	deterioration left
	verbal memory	732	27%	< 40%
	figural memory	732	27%	31%
	language	653	14%	< 21%
	motor fct.	717	15%	16%
	attention	717	11%	11%
	visuo-construction	602	14%	9%

Epilepsia 48: 14-14 Suppl. 3 2007 [15yrs. Epilepsy surgery in Bonn]

Mesial versus Cortical Reserve Capacities



Cortex *[Broca's patient Leborg]*:
dependent on the age of the patient, unilateral damage is sufficient for total loss of a function [aphasia]



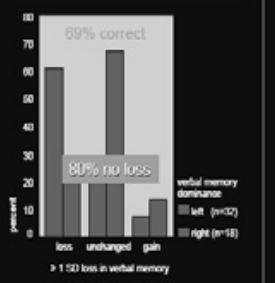
Mesial structures *[Milners patient HM]*:
independent on age bilateral damage is required to cause total loss of a function [global amnesia]

Reserve Capacity

- language & memory dominance [discordance 30% N=97] -

- predictive power ~ 70%
  - literature: ~ 45-76%*
  - varies with procedure
- memory WADA may predict change but not its degree!
- prediction only of verbal memory only in left TLE
  - ➢ applies to 30-40% pts. only
  - + loss in verbal memory also in 20-30% after right surgery

intra-post IAT memory in L-TLE [50]

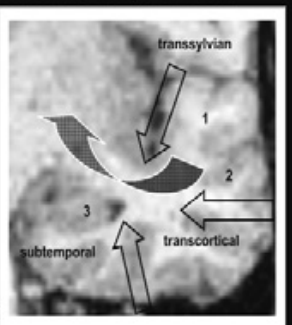


see also Elodrill Brain & Cognition 1997, Seattle Protocol [learning and recall during procedure] 78%, and Lee Epilepsia 2005

How Selective is Selective Surgery?

- preservation vs. dissection of the temporal stem -

- Hori et al. *Neursurgery* 1993
  J. Neurosurg 2007
  „no memory decline after SAH via a subtemporal approach"
- Lutz et al. *Epilepsia* 2004
  „greater improvement of extratemporal fcts. after a transcortical approach"
- Helmstaedter et al. Epilepsia 2008
  „better outcome after SAH in RTLE, and after pole resection+AH in L-TLE



Epilepsia 49/1 2008

The Traditional Clinical Approach

- regression based prediction models -

	v. learning	v. memory	f. learning
Lineweaver et al.	18%	26%	20%
Epilepsia 47/11 2006	side	side	side
WMS	baseline	baseline	baseline
87 left dom. TLE	MR volume [WADA]	MR volume [WADA]	MR volume [WADA]
predicted	85%	78%	83%
own data	19%	22%	25%
VLMT	side	side	baseline
DCS-R	baseline	baseline	IQ
N=336 TLE	age /	onset /	age AH
predicted	82%	78%	77%

Can Memory Outcome be Predicted?

- Outcome can be estimated by reserve capacities, functionality of resected tissues/fiber tracts, expected seizure outcome
  - WADA language/memory/selective
  - fMRI
  - ERP's
  - Baseline clinical conditions and baseline performance
- There is no method, which, taken alone or in combination, provides an "individual" prediction of a graded memory change.
  - Variability in baseline pathology
    - Different surgeries and approaches
    - No common sense on test paradigms
    - Different memory tests as outcome parameters
- Those who start better are better at the end [the double winners]
  - good performance at entrance indicates: less pathological brain, less severe epilepsy, greater chance to become seizure free?, better final performance despite greater risk for losses, greater reserves for compensation, better pre-requisites for rehabilitation.
- Catastrophic memory outcomes apart from complications are rare!
- Seizure control is and remains the major aim of epilepsy surgery!

DEEP BRAIN STIMULATION: IS IT A REAL TREATMENT OPTION IN EPILEPSY ?

Paul A.J.M. BOON, MD, PhD
Department of Neurology, Reference Center for Refractory Epilepsy, Laboratory for Clinical and Experimental Neurophysiology, Ghent University Hospital, Belgium

Despite the advent of new pharmacological treatments, vagus nerve stimulation and the high success rate of many surgical treatments for epilepsy, a substantial number of patients do not become seizure-free and/or experience major adverse events. Neurostimulation-based treatments have gained considerable interest in the last decade.
Acute deep brain stimulation (DBS) in various thalamic nuclei and medial temporal lobe structures has recently been shown to be efficacious in small pilot studies of patients with medically refractory epilepsy. Only limited data on chronic thalamic and amygdalo-hippocampal stimulation are available. Chronic DBS in these structures requires resolving many conceptual and technical issues. There is little evidence based information on rational targets and stimulation parameters. Currently available depth EEG recording electrodes are unsuitable for chronic use. Inversely, the use of DBS electrodes for intracranial EEG recording and localization of the ictal onset zone prior to stimulation has only been reported by a single group. Results from feasibility and pilot studies in the literature will be presented.
The experience with DBS in temporal lobe epilepsy using quadripolar DBS electrodes bilaterally implanted in the amygdalo-hippocampal region to identify and subsequently stimulate the ictal onset zone will be described. This technique has yielded a significant decrease of seizure counts and interictal EEG abnormalities during long-term follow-up. Early experience with responsive neurostimulation is currently being reported but results from a large US multicenter trial are pending. Another trial with anterior nucleus stimulation has recruited a significant number of patients but results have not been reported yet.
Various hypotheses on the possible mechanism(s) of action will also be discussed using EEG, cerebral blood flow and metabolic measures including results from animal experiments.
Data from pilot studies suggests that chronic DBS for epilepsy may be a feasible, effective and safe procedure that reduces interictal EEG abnormalities and seizures. However, the stage of large-scale clinical use has not been reached yet. Further trials with larger patient populations, controlled and randomised designs should now be initiated.

Supported by grants BOZF-011A099 and BOZF-01104495 from Ghent University and by grant 1.5.236.99 from the Fund for Scientific Research-Flanders.

THE FUTURE OF EPILEPSY SURGERY

Frederick Andermann, M.D., FRCP©
From the Montreal Neurological Hospital and Institute, McGill University

The ability to generate electrical potentials is a fundamental property of the brain. Vitiation of these potentials can lead to the appearance of epileptic seizures. Long before these properties and mechanisms were recognized, clinical observations showed that brain injuries or lesions could lead to scars and seizures. This prompted attempts to remove these lesions. The work of pioneers like Victor Horsley and Fedor Krause is well recognized. A prolonged hiatus then ensued until Otfried Foerster in Breslau (now Wroclaw in Poland) began to advance this approach to treatment further. Wilder Penfield, looking for new horizons, spent some months with Foerster and, as one may describe in present terms, was the first epilepsy fellow.

At the Montreal Neurological Institute, which Penfield founded in 1934, he learned of Hans Bergerís work in electroencephalography, which promised the ability to recognize epileptic potentials and discharges and to help in localization of epileptic activity. He attracted Herbert Jasper then working as a psychologist at Brown University in Rhode Island, and their fruitful collaboration provided great impetus to the field of surgical treatment of epilepsy. One of their main advances was the recognition of temporal lobe epilepsy, which later was shown to be the most important cause of intractable epilepsy. The school of Penfield and Jasper attracted numerous disciples from many parts of the world and after the Second World War, there was considerable and widespread flowering of interest in the surgical treatment of epilepsy. This enthusiasm however was short lasting, and surgical treatment was widely de-emphasized. In some countries, such as Germany or Japan in was virtually proscribed. When I asked Dr. Theodore Rasmussen why this enthusiasm had waned at that time, he replied, ìIt was the wrong surgeons, operating on the wrong patientsî.

For years surgical treatment of epilepsy was confined to very few centers, notably the Montreal Neurological Institute with Theodore Rasmussen and Bill Feindel and their disciples, Kingís Maudsley in London with Murray Falconer and his school and the Hopital Ste. Anne in Paris with Jean Bancaud and Jean Talairach. Careful keeping of the score, as Dr. Rasmussen put it, in both groups led to recognition of optimal candidates for surgical treatment and the recognition of more informed prognosis in the different forms of epilepsy. Interestingly, during that period, the role of structural lesions, such as indolent tumors, was not accepted or well understood. The emphasis was on electrographic localization of the epileptogenic area.

The advent of modern imaging with computed tomography, and even more after the development of magnetic resonance, provided a second and very powerful impetus to surgical treatment of intractable epilepsy. It allowed recognition of the significance of the lesions and their epileptogenic potential was increasingly recognized. In the same period in the 80s and early 90s, the ability to identify a plethora of previously invisible lesions during life provided an additional stimulus to surgical treatment. A major step was the recognition during life of cortical dysplasia. This had been described by David Taylor from Falconerís group based on pathological studies of material resected, and of course in those patients the lesion was not visible preoperatively. There was a tremendous explosion of interest in this topic resulting in an enormous literature, with hundreds of contributions since, addressing the different modalities of investigation and of treatment.

The financial rewards of video telemetry stimulated hospital administrators and neurologists to introduce this investigative approach, which promised to generate important economic benefits. This was not necessarily combined with the development of the required team approach. Many centers had planned to develop surgical treatment without being adequately prepared or willing to provide support for the required multidisciplinary team. They soon dropped out of the field. We have however witnessed the development of a number of centers of excellence in the United States, and in Canada where this was spearheaded by Penfieldís disciples across the country. Comprehensive epilepsy centers with expert investigation and surgical expertise also developed in many parts of Europe, Germany, Italy, France, Finland, United Kingdom and elsewhere.

The recognition of ideal candidates for surgical treatment was further refined and also enabled the development of centers for surgical treatment in the developing world, geared to the treatment of patients with identifiable lesions or unilateral mesial temporal sclerosis. There always remained a temptation to tackle difficult problems, such as for example operating on patients with frontal epilepsy without a lesion which can be demonstrated by imaging, and where the results are considerably inferior to those in well-selected cases.

Surgical treatment of epilepsy has always been complicated by prejudice on the part of neurologists and

other physicians and the amount of prejudice was inversely proportional to the knowledge and expertise of these doctors.

It was recognized early that the search for surgical treatment by patients and families was driving the referrals, much more than the initiative of the treating neurologists and other physicians. Though this type of prejudice seems to be diminishing, it continues to exist. There are also obvious financial incentives in not referring patients for surgical treatment. There were numerous examples during the recent flowering of trials of new antiepileptic agents of patients going through trial after trial even though the chances of success were minimal. These patients may have had a much better chance for a more normal life with surgical treatment.

The lack of awareness of the possibilities and advantages of surgical therapy however was probably an even greater factor and this was coupled in many instances by inadequate interpretation to the patients and their family and of course by their inadequate understanding of the process.

After this lengthy preamble we turn to the future of surgical treatment. That surgery has been underutilized has been stressed repeatedly by the Commission on Surgical Treatment of the International League Against Epilepsy. Calculated estimates of surgical candidates in the population yielded high figures, but it is not entirely clear whether these figures were always based on discrimination between patients with a very good chance of successful outcome compared to those who, though quite intractable, presented much more difficult problems and a lesser promise of a good result. Furthermore, there are important geographic considerations. In regions or countries where surgical treatment becomes available for the first time, there are a large numbers of patients with eminently treatable forms of epilepsy, such as for instance, people with temporal lobe epilepsy associated with unilateral mesial temporal sclerosis. Initial reports from such areas or centers are able to describe large series with good results obtained in a relatively short period of time. In areas where surgical treatment has been available for some time and where there is much better awareness of what surgery can accomplish, such patients with optimal prognosis are becoming increasingly rare. I asked the senior surgeon at a major epilepsy center in the Eastern United States how many such ideal surgical candidates he would see in a year and he replied: 6 or 7. He then proceeded to mention also that since imaging findings are more readily recognized now, such patients are often referred and operated by general neurosurgeons without an abiding interest in the treatment of epilepsy and without the benefit of more complete preoperative investigation. Such a comprehensive study would be likely to lead to better results in the long run. Similar situations prevail, no doubt, in countries where surgical treatment is introduced for the first time. For example, impressive results were obtained in centers such as the one at Sri Chitra Tirulam in Trivandrum in Kerala, South India.

In all these situations because of the severity of the epilepsy, and the gradual deterioration of many patients, there is continuing temptation to address problems which are not as likely to lead to very good outcomes. Patients and their families however are generally very grateful even for improvement rather than complete control of their attacks, an often unexpected and gratifying attitude.

There is a hope that improved technology and refining of functional imaging as well as electrographic localization may lead to improved understanding of the epileptogenic process and thus to improved outcome. The use of innovative PET ligands, PET activation techniques, various forms of morphometry, magnetoencephalography, spike driven FMRI and recording from dense arrays of electrodes are amongst the techniques being developed which hold promise of increasing clinical usefulness.

An example of how new insights develop is provided by gelastic epilepsy related to hypothalamic hamartoma. First the clinical pattern was recognized to be associated with the hypothalamic lesions, and the advent of MRI greatly facilitated identification of these. Attempts of resecting the lesion were initially not encouraging. Identifying epileptogenic areas based on electrographic localization, even with depth electrode studies, led to a number of temporal and at times frontal resections. These were also fruitless. That the lesions themselves could generate epileptic potentials, was then found by Munari and his group using depth electrodes placed in the lesions. This then led to a multiplicity of approaches designed to resect or destroy the hypothalamic hamartoma itself. It became clear that some approaches were preferable to others and at the moment a transcallosal approach appears to be optimal, particularly in lesions which are within the lumen of the third ventricle or not very extensive. The completeness of the resection, in so far as it can be determined by imaging and by direct visualization, appears to correlate with the outcome. The role of other approaches such as gamma knife surgery is yet to be confirmed. Despite the proven benefits of resective surgery, there continues to exist considerable reluctance on the part of many neurosurgeons to approach these lesions for fear of disastrous complications. Though some endocrine and other complications may occur with surgical

treatment, the benefit, particularly in patients with gelastic seizures and catastrophic secondary generalization far outweigh these risks. Finally, somatic mutations have been found in patients with syndromes such as the Pallister Hall who have hypothalamic hamartomas and in at least 1 patient who had a sporadic hamartoma.

How do other approaches to the treatment of intractable epilepsy impact on surgical treatment? The new generation of antiepileptic drugs are comparable in their effect to that of the previous generation of agents. It is generally recognized that their main benefit lies in reduction of side effects and that only less than 10% of patients who have intractable epilepsies are fully controllable by any of the new agents. To wait for new agents to be developed is to deprive patients of the benefit of a much better outcome obtainable by surgical treatment. Devices such as vagal nerve stimulation are strongly driven by industrial support and do not require complicated and technically difficult and prolonged investigations. There is also strong support for the utilization of this apparatus by industry sponsored specialized nurses working with the patients. Whether some forms of epilepsy are more likely to respond than others to vagal stimulation is not currently clear. The results appear to be better in children compared to adults. Cerebral stimulation and prostheses designed to arrest seizures at their onset are currently studied and remain experimental.

In reviewing a series of reports on postoperative psychosis arising de novo from Denmark, Finland and the United Kingdom it becomes clear that the risk of postoperative psychosis is present mainly in individuals whose seizures have not ceased following surgery. Only a very small number of patients whose seizures have been fully controlled by surgery develop psychosis, probably related more to the preexistent terrain and pathology than to the surgery itself.

One of the criticisms leveled at surgical treatment was that no controlled studies were present. This type of criticism could be leveled also at operations such as appendectomy. However, since some objective evidence seemed required, studies such as the one by Wiebe et al., have confirmed the benefit of surgical treatment in patients with temporal lobe epilepsy compared to continued medical treatment. Further attempts based on multicenter trials are also planned or underway.

New and as yet unplanned developments in neuroscience may open new perspectives in our understanding of intractable epilepsy and may lead to new approaches, which cannot at present be foreseen.

The possibility that surgery may provide resolution of a personís epileptic problem as far as recurrent seizures are concerned must be kept in mind when seeing or reviewing a patient with epilepsy. It is important not to make value judgments about the severity and dangers of the epilepsy itself. Rather, one should be guided by the personís perception of his problem, within reason. Wanting to avoid antiepileptic medication completely is not necessarily a frivolous request. Though this usually cannot be promised such requests need to be weighed against the possible side effects of a lifetime of possibly heavy antiepileptic medication. Often the medication can be reduced postoperatively for a period of time and in some patients, eventually discontinued.

The available information at the time of the patientís first review is most often inadequate and further investigation is required before the options can be presented to the patient and the family. Obsessive trials of every conceivable antiepileptic are not a very fruitful exercise. Above all, the pros and cons, risks and benefits of surgery need to be explained to the patientís satisfaction and it is essential to have some idea as to whether this has actually been understood and carefully considered.

Surgical treatment offers a resolution of the problem of recurrent attacks to many people with epilepsies both in developed and in the developing world and these patients should not be deprived of this option. Even politicians and governmental agencies have a role to play in enabling patients to benefit from surgical treatment. The situation in Brazil where this approach is given some priority by the government is a good example of what can be accomplished in the developing world.

One may conclude that surgical treatment, despite its invasive nature, and often uncertain outcome, will continue to provide a valuable option unless it is surpassed in the unforeseeable future by different, less invasive, but equally effective approaches.

SATURDAY, MARCH 29TH, 2008
SESSION: GENETICS AND PHARMACOGENOMICS: HYPE, HOPE AND REALITY

HOW HAS GENETICS HELPED US TO UNDERSTAND THE NEUROBIOLOGY OF EPILEPSY?

Ingrid E Scheffer
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Departments of Paediatrics and Medicine, The University of Melbourne, Austin Health and Royal Childrenís Hospital, Australia

The discovery of epilepsy genes is merely the beginning of the journey to understanding the neurobiology of seizure disorders. Over the last 12 years, the discovery of >15 genes for monogenic epilepsies has shed major insights into our understanding of the underlying mechanisms. The emerging theme has been of ion channelopathies with voltage-gated and ligand-gated ion channel genes implicated in idiopathic epilepsies. Sodium, potassium, chloride and calcium channel subunits are associated with a range of phenotypes including idiopathic generalized epilepsies (IGE) and autosomal dominant seizure syndromes of the first year of life. Nicotinic acetylcholine receptor subunits and GABAA receptor subunits are associated with nocturnal frontal lobe epilepsy and IGE phenotypes.

Functional studies are critical in understanding the effects of mutations. Unfortunately no consistent picture has emerged from in vitro testing of ion channel mutations although many show a loss of function in a range of model systems. In vivo functional studies are clearly more pertinent as they allow network and background effects to be studied.

The most clinically relevant epilepsy gene, SCN1A, encodes the pore-forming alpha 1 subunit of the sodium channel. Truncation and missense mutations can result in the severe phenotype of Dravet syndrome. Recent knock-in animal models recapitulate the human phenotype. Heterozygote mice show significant background effects mimicking the variability of severity in humans with Dravet syndrome. Cellular studies show that Dravet syndrome is actually an interneuronopathy rather than a disorder of excitable cells. For the first time, genetics is allowing us to delve in to the neurobiology of this devastating disorder. This is the first step to discovering targeted therapies and ultimately prevention of the epilepsies.

Genetics of Epilepsies

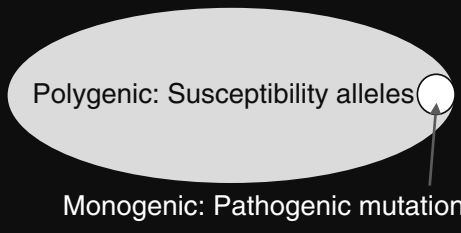
Majority of cases: Complex inheritance
Polygenic - many genes, currently unknown
Modified by environmental factors

Rare families: Simple inheritance
Multiple single gene disorders
? genes relevant to majority of cases

Monogenic Epilepsies: Genetic defects 2008

- Voltage-gated ion channel subunits
  - Sodium - GEFS+, Dravet, infantile seizures
  - Potassium - neonatal seizures, absence epilepsy
  - Calcium - absence epilepsy, generalized epilepsies
- Ligand-gated ion channel subunits
  - Nicotinic receptors - frontal lobe epilepsy
  - GABA receptors - GEFS+, absence epilepsy, juvenile myoclonic epilepsy
- LGI1 - temporal lobe epilepsy

Genetics of Epilepsies



Monogenic: Pathogenic mutations

Idiopathic Epilepsies: Complex Inheritance Susceptibility Genes: 2008

Juvenile Myoclonic Epilepsy	
Pro-apoptotic, calcium sensing, ciliary function	*EFHC1* **
Transcriptional regulator	*BRD2 (??)*
Childhood Absence Epilepsy	
Calcium T channel gene	*CACNA1H* **
Idiopathic Generalized Epilepsies	
Chloride channel gene	*CLCN2*
GABA delta subunit gene	*GABRD*
Ion channel regulator	*NEDD4-2*

Epileptic Encephalopathies - 188 cases

Phenotype	n	*SCN1A* +
SMEI / Dravet	66	52 (79%)
SMEB	36	25 (69%)
Cryptogenic Generalized Epilepsy	25	6 (24%)
Cryptogenic Focal Epilepsy	18	4 (22%)
Myoclonic-Astatic Epilepsy	10	2 (20%)
Lennox-Gastaut Syndrome	12	1 (8%)

Harkin et al, Brain 2007

Conclusions

Genetics has helped us to understand neurobiology:

- Channelopathies
- Susceptibility genes emerging
  - Calcium channel variants important
  - Others need confirmation: functional data
- *In vivo* functional data suggests "interneuronopathies" underlie hyperexcitability
- Genetic background critical - ? rescue phenotype
- Genetics will change clinical practice and outcomes for people with epilepsy

CNS CHANNELOPATHIES WITH EPILEPSY - IS THERE A COMMON LINK BETWEEN CO-MORBIDITIES?

Mikko Kallela

Disorders in ion channels, channelopathies, are well known for their tendency to cause episodic ”paroxysmal” symptoms. This is true also for channelopathies of the central nervous system (CNS). For example, several monogenic epilepsy syndromes are caused by mutations in ion channel genes. Another familiar (and familial) CNS disorder, migraine, is episodic as well and sometimes caused by dysfunctional ion channels. While epilepsy is co-morbid with a number of disorders, the link between migraine and epilepsy is chosen for closer inspection in this presentation.

An epidemiologic overlap between migraine and epilepsy has been observed in several studies. Despite this, some scientists are not convinced, and see more differences than similarities between epilepsy and migraine. The modern molecular genetic methods have added important standpoints to the controversy.

A rare form of migrane with aura (MwA), familial hemiplegic migraine (FHM) is caused by mutations in ion channels. Mutations in genes coding for subunits of a calcium channel (the CACNA 1A-gene), a Na/K pump (the ATP1 A2 gene) and a sodium channel (the SCN 1A-gene) have been discovered in families affected by FHM. The functional consequences of these genes are thought to underly the ”migraneous sensitivity”, the tendency to have repeated headache attacks. In addition to migraine, several families with FHM present with clear epileptic phenomena. The treshold for both migraine and seizures seems to be lowered in these families.

Maybe this is to be expected. In addition to their common episodic nature there are several other clinical similarities between migraine and epilepsy. Migraine has sometimes been called ” an epileptic attack in slow motion”. This is especially true for the migraine aura. The current wisdom says that Cortical Spreading Depresion (CSD) is the phenomenon underlying migraine aura. Interestingly topiramate and valproate, drugs effective both in epilepsy and migraine, suppress CSD. Also propranolol, amitriptyline and methysergide have the same effect. Thus both antiepileptic drugs (AEDs) and migraine prophylactics seem to share this mechanism of action.

Despite undeniable similarities epilepsy and migraine have fundamental differences. In a broad sense both are clinically and pathophysiologically multifactorial disorders with several divergent and convergent mechanisms. Ion channels are not the whole story, far from it. So far genes mutated in rare families with a clear Mendelian inheritance seem to contribute little to the overall liability to have a seizure or a migraine headache in the general population. Environmental influences are often as important as genetic. In migraine half is nature, half is nurture. New methods, both clinical (novel ideas in endophenotyping) and molecular genetic (genome wide association studies), seem to be needed to take the next challenging steps into better understanding the complex basis of epilepsy and its co-morbidities.

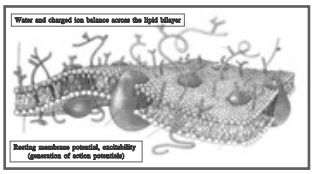
CNS Channelopathies with Epilepsy - Is There a Common Link between Co-morbidities?

Mikko Kallela
Neurologist

A clinicians perspective

Ion channels in medicine

- Paroxysmal "channelopathies"

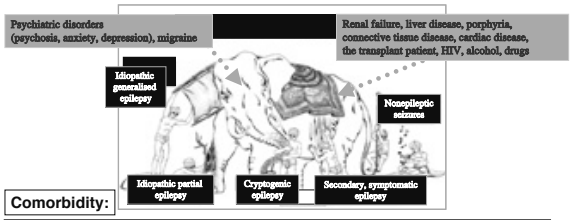


- QT-syndromes
- Ataxia, epilepsy, migraine

Types

- Alternating hemiplegia of childhood
- Barter syndrome (a renal potassium wasting sdr.)
- Brugada syndrome (sudden unexpected death sdr.)
- Congenital hyperinsulinism
- Cystic fibrosis
- Episodic Ataxia
- Erythromelalgia
- Generalized epilepsy with febrile seizures plus
- Hyperkalemic periodic paralysis
- Hypokalemic periodic paralysis
- Long QT syndrome
- Malignant hyperthermia
- Migraine
- Myasthenia Gravis
- Myotonia congenita
- Neuromyotonia
- Nonsyndromic deafness
- Paramyotonia congenita
- Periodic paralysis
- Retinitis pigmentosa
- Romano-Ward syndrome (a long QT syndrome)
- Short QT syndrome
- Timothy syndrome (a disorder of physiological and developmental defects)

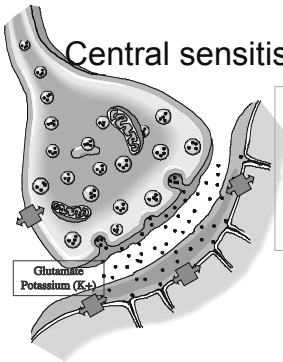
Comorbidity of epilepsy



Comorbidity:

The presence of one or more disorders (or diseases)
in addition to a primary disease or disorder
or
The effect of such additional disorders or diseases

Central sensitisation in pain



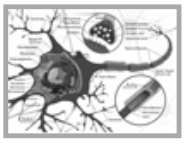
Presynaptic structures
Calcium channels
Opiate receptors
GABA
AMPA
Adenosine
NMDA
P2X3 (purinergic receptors)
EP (prostaglandin receptors)

Postsynaptic structures
Glutaminergic receptors
NMDA
AMPA
Calcium channels
GABA-receptors

Synaptic plasticity
LTP = "long term potentiation"
LTD = "long term depression"
Memory, epilepsy, pain, chronic migrane

High glutamate and K+ lower seizure treshold

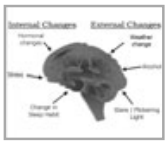
Kindling in epilepsy, epileptogenesis



Neuronal membrane

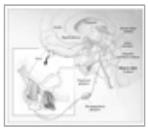
Neuronal networks
Network plasticity
New neurons
Apoptosis

Neuronal synapse
Synaptic plasticity
Injury and sprouting
New synapses and dendrites

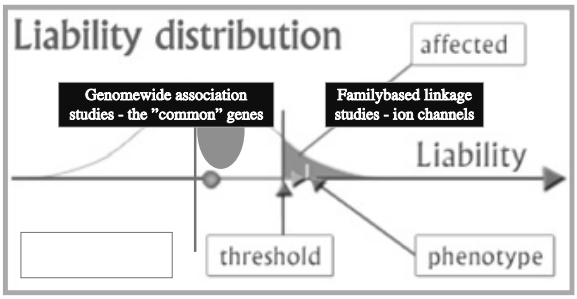


Cortex Subcortex

Epilepsy Migraine



Liability distribution



Common phenotype, "sporadic" cases
Common liability genes

Several affected family members
Family syndrome spesific genes

Common mutations with a modest effect

Rare mutations with a major effect

CAN GENETIC ABNORMALITY BE NEUTRALIZED BY MODULATING DOWN-STREAM

David Neal Franz, MD

Professor of Pediatrics and Neurology, Director, TSC Clinic and Clinical Affairs, Departments of Neurology and Pediatrics, Cincinnati Childrenís Hospital Medical Center, University of Cincinnati College of Medicine

Tuberous Sclerosis (TSC) is a neurocutaneous disorder characterized by hamartomatous growths in various organs, including the brain. It is highly correlated with seizures (90%) which are frequently intractable, cognitive impairments which can be severe (40 ñ 50 %),
as well as giant cell astrocytomas (15%). The TRSC gene products ñ hamartin and tuberin ñ act to inhibit the protein kinase mTOR (mammalian target of rapamycin) which functions broadly as a regulator of cellular growth and division, protein synthesis, and mRNA transcription. A variety of pharmaceutical agents, most notably rapamycin, are now available which act to inhibit mTOR, thereby mimicking the function of the hamartin-tuberin complex and offering the potential to specifically reverse the molecular defect in TSC. Excessive activation of mTOR is often present in non-TSC human malignancies, such as breast, lung, and colon cancer. It is also implicated in other non-TS neurologic disorders such as ceroid lipofuscinosis, Huntingtonís disease, Alzheimerís disease, Downís syndrome and epileptic encephalopathies. mTOR inhibition offers a novel means to treat neurologic and other manifestations of TSC, and perhaps aother neurologic disorders.

Subependymal giant cell astrocytomas (SEGA) in patients with tuberous sclerosis have been treated with the mTOR inhibitors rapamycin or RAD001 either for clinical reasons (n=18) or a part of ongoing clinical trials (n=17 to date). All patients who have received either agent have shown objective regression in size of their tumor often with resolution of concomitant hydrocephalus.

Many patients/caregivers have reported cognitive improvements and reductions in seizure frequency or severity. There have been infrequent parent reports of hyperkinesis or agitated behaviors, none of which has resulted in drug discontinuation. No conclusions can drawn from these anecdotal observations. Serial neuropsychometric testing in the RAD001 SEGA trial are consistent with improved memory and attention, but remain preliminary.

Our center recently published results of a clinical trial with rapamycin for angiomyolipomas in TSC and sporadic lymphangioleiomyomatosis (LAM). Subjects received rapamycin at progressively increasing doses until either a tumor response was seen, or serum levels in the upper therapeutic range for immunosuppression where achieved (i.e. 10 -15 ng/ml). Subjects received active treatment for one year and were then were monitored for one year off drug. Regression of angiomyolipoma volume was seen in all subjects, although cessation of therapy led to a return in lesion volume to baseline values in about two thirds of patients. Patients with abnormal lung function however demonstrated a durable improvement in ventilatory function (FVC and FEV1) following completion of active treatment.

Notes:

PHARMACOGENOMICS - WHAT HAS IT ADDED TO OUR UNDERSTANDING ABOUT DRUG TREATMENT?

Sanjay Sisodiya
Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology
London UK

Enormous advances in genetic concepts, technology and resources have encouraged ideas of individualised medicine, an aim of pharmacogenomics. The appeal in epilepsy is obvious: selecting the right drug in advance, quickly achieving the correct dose, avoiding adverse effects whilst achieving rapid control.

To date, the reality has been more sobering. The number of studies in epilepsy has been limited, and focussed mainly on a few genes, particularly ABCB1, SCN1A, CYP2C9 and HLA-B alleles. Some findings have found clinical application, but by and large studies have not yet had a clinical impact.

Genome-wide studies of disease susceptibility across the spectrum of human diseases have had some spectacular successes. The methodology for such studies of susceptibility traits is well-established. Whether it is possible to extrapolate from studies of susceptibility to studies of drug response is less clear. Without a doubt, robust clinical phenotypes with clear definitions and efficient association strategies will be required: the numbers of cases that need to be studied to identify causative genetic variants is more uncertain. We can reasonably anticipate the numbers required will prove to be smaller.

Major international collaborative studies are now underway in epilepsy that may bring some answers.

Pharmacogenomics - what has it added to our understanding about drug treatment?

Sanjay Sisodiya
Department of Clinical and Experimental Epilepsy
UCL Institute of Neurology
London UK

Heterogeneity in epilepsy

Seizures

Syndromes

Aetiology

Phenotypes – clinical and investigational

Lumping together …….

Heterogeneity and genomics…

Biology in epilepsy

Seizures – final common pathways

Syndromes – evidence of genetic architecture

Aetiology

Phenotypes – drug response, outcomes

Lumping together …….

Heterogeneity and genomics…

Carbamazepine dosing

Conclusions

Association study can identify biologically important causal variants

Association study can identify clinically relevant causal variants?

Amount of variation explained small

Move to genome-wide association

More tractable

Conclusions: caveats

- Pharmacogenomics: clues to mechanisms
- Not a panacea – not an answer to everything
- Other factors
- Environment
- Complexity
- Iterate phenotype-genotype

Conclusions: recommendations

- Genetic answers CAN be found
- Phenotype is king
- Numbers – power
- Phenotype homogeneity, collection and curation
- DNA collection and curation
- Genome-wide competent analysis
- Follow-up: replication and function
- Presentation and translation

MECHANISM OF DRUG-REFRACTORINESS - HOW TO CONQUER THE PROBLEM IN CLINICAL PRACTICE

Wolfgang Löscher

Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine Hannover, and Center for Systems Neuroscience Hannover, Hannover, Germany

The issue of pharmacoresistance in epilepsy has received considerable attention in recent years, and the search for mechanisms that might explain why around 30% of patients fail to respond to current medications continues apace.

A number of plausible hypotheses have been proposed, including inadequate penetration of antiepileptic drugs (AEDs) across the bloodñbrain barrier (BBB); acquired alterations to the structure and/or functionality of ion channels and neurotransmitter receptors that represent the principal targets of AEDs; and an inherent resistance, governed by genetic variants of proteins involved in the pharmacokinetics and pharmacodynamics of AED action. Of these, the so-called transporter hypothesis, which proposes that refractory epilepsy may be the consequence of a localized overexpression of drug efflux tranporters such as P-glycoprotein (Pgp) that prevents AEDs from penetrating the BBB in sufficient concentration, is the most extensively researched and documented. Localized overexpression of Pgp in the brain has been reported both in patients and rats with AED-resistant epilepsy, the Pgp-overexpression is associated with decreased brain levels of AEDs, and, most importantly, coadministration of the selective Pgp inhibitor, tariquidar, has recently been shown to counteract AED resistance in a rodent model of temporal lobe epilepsy. Initially, tariquidar had been developed for treatment of pharmacoresistant cancer, but currently studies are under way to prove whether this Pgp inhibitor increases brain penetration of drugs in humans and - as a next step improves AED efficacy in patients with pharmacoresistant epilepsy.

If the promising data on tariquidar in epileptic rats can be extended to humans, this could form a promising new strategy to conquer drug-refractoriness in clinical practice.

Pharmacoresistance in epilepsy

- **Pharmacoresistance is the major problem in epilepsy therapy**
  - Defined as the persistence of seizures despite treatment with a range of AEDs with different mechanisms of action used singly or in combination at maximum tolerated doses
- **Consequently, there is a pressing need to develop more effective treatments and strategies**
- **For this goal, we need to understand the mechanisms underlying drug resistance**

The target hypothesis

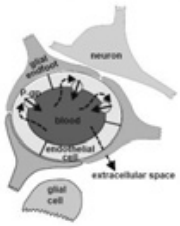
- **Do drug-resistant individuals differ from drug-responsive individuals in their target sensitivity in the brain?**
- **Clinical evidence**
  - Remy et al. (*Ann. Neurol.* 2003): Carbamazepine
    - Loss of carbamazepine's effect on voltage-dependent Na^+-channels in AED resistant patients
- **Experimental evidence**
  - Volk et al. (*Neurobiol. Dis.* 2006): Phenobarbital
    - Alteration in the pharmacological sensitivity of $GABA_A$ receptors in phenobarbital-resistant rats

The network hypothesis of pharmacoresistant epilepsy

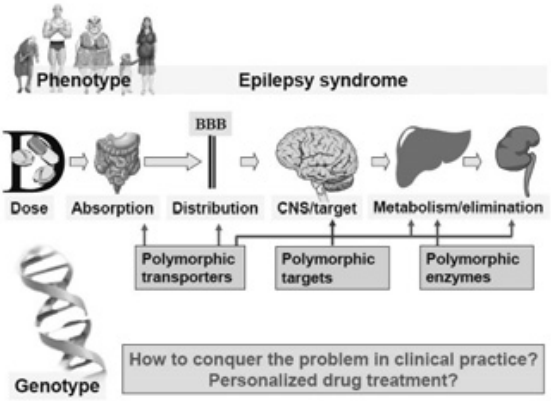
- **Do drug-resistant individuals differ from drug-responsive individuals in structural brain alterations and/or network changes?**
- **Can be evaluated by brain imaging in patients with epilepsy, but important differences may be missed**
  - In TLE, hippocampal sclerosis is often associated with drug resistance
- **Can be examined histologically by morphometric and immunohistochemical methods in animal models of drug resistant epilepsy**
  - Volk et al. (*Neurobiol. Dis.* 2006): Comparison of phenobarbital-resistant vs. –responsive rats vs. controls

The multidrug transporter hypothesis of refractory epilepsy

- **Localized overexpression of drug efflux transporters such as P-gp at the BBB is proposed to reduce the concentration of antiepileptic drugs at their brain targets**



- How to conquer the problem in clinical practice?
  - Inhibit or by-pass the transporters



SYNDROME IDENTIFICATION AS A BASIS FOR TREATMENT DECISION WHAT IS THE PROBLEM: HOW COMMON IS "COMMON EPILEPSY" ?

Dr. Reetta Kälviäinen Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland

Accurate diagnosis is the golden rule in medicine and epilepsies should not be an exception to this. Medical diagnosis provides the basis for the treatment and prognosis of the individual patient. Current practice of diagnosing epilepsy limits the diagnosis often to "undefined epilepsy" after the first seizures. We also speak about "common epilepsies" or "common epilepsy syndromes" in cases where known monogenic epilepsy syndrome cannot be readily identified.

Defining the type of epilepsy should be considered mandatory because both the prognosis and the management of the epilepsy is syndrome-related and differs markedly between various syndromes. The etiologic diagnosis requires identification of the cause of the epileptic seizures. The causes range from obvious structural abnormality of the brain to usually still obscure genetic abnormality. Every patient deserves a search for the etiologic diagnosis and appropriate specific therapy for this etiology, when possible. In most patients, the correct classification of seizure type(s) and, possibly, epilepsy syndrome permits the correct choice of therapy and the correct choice of antiepileptic drug. Our ability to establish an accurate diagnosis has been greatly aided by technical advances such as brain imaging (improved etiologic diagnosis) and intensive EEG-video monitoring (more precise seizure diagnosis). Although the seizure type diagnosis alone can help with the choice of medication, the epilepsy syndrome diagnosis is more important for predicting the prognosis and, potentially, the duration of therapy.

Recently major improvements have been made in both the seizure classification and the classification of the epilepsies as well as their etiologies. However a better clinical description of the epileptic phenotypes is needed to explain more precisely the genotypic and phenotypic heterogeneity, before major breakthroughs in the genetics of any of the complex epilepsies may be anticipated. The complexity and heterogeneity of the epilepsies make it difficult to ascribe a given phenotype to its underlying genotype. Many of the failures in finding susceptibility genes or positive findings in pharmacogenomics may have been caused by the lack of rigorous, reproducible, valid, methods of phenotyping for research. However, in addition to guiding rational subdivision of epilepsy syndromes for genetic analysis, phenotype definition provides a path to understanding molecular mechanisms and this in turn will improve our possibilities to treat our patients in future. So instead of "common" epilepsies we should have well specified epilepsy phenotypes in future as the basis of our treatment decisions, but do not necessaLinkage results from multiple genome scans, while supporting a genetic component, have given conflicting results, presumably due to genetic heterogeneity.

Syndrome identification as a basis for treatment decision
What is the problem: How common is "common epilepsy"?

Reetta Kälviäinen,
MD, PhD, Director
Kuopio Epilepsy Center
Kuopio University Hospital,
Kuopio

Medical Diagnosis

- Disease identification which provides a sure basis for the treatment and prognosis of the individual patient Critchley, 1986
- Patients with epileptic seizures are entitled to a diagnosis, prognosis and management that are specific and precise

Panayitopoulos, 2002

Factors influencing the prognosis and the progression in the epilepsies

- Seizure / epilepsy / syndrome type
- Age at onset
- Etiology
  - Initial Precipitating Insult (IPI)
- Seizure Burden
  - Duration
  - Frequency
  - Localization
- Epileptiform activity
- Treatment
  - Appropriate and inapproapriate AEDs, responsiveness
  - Surgical treatment, adequate timing

PROPOSED **DIAGNOSTIC SCHEME** FOR PEOPLE WITH EPILEPTIC SEIZURES AND WITH EPILEPSY

Engel et al. *Epilepsia* 2001;42(6):796-803

Axis 1 **Ictal phenomenology**
- detailed eye-witness description of symtoms during the seizure

Axis 2 **Seizure type or types**
- according to ictal phenomenology and EEG

Axis 3 **Syndrome**
- list of syndromes, syndromic diagnosing is not always possible

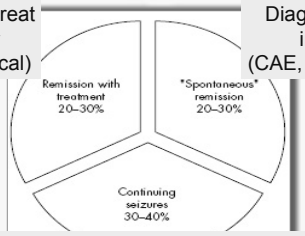
Axis 4 **Etiology**
- genetic defects, or specific pathological substrates for symptomatic focal epilepsies (imaging)

Axis 5 **Impairment**
- disability caused by epilepsy

Natural history of newly diagnosed epilepsy

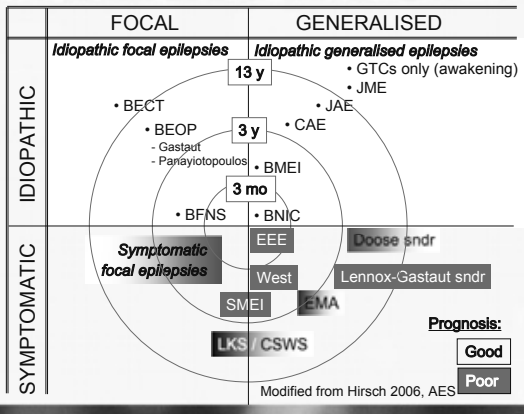
Diagnose and treat accordingly (JME, many focal)

Diagnose and give information (CAE, rolandic, stress)



Try to detect intractability early and look for necessary treatment options; epilepsy surgery etc. (TLE, ETLE with cortical malformations Epileptic encephalopathies)

Kwan et al. *JNNP* 2004



Modified from Hirsch 2006, AES

SYNDROME IDENTIFICATION AS A BASIS FOR TREATMENT DECISION
WILL GENETICS SOLVE THE PROBLEM?

Serratosa, JM.
Epilepsy Unit, Neurology Service, Fundacin Jiménez Diaz, and Autonoma University of Madrid, Madrid, Spain

Advances in the field of the genetics of the epilepsies are leading to a wide and more precise definition of epilepsy syndromes. Knowledge of these genetic advances may help the clinician reach a correct diagnosis and provide the most adequate treatment.

Family studies have lead to the definition of a significant number of previously undescribed epilepsy syndromes. Examples of genetic epilepsies described in the last decade include autosomal dominant nocturnal frontal lobe epilepsy, familial temporal lobe epilepsy, familial medial temporal lobe epilepsy with auditory features, autosomal dominant partial epilepsy with variable foci, autosomal dominant rolandic epilepsy with speech dyspraxia, and generalized epilepsy with febrile seizures plus, among others. Genetic research has been particularly useful to clearly define the main forms of progressive myoclonus epilepsy for most of which confirmatory genetic testing is now available and to better define the syndrome of Severe Myoclonic Epilepsy of Infancy and it¥s variants. Many malformations of cortical development have also been described by means of genetic studies and can now be considered specific epilepsy syndromes. In the future genetic testing may be used to detect increased risk to seizure recurrence and to predict drug response with respect to both efficacy and side effects.

The genetic approach to epilepsy syndromes implies understanding that a correct diagnosis may only be reached if the epilepsy phenotype expressed by each affected member is delineated and that genetic heterogeneity and wide and variable expression of gene mutations are the rule in the genetic epilepsies.

Finally, trials comparing outcome and quality of medical care comparing groups of patients that have undergone genetic testing with those that have not are necessary in order to assess the usefulness of genetic testing in clinical practice.

Syndrome identification as a basis for treatment decision

Will genetics solve the problem?

José M Serratosa
Unidad de Epilepsia
Fundación Jiménez Díaz
Madrid, Spain

Objective

To answer this question: Will genetic research affect treatment decision by means of more precise syndromic diagnoses?

Questions

Does syndromic diagnosis help in treatment decision? Yes

Does syndromic diagnosis direct to specific treatments? Sometimes

Genetic contribution to epilepsy syndromes

- New epilepsy syndromes
  - Must be considered when approaching a patient
- Epilepsy syndromes which can now be diagnosed using molecular genetic testing in clinical practice
  - Progressive myoclonus epilepsies (several genes)
  - Dravet syndrome (*SCN1A*)
  - Other rare epilepsies: Some MCDs or some West syndrome
- Genetic testing directed to the identification of allelic variants that contribute to the common epilepsies may be useful in the future in order to
  - Predict increased seizure risk
  - Select the most appropriate drug for each individual (highest efficacy - least side effects)

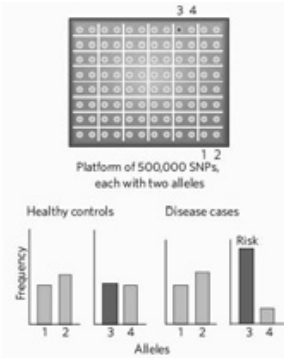
Syndromes that respond to specific treatments 1989 ILAE Classification

- **Idiopathic generalized epilepsies**
  - JME: VPA, LTG, LEV, ZNS
  - CAE: ETX, VPA, LTG, ZNS
  - JAE: VPA, LTG, ZNS
  - EGTCS: VPA, LTG, ZNS
- **Cryptogenic or symptomatic generalized epilepsies**
  - West syndrome: ACTH, VGB
  - Lennox-Gastaut syndrome: RUF, VPA, LTG, TPM
  - Epilepsy with myoclonic absences: VPA+ETX
  - PMEs: VPA, CZP, LEV, ZNS
- **Idiopathic partial epilepsies**
  - Benign occipital epilepsy of childhood: CBZ
- **Symptomatic/probably symptomatic partial epilepsies**
  - Lobar epilepsies: Almost all AEDs
- **Undetermined whether focal or generalized**
  - Dravet syndrome: STP+VPA+CLB

With a few exceptions (i.e. SMEI, PMEs), reported mutations represent only a minority of families and even less of sporadic cases

Low yield of genetic testing in the epilepsies

Near future: Identification of common variants



ROLE OF IMAGING IN PRACTICAL TREATMENT DECISION

Frank. Semah SHFJ, Orsay, France

Imaging is a very useful tool for the diagnosis of the aetiology in partial epilepsies. But MRI, SPECT and PET are also useful for the follow-up and for the treatment decision in patients with partial epilepsy.
MRI can be used for the early prediction of intractability in epilepsy that is a main challenge for clinicians.

Some prognostic factors have been pointed out. In adults, most of the prognostic factors underlined that partial epilepsy is more difficult to control than idiopathic generalized epilepsy. The main prognostic factors are the presence of a brain lesion (MRI or CT evidence of a lesion, neurological deficits,) or the consequences of such a lesion (developmental delay, focal EEG abnormalities, complex partial seizures). Little is known about the relationships between the location of the epileptogenic area and the chance of being seizure-free.

There are some evidences that temporal lobe epilepsy is often very difficult to control, but one explanation for that could be that hippocampal sclerosis is the main prognostic factor in partial epilepsy and that hippocampal sclerosis occurred mainly in temporal lobe epilepsy. Some studies have investigated if the epileptic syndrome itself or if the nature of the brain lesion are reliable prognostic factors. They are some clear evidences that the nature of the lesion is one of the main prognostic factors for partial epilepsy.

Several studies have shown that patients with partial epilepsy associated with hippocampal sclerosis or with cortical malformation demonstrated by MRI often suffered from medically refractory epilepsy. PET and SPECT are used in the presurgical evaluation of patients with medically refractory partial epilepsy. They can also be used for the preselection of patients candidates for surgery.

Role of the epileptic syndrome

Semah et al. Neurology 1998

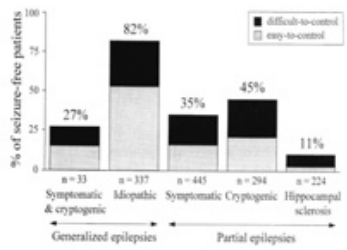
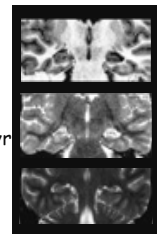


Figure 1. Seizure control according to the International League Against Epilepsy Classification of Epilepsies and Epileptic Syndromes.

Role of the etiology of partial epilepsy

Van Paesschen et al. Neurology 1997

- 63 patients with newly diagnosed partial epilepsy
  - Normal MRI : 76 %
  - Hippocampal sclerosis : 10 %
  - Other MRI abnormalities : 14 %
- Rate of seizure-free patients (after 1 yr of treatment)
  - 0 % : patients with HS
  - 49% : other patients



Role of the etiology in partial epilepsy

Semah et al. Neurology 1998

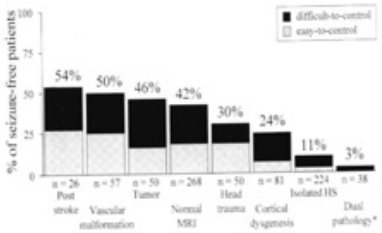
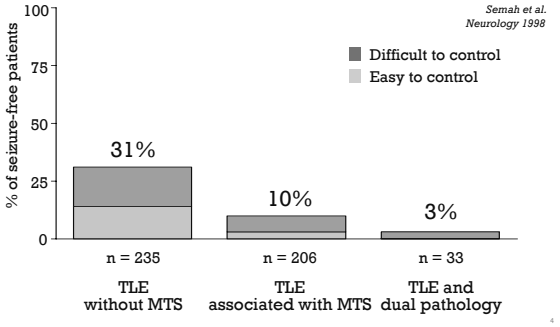


Figure 3. Seizure control in patients with partial epilepsy: The role of the brain abnormalities detected by MRI (association of HS with another lesion).*

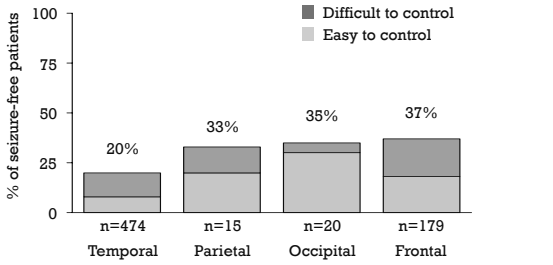
Role of the localization of the epileptogenic zone

Semah et al. Neurology 1998



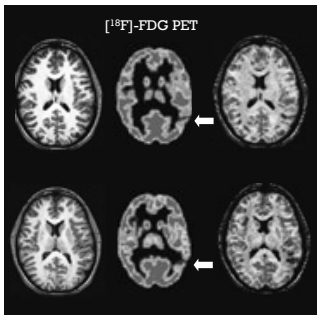
3. Role of the localization of the epileptogenic zone

Semah et al. Neurology 1998



Non lesional epilepsy : PET vs MRI

- Patients
  - 100 patients
  - Medically refractory partial epilepsy
  - Normal high-resolution MRI
- FDG-PET results
  - Abnormal FDG-PET
    - 82/100 patients
  - Hypometabolism
    - 86 % TLE
    - 75 % ETLE
  - FCD in 13/35 operated patients



ORAL PRESENTATIONS I - V
Saturday 29th march 10.35 - 10.50

I

FIBRILLAR B-AMYLOID ASSOCIATES WITH EPILEPTIC SEIZURES IN APPSWE/PS1DE9 MICE AND CHANGES EXCITABILITY IN CORTICAL AND HIPPOCAMPAL NEURONS

Minkeviciene R, Zilberter Y, Dobszay MB, Hartikainen J, Harkany T, Pitkänen A, Tanila H
A.I. Virtanen Institute, University of Kuopio, Finland, Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden, Division of Molecular Neurobiology, Department of Medical Biochemistry and Biophysics Karolinska Institutet, Stockholm, Sweden, Department of Neurology, Kuopio University Hospital, Finland

RATIONALE: Subjects with Alzheimer's disease (AD) have a higher risk to develop epileptic seizures as compared with non-demented patients of similar age. The occurrence of seizures is especially high in rare familial cases of AD with mutation in presenilins. However, until now there is no animal model for AD-related epilepsy.
METHODS: Video-EEG was recorded in 20 transgenic male C57BL/6 J mice carrying mutated human APPswe and PS1dE9 genes (APdE9 mice) and their wild-type littermates (n= 10) at 11-13 and 17-18 weeks of age. A separate group of 4-month-old APdE9 and control mice were tested for their behavioural reactivity by using the acoustic startle reflex. Finally, brain slices were prepared from an additional group of 3.5-month-old APdE9 and control mice for patch-clamp recordings.
RESULTS: APdE9 mice progressively developed seizures as they aged, so that by the end of the second recording period 65 % of APdE9 mice displayed electrographic seizures and 38% exhibited secondary-generalized seizures. No wild-type animals had seizures during the entire recording priod. The startle response was more robust in APdE9 mice than in wild type littermates. Patch clamp recordings in cortical slices revealed AB induced increase in pyramidal cell excitability. Somatic current injections showed lower threshold for action potential firing in APdE9 compared to wild-type mice. Extracellular stimulation induced higher EPSP and lower threshold for AP firing in APdE9 mice.
CONCLUSION. The APdE9 mouse model of AD provides a promising tool to study molecular mechanisms of AD-related epilepsy.

II

WHOLE BRAIN DIFFUSION TENSOR IMAGE (DTI) ANALYSIS BY TRACT-BASED SPATIAL STATISTICS (TBSS) IN A KAINIC ACID MODEL OF EPILEPSY.

A. Sierra, K. K. Lehtimäki, T. P. Laitinen, J. Nissinen, A. Pitkänen, and O. Gröhn
Department of Neurobiology, A,I.Virtanen Institute for Molecular Sciences, University of Kuopio, Finland, Department of Biotechnology and Molecular Medicine, A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, Finland, Department of Neurology, Kuopio, University Hospital, Kuopio. Finland.

RATIONALE: Diffusion tensor imaging (DTI) enhances anatomic details in rodent brain and can detect many pathological changes1. We have implemented a novel statistical analysis method, tract-based spatial statistics (TBSS)2, for the comparison of DTI data between control and epileptic animals. While the method has been successful in human applications3, no reports of TBSS analyses in the rodent brain exist.
METHODS: Status epilepticus (SE) was induced with kainic acid in male Wistar rats (n=6) and controls received saline (n=4). Six months after SE, animals were perfused intracardially using Timm fixation. DTI was carried out in a 9.4 T magnet using a 3D spin echo sequence. Imaging data were aligned to a common template and a mean fractional anisotropy (FA) map was created, thinned to represent mean FA skeleton. FA maps from individual subjects were projected onto this common skeleton and fed into the statistical group-analysis.
RESULTS: One of our main findings from TBSS analysis was dentate gyrus (DG) in which increased FA in kainic acid animals, i.e. higher directional dependency of water diffusion was detected, consistent with mossy fiber sprouting in DG4. Also other areas related to epilepsy were found including medial and lateral septum (FA increased), lateral habenular nucleus and superficial gray layer of superior colliculus (FA decreased). Additionally, we detected several new brain areas with altered FA in epileptic animals not discussed in the current epilepsy literature, such as stria medullaris.
CONCLUSION: Diffusion tensor imaging and TBSS combined with animal models have a great potential to serve as a robust screening method to guide tedious histological analysis to novel target areas in the brain.

III
MYELINIZATION IN THE CLN8MND CENTRAL NERVOUS SYSTEM

Mervi Kuronen, Ulla Lahtinen, Pentti Somerharju, Antti Pertovaara, Anna-Elina Lehesjoki, Outi Kopra
Folkhälsan Institute of Genetics and Neuroscience Center, University of Helsinki, Finland, Institute of Biomedicine, Department of Biochemistry, University of Helsinki, Finland, Biomedicum Helsinki, Institute of Biomedicine/Physiology, University of Helsinki, Finland

RATIONALE: Neuronal ceroid lipofuscinoses (NCLs; CLN1-CLN10) are a group of inherited neurodegenerative diseases characterized by accumulation of autofluorescent lysosomal storage material to various cell-types, notably to neurons. Clinical course includes progressive mental and psychomotor retardation, epilepsy and premature death. Mutations in the CLN8 gene account for two NCL disease phenotypes: Northern epilepsy enriched in Finland and the late infantile form enriched in Turkey. The orthologous Cln8 gene is mutated in motor neuron degeneration (Cln8mnd) mouse, a naturally occurring model for CLN8-deficiency. Mechanisms of neuronal dysfunction in the CLN8-related NCLs are largely unknown.
METHODS;Based on sequence homology, CLN8 has been proposed to have a role in lipid biosynthesis, metabolism and sensing. Thus, we have performed a large-scale lipid analysis of the one month-old Cln8mnd mouse cortices, which show a reduction in myelin-specific lipids (galactocerebroside and sulphatide) in the Cln8mnd brain. We are currently studying, whether the imbalance of galactolipids in Cln8mnd brains could reveal differences in Cln8mnd myelin formation and functionality.
RESULTS: Preliminary results show normal oligodendrocyte maturaturation in vitro as well as light microscopically normal myelin formation in the Cln8mnd brain. However, electron microscopical analysis indicates disrupted axon profiles in Cln8mnd mouse. Nerve conduction measurements are currently in progress to test the functionality of myelin.
CONCLUSION: This study indicates that myelin homeostasis has a key role in the pathophysiology of CLN8-deficiency. Dissecting disease mechanisms of individual NCL disorders will help us in understanding not only the pathophysiology of this related disease group but also neurodegenerative mechanisms in more common disorders.

IV
USE OF NAVIGATED TMS AND MEG FOR DETAILED FUNCTIONAL LOCALIZATION BEFORE EPILEPSY SURGERY
Vitikainen A-M, Lioumis P, Paetau R, Salli E, Komssi S, Metsähonkala L, Paetau A, Kicic D, Blomstedt G, Valanne L, Mäkelä J P, Gaily E.

RATIONALE: Conventionally invasive electrical cortical stimulation (ECS) mapping is required for preoperative identification of epileptogenic and eloquent cortical regions before epilepsy surgery. We present a case study of two young patients, who underwent two additional preoperative protocols to localize these essential cortical regions non-invasively before subdural recordings.
METHODS: Magnetoencephalography (MEG) was used to determine the primary somatosensory cortex (S1) and the ictal onset zones. Navigated transcranial magnetic stimulation (nTMS) was used to determine the location and particularly the extent of the primary motor representation areas, located in the vicinity of the epileptogenic areas in both patients. The localization results from these non-invasive methods were registered and compared with the results from ECS mapping using subdural grids, and displayed on the patientís 3-D MRI anatomy. The final validation was determined by surgery outcome
RESULTS: In these two patients, the results from MEG and nTMS localizations were consistent with the results obtained during ECS and subdural EEG recording. In addition, MEG and nTMS provided better spatial precision of the localizations than ECS. Based on ictal recordings with subdural grids, the epileptogenic region of the patients partly overlapped with the primary sensory area (of the hand in one patient and of the foot in the other). Both patients are free from disabling seizures after surgery and have only mild sensory defects, as expected.
CONCLUSION: The encouraging results suggest that the non-invasive methods may be able to replace ECS and subdural EEG recordings in epilepsy patients whose seizures are frequent enough for ictal MEG.

V

UNVERRICHT-LUNDBORG DISEASE (ULD): MAGNETIC RESONANCE IMAGING WITH VOXEL-BASED MORPHOMETRY IN THIRTY PATIENTS AND THIRTY MATCHED CONTROLS

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RATIONALE: Unverricht-Lundborg disease (ULD), progressive myoclonic epilepsy type 1 (EPM1, OMIM254800) caused by mutations of the cystatin B (CSTB) gene, is a rare autosomal recessive neurodegenerative disorder characterized by age of onset from 6-16 years, stimulus-sensitive myoclonus, and tonic-clonic epileptic seizures. Thus far, imaging studies of ULD patients are scanty and include only small numbers of patients.
METHODS: Thirty patients with genetically verified ULD (4 compound heterozygotes, 26 homozygotes) underwent MRI (1.5 Tesla, Siemens Avanto). MR imaging included T1- and T2-weighted spin-echo sequences, fluid attenuated inversion recovery sequence (FLAIR), T1-weighted three-dimensional images, MR spectroscopy and diffusion tensor imaging. Motion correction software was used if necessary. T1-3D images were analyzed using optimized voxel-based morphometry (VBM) and statistical parametric mapping (SPM2 running under Matlab 6.5) and compared with matched controls (n=30).
RESULTS: Conventional images revealed no focal abnormalities. In VBM ($p<0.001$), ULD patients showed gray matter volume loss in frontal premotor and supplementary motor areas, cuneus and thalamus bilaterally. No differences were seen in cerebellum or brain stem.
CONCLUSION: In spite of the stimulus-sensitive myoclonus, MR imaging was feasible in all patients. Detailed MR imaging, together with neurophysiologic evaluation may help to reveal the pathogenesis of ULD.

SCIENTIFIC ABSTRACTS

Poster presentations
Authors present on Saturday 29th march 2008
10.05 - 10.35 in the hall of light

1.KAINATE RECEPTORS IN THE ENTORHINAL CORTEX

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RATIONALE: The entorhinal cortex has been implicated to play a significant role in the origin of temporal lobe epileptsy (TLE). TLE leads to a massive neuronal loss in medial entorhinal cortex layer III (MEC-III) both in patients and in in-vitro studies of kainate-induced epilepsy. The functional role and the contribution of synaptic versus extrasynaptic kainate receptors (KARs) in the MEC-III neurons have not been elucidated so far.
METHODS: Whole cell voltage clamp recordings of locally evoked excitatory postsynaptic currents and focal uncaging of glutamate for recording extrasynaptic currents were made from MEC-III neurons in combined entorhinal cortex-hippocampal brain slices of rats.
RESULTS: The functional presence of KARs was shown by kainate concentration dependent changes in holding current. The IV-curve revealed the presence of
Ca2+ impermeable, edited form of the receptor. Extrasynaptic receptors
mediated a siginificantly larger KAR-current in comparison to the KAR-mediated synaptic currents. The KAR-current was resistant to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor antagonist GYKI-53655 (20microM) and sensitive to 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzoquinoxaline-7-sulfonamide (NBQX, 25 microM).
CONCLUSION: To conclude, KAR mediated currents and the functional role depend on receptor localization in the MEC-III neurons. Characterizing differences of these two types of receptors expressed in injury prone versus injury resistant MEC-III neurons represents an important step toward understanding the vulnerability of layer III neurons seen in epilepsy.

2.

INCREASED SEIZURE SUSCEPTIBILITY IN UPA+/- MICE

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RATIONALE: Urokinase-type plasminogen activator (uPA) regulates the developmental migration of cortical and hippocampal inhibitory interneurons. To investigate, whether abnormalities in uPA signalling associate with seizure susceptibility, we compared the seizure threshold between heterozygote uPA knock-out mice (uPA+/-) and wild type (wt) controls.

METHODS: Six uPA+/- and 10 wt controls (age 14-17 weeks) were injected with a single dose of pentylenetetrazole (60 mg/kg i.p.) under video-EEG control. Latency to the first spike and electrographic seizure activity as well as the total number of spikes and duration of epileptiform dischages were analyzed during the 60 min following PTZ administration.

RESULTS: uPA+/- mice showed shorter latencies (145 ± 66.6 sec) to the first electrographic epileptic seizure as compared with wt controls (mean 319 ± 181 sec, $P<0.05$, Mann-Whitney U-test). There was a trend towards shortened latency to the first electrographic epileptiform discharge and the first behavioural seizure manifestation in uPA+/- mice as compared to controls.

CONCLUSION:This study demonstrates that even a reduced uPA gene expression causes lowering in seizure threshold.

3.

CALRETININ-IMMUNOREACTIVITY IN THE DENTATE GYRUS IN TWO RAT MODELS OF ACQUIRED EPILEPSY

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RATIONALE: Calretinin (CR) is a Ca2+-binding protein that participates in transcellular Ca2+ transport. Injury-induced alterations in Ca2+ homeostasis play a pivotal role in synaptogenesis leading to epilepsy. According to our hypothesis, different epileptogenic etiologies trigger common alterations in neuronal circuits that underlie the development of spontaneous seizures. Here we compared reorganization of CR-immunoreactive (ir) circuits in the dentate gyrus in status epilepticus (SE) and traumatic brain injury (TBI) induced epilepsy.

METHODS: Brains from 12 controls and 12 adult male Sprague-Dawley rats with electrically induced SE (n=5) or lateral-fluid percussion-induced TBI (n=7) as models for epilepsy were used for analysis. One series of coronal 30-?m thick sections (1-in-5 series) was immunohistochemically stained with an antibody raised against CR (#7696, SWant). Distribution and morphology of CR-ir cells and processes were assessed semiquantitatively under light microscope. Estimation of total number of hilar CR-ir positive cells was done using unbiased stereology (MicroBrightField).

RESULTS: Semiquantitative analysis revealed no major differences in the distribution or morphology of CR-ir neurons in the dentate gyrus between the control, SE, and TBI groups. In the SE group, the total number of CR-ir neurons in the hilus did not differ from that of controls. In the TBI group, there was a 27% decrease in the number of CR-ir neurons ipsilaterally as compared to that controls ($p<0.05$).

CONCLUSION: Our data suggest that alterations in the CR-ir circuits are model-specific rather than universal in different epileptogenic etiologies.

4.

QUANTITATIVE MRI PARAMETERS IN HIPPOCAMPUS ACUTELY AFTER TRAUMATIC BRAIN INJURY CORRELATE WITH LONG TERM FUNCTIONAL AND HISTOPATHOLOGICAL OUTCOME

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RATIONALE: Aim of this study was to characterize the potential of quantitative MRI to predict the long-term functional outcome and the neuroplastic developments of the hippocampus following traumatic brain injury (TBI).
METHODS: Pathological changes of quantitative magnetic resonance imaging (MRI) parameters T2, T1? and diffusion in hippocampus were measured at 4.7T magnet in acute and subacute phase (3h, 3d, 9d and 23d) after traumatic brain injury (TBI). In this clinically relevant rat model of post-traumatic epilepsy (PTE) the TBI was induced by lateral fluid percussion and the animals were followed for a year. Long-term functional outcome measures were acquired using Morris water maze to test hippocampus related learning and memory impairment. In histological studies the density of mossy fiber sprouting and neuronal loss were assessed.
RESULTS: All T2, T1 and diffusion in the hippocampus ipsilateral to the impact site displayed pathological changes. The swimming latency in water maze correlated with T1 in acute (3h post-TBI, r=0.642*), subacute phase at 3d (r=0.684**) and at 23d (r=0.544*) and with diffusion at 9d (r=0.609*) and at 23d (r=0.560*). The final density of mossy fiber sprouting correlated with diffusion at 3h (r=-0.929**). The neuronal loss correlated with T2 at 23d post-TBI (r=0.613*), with T1? at 9d (r=0.649*) and 23d (r=0.632*) and with diffusion at 23d (r=0.556*). [*, $p<0.05$; **, $p<0.01$]
CONCLUSION: Quantitative MRI was able to detect acute primary changes and subacute, secondary processes in the hippocampus. Importantly, these MRI findings correlated with the long-term learning impairment and axonal plasticity in the dentate gyrus.

5.

PILOCARPINE-INDUCED STATUS EPILEPTICUS TRIGGERS ANGIOGENESIS IN ADULT RAT HIPPOCAMPUS

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RATIONALE: Angiogenesis is one of the molecular processes associated with the development of epilepsy. It is not clearly understood however, when this process actually starts, the rate at which it occurs during epileptogenesis and how it influences subsequent progression of epilepsy.
METHODS: To address some of these questions we used pilocarpine-induced status epilepticus (SE) model of temporal lobe epilepsy and determined using unbiased stereological methods, the microvessel length changes and the number of proliferating endothelial cells in the hippocampus at 2 days, 4 days and 2 weeks post SE.
RESULTS: When all the sub-regions (CA1, CA3 and Molecular Layer) were pooled together, there was a 17% ($P<0.05$) decrease in microvessel length at 2days post SE compared to controls. Nevertheless there was an increase in vessel length in the CA3 at 2weeks post SE ($P<0.01$). We observed, as well an increase in number of proliferating endothelial cells in all sub-regions of the hippocampus at 4days post SE compared to controls ($P<0.001$). No difference was seen in the number of proliferating endothelial cell between the CA1, CA3 and molecular layer of the hippocampus at any time points.
CONCLUSION: This findings goes to demonstrate that angiogenesis is an active process during epileptogenesis. It start as early as 2 days following SE, suggesting that this process can serve as a possible novel target for studying epileptogenesis.

6.

QUANTITATIVE T2 MAPPING AS A POTENTIAL MARKER FOR SEVERITY OF POST-TRAUMATIC DAMAGE AFTER FLUID PERCUSSION BRAIN INJURY IN RAT

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RATIONALE:Occurrence of post-traumatic epilepsy (PTE) positively correlates with severity of traumatic brain injury (TBI). This project aimed to identify reliable markers for severity of post-traumatic tissue damage at an early, seizure free stage in a clinically relevant model of closed head injury, which results in PTE in severe cases.
METHODS: Lateral fluid-percussion injury was used as a model of TBI. Adult male Sprague-Dawley rats (n=48, 12 controls) were divided into moderate (mTBI) and severe (sTBI) groups according to impact strength. MRI data were acquired 3 days post-injury. Motor deficits were analysed using neuroscore and beam balance (BB) tests 2 and 3 days post-injury, respectively. Spatial learning and memory was tested in Morris water maze (MWM) 10 days post-injury.
RESULTS:T2 values in the lesion area were higher in injured animals compared to controls ($p<0.01$), and in sTBI compared to mTBI ($p<0.01$). T2 values in the hippocampus ipsilateral to injury were increased in TBI animals compared to controls ($p<0.01$). Latency in MWM correlated positively with the increased T2 values of the lesion ($p<0.001$) and the hippocampus ($p<0.05$). Neuroscore and BB test results showed negative correlations with T2 values of the lesion ($p<0.001$). Also, neuroscore correlated negatively with T2 values of the hippocampus ipsilateral to injury.
CONCLUSION: Quantitative T2 measurement of the lesion and hippocampus early after TBI can serve as an indicator of the severity of post-traumatic tissue damage and functional impairment and thus, has a potential as a clinical marker for identification of individuals with elevated risk of PTE.

7.

NEW CANDIDATE LOCUS ON CHROMOSOME 17Q12-Q24 FOR FEBRILE AND BENIGN SENSORY SEIZURES AND CHILDHOOD ABSENCE EPILEPSY - A CLINICAL AND GENETIC STUDY IN A FINNISH FAMILY

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RATIONALE: To describe the clinical and genetic features in a family with febrile seizures (FS), childhood absence epilepsy (CAE) and benign sensory seizures.
METHODS: Clinical, EEG and imaging data were collected by interviews and from medical records. DNA samples were obtained and linkage analysis was performed with microsatellite markers throughout the genome and finally with closely spaced markers in the linked region. Multipoint location scores were calculated with SimWalk2. Of the candidate region nine candidate genes coding ion channel proteins expressed in the brain were sequenced. mRNA profiling of the whole blood samples was performed with Illumina whole genome chips to identify candidate genes.
RESULTS: The pedigree included nine affected subjects. Three patients presented with a simple FS and one with CAE. Two patients had complex FS. Four patients had experienced sensory seizures. Inheritance pattern was autosomal dominant. After the genome wide scan, a significant linkage was detected on chromosome 17q12-q24 with a maximum location score of 3.1. No causative mutation was found in the sequenced genes. Blood gene expression analyses revealed one up-regulated and five down-regulated genes in the mapped area.
CONCLUSIONS: We report a new locus for febrile and afebrile seizures on chromosome 17q12-q24. The disease gene remains to be identified.

8.

EPILEPTIC ENCEPHALOPATHY IN PATIENTS WITH TWINKLE MUTATIONS

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RATIONALE: Infantile onset spinocerebellar ataxia (IOSCA) (MIM271245) is caused by a homozygous mutation - Y508C - in PEO1 gene, coding for mtDNA helicase Twinkle, which is associated with mtDNA maintenance. We diagnosed 24 patients with Twinkle mutations (22 homozygous for Y508C , 2 Y508C /A318T compound heterozygotes). The disease manifests as progressive symptoms in young children with early normal development. Ataxia, hypotonia, hearing deficits and neuropathy develop by school age. We report on the epileptic encephalopathy, which is a late and often fatal manifestation of the disease.
METHODS: Seventeen of the 24 patients developed epilepsy. We present the clinical progress from the onset of seizures to the development of catastrophic encephalopathy, problems with the choice of antiepileptic drugs, MR images and neuropathological findings.
RESULTS: Epilepsy manifested between 2 and 31 years of age (mean 22 years). Focal clonic seizures proceeded through a phase of continuous partial seizures to status epilepticus in 15 patients, 8 of whom died. The seizures were preceded by abdominal pain, nausea, restlessness and migraine. Stroke-like lesions were seen in MRI and brain atrophy with focal laminar cortical necrosis and hippocampal damage on neuropathological examination.
CONCLUSIONS: Recessive Twinkle mutations cause epileptic encephalopathy, stroke-like lesions and laminar cortical necrosis similar to those seen in other mitochondrial disorders, e.g. MELAS.

9.

POLG MUTATIONS CAUSE SEVERE EARLY ONSET EPILEPSY WITH LIVER FAILURE

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RATIONALE: Mutations in mitochondrial polymerase-gamma (POLG) can present from infancy to adulthood with variable clinical presentations like Alpers-Huttenlocher syndrome, recessive ataxia-neuropathy syndrome (MIRAS) and PEO (progressive external ophtalmoplegia). We describe five Finnish patients of infantile/childhood-onset encephalopathy with compound heterozygous missense mutations in POLG1 gene.
METHODS: Patients were evaluated clinically. Neuroradiological and neurophysiological investigations were done. Muscle biopsy was performed with respiratory chain enzyme analysis and immunohistochemical studies. Neuropathological examination was performed on two patients. POLG1 gene was sequenced.
RESULTS: We found 5 children with 5 different mutations in POLG1. All patients had either W748S or A467T mutation, the other mutation varied. The disease onset was encephalitis-like with vomiting, decreased consciousness and recurring seizures progressing to epilepsia partialis continua and status epilepticus, myoclonias, hemiparesis, ataxia, tremor and visual disturbance. Age at onset was 9 months ñ 6 years. Elevated liver transaminases were detected, often connected with the start of antiepileptic medication, but the administration of sodium valproate caused irreversible liver failure. Patients died 5 months-11 years after disease onset. They had no typical mitochondrial pathology in muscle biopsy or respiratory chain enzyme analysis. EEG findings consisted of focal slow wave or spike-slow wave discharges shifting from one hemisphere to the other. MRI findings included transient lesions and atrophy; laminar cortical necrosis and hippocampal atrophy were seen in neuropathological examination.
CONCLUSIONS: POLG mutations are an important cause of early-onset encephalopathy with severe epilepsy, and sodium valproate is toxic to these patients and can lead to fatal liver failure.

10.

MOLECULAR GENETICS OF AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY (ADNFLE) IN FINLAND

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RATIONALE: ADNFLE was the first epileptic disorder for which the defective gene was identified, in 1995. Eight different ADNFLE causing mutations, involving the genes CHRNA4, CHRNB2 and CHRNA2, have been reported, implying genetic heterogeneity. In Finland, no ADNFLE-associated mutations have so far been described. Here we aimed to determine the molecular genetic background of ADNFLE in Finnish families.
METHODS: Four Finnish families and one sporadic patient with nocturnal frontal lobe epilepsy were included in this study. Altogether 11 candidate loci harboring genes encoding for nicotinic acetylcholine receptor (nAChR) protein family subunits, were evaluated by haplotype and linkage analysis. Sequence analysis was performed for CHRNA4, CHRNB2 and CHRNA2.
RESULTS: In a large pedigree segregating ADNFLE in four generations, possible linkage was detected in regions 15q14 and 20q13.3 harboring CHRNA7 and CHRNA4, respectively. Sequencing of CHRNA4 revealed a missense mutation (c.839C>T) resulting in the p.Ser280Phe substitution. p.Ser280Phe has previously been described in three ADNFLE families of Australian, Spanish and Norwegian origins. Sequencing analysis of CHRNA7 is ongoing. In the three smaller families and the sporadic patient CHRNA4, CHRNB2 and CHRNA2 were sequenced, with no coding mutations or sequence variants identified.
CONCLUSIONS: We report a fourth family with the CHRNA4 p.Ser280Phe mutation, which comprises the most common known mutation underlying ADNFLE, possibly due to a mutation hot spot. Sequencing analysis of CHRNA7 will reveal whether this gene exerts a modifying effect on the ADNFLE phenotype. In the other patients from four families no ADNDLE associated mutations were identified. Whether these cases are due to mutations in other nAChR protein family subunits remains to be studied.

11.

INTRACTABLE STATUS EPILEPTICUS IN PATIENTS WITH JUVENILE-ONSET ALPERS SYNDROME AND WITH HOMOZYGOUS W748S MUTATION IN THE POLG1 GENE

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RATIONALE: Polymerase gamma (POLG) is the sole enzyme in the replication of mitochondrial DNA (mtDNA). Mutations in the POLG1 gene have been detected in patients with various phenotypes including a classic infantile-onset Alpers-Huttenlocher syndrome (AHS). Here we describe three teenagers with juvenile-onset AHS manifesting with status epilepticus and liver disease.
METHODS: We examined 14- and 17-year-old female siblings (patients 1 and 2) and an unrelated 15-year-old girl (patient 3) with juvenile-onset AHS, sequenced POLG1 and the entire mtDNA, examined mtDNA deletions by amplification of the full-length mtDNA with the long PCR method and used real-time PCR to quantify mtDNA in the tissue samples.
RESULTS: The initial manifestations were migraine-like headache and epilepsy, and the terminal manifestations status epilepticus and hepatic failure. A homozygous W748S mutation in POLG1 was detected in each patient. No deletions were found in mtDNA, but all three patients had mtDNA depletion.
CONCLUSIONS: POLG mutations should be considered in teenagers and young adults with intractable seizures or status epilepticus and acute liver failure. The W748S POLG1 mutation seems to lead to tissue-specific, partial mtDNA depletion in patients with juvenile-onset Alpers syndrome. Valproic acid should be avoided in the treatment of epileptic seizures in these patients.

12.

CLINICAL PHENOTYPES OF FINNISH PATIENTS WITH SCN1A MUTATIONS

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RATIONALE: Mutations in SCN1A are associated with many epilepsy syndromes such as severe myoclonic epilepsy of infancy (SMEI). We studied the clinical phenotype in 13 Finnish patients with SCN1A mutations.
METHODS: Clinical data were collected from patients that had been referred to the Epilepsy Unit at HUCH because of drug-resistant seizures and followed up from 6 to 18 years. The exons and exon-intron boundaries of SCN1A were amplified from genomic DNA and the PCR products sequenced with an ABI 3730 DNA Analyzer.
RESULTS: We found two nonsense, one frameshift-causing, two splice site, and eight missense mutations in SCN1A. Two mutations were also detected in other family members with history of epilepsy or febrile seizures. Seizure onset was from three to nine months of age. The first seizure was tonic-clonic in twelve patients and myoclonic jerks in one. Twelve patients had myoclonic seizures and eleven had episodes of convulsive status. In MRI, three patients showed mesial temporal sclerosis, two had dysmyelinization in the anterior temporal lobes and one had mild atrophy. Ten patients were mentally retarded, two had significant learning difficulties, and one was cognitively normal.
CONCLUSIONS: Eight patients had classical SMEI with episodes of status epilepticus, myoclonias and mental retardation. A milder phenotype with one or two of these features missing was observed in five patients. Structural abnormalities in the temporal lobe were common. Our findings are compatible with previous findings showing that de novo SCN1A mutations are a major cause of SMEI although the clinical presentation may vary.

13.

IMPLEMENTATION OF THE MODIFIED ATKINS DIET IN REFRACTORY CHILDHOOD EPILEPSY

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RATIONALE: Recent studies have suggested that the ketogenic diet could be replaced by the modified Atkins diet (MAD) which is less restrictive. The aim of this study was to assess how MAD can be implemented as a treatment for refractory childhood epilepsy in Finland.
METHODS: Six 2-11-year-old patients were started on MAD in-hospital from June 2006 through June 2007 and followed prospectively for at least six months. Five patients had symptomatic epileptic encephalopathy with severe mental deficiency and one had partial epilepsy with milder cognitive delay. Previous therapies included drug polytherapy (all patients), epilepsy surgery (two) and VNS (one).
RESULTS: Five patients discontinued the diet before six months. The diet was stopped because of side effects in two patients, refusal to eat the diet meals in two and lack of efficacy in one patient. One patient with concomitant high-dose topiramate had recurrent hypokalemia and acidosis which resolved after diet discontinuation. Other observed side effects included gastrointestinal symptoms, fatigue, retarded weight gain, lack of appetite and disturbed sleep. One patient continued MAD because it was better tolerated than medication. None of the patients had a >50% seizure reduction.
CONCLUSION: Severe intractability may partly explain the poor success of MAD in our patients. We also observed poor compliance with the diet, emphasizing the importance of easily available support from experienced staff members. Children whose natural diets are largely based on carbohydrates should try MAD meals at home before starting the diet. High-dose topiramate should probably be avoided during MAD.

14.CORTICAL EXCITABILITY IN UNVERRICHT-LUNDBORG DISEASE (EPM1)

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RATIONALE: Unverricht-Lundborg disease (ULD) is the most common form of progressive myoclonus epilepsies. The main symptoms include stimulus-sensitive myoclonic jerks and generalized epileptic seizures1. By using MRI-navigated brain stimulation (NBS)2 we aimed to study, whether these symptoms could derive from changes of cortical excitability.
METHODS: Twenty-four genetically verified ULD patients (12 male, 12 female, age 32±10 years) were studied and compared with healthy, age- and gender-matched subjects. All ULD patients were homozygous for the CSTB gene mutation. Individual T1-weighted MR-images were used to target the magnetic stimulation at the primary motor cortex (M1) to locate the representation area of the thenar muscles. Motor thresholds (MTs) were determined on both hemispheres to evaluate the level of cortical excitability. MTs were defined as the percentage of maximum stimulator output intensity that produced 5 peripheral EMG responses out of 10 trials3. Latencies and amplitudes were measured by averaging the EMG responses of 10 consecutive stimuli induced at 120% intensity of the MT.
RESULTS: The MTs were significantly ($p<0.001$) higher in ULD patients (65±11%) than in control subjects (43±10%). The latencies and the amplitudes of the EMG responses did not differ significantly between the groups.
CONCLUSIONS: The higher MTs in ULD patients suggest a prevailing inhibitory tonus of the M1 indicating a possible reactive change to the disease itself. Although antiepileptic drugs may contribute to the reduced excitability, it seems unlikely that the symptoms of ULD are caused by cortical hyper-reactivity. The observed changes may in the future give more information on the origin of ULD.

15.

QUALITY OF LIFE AFTER EPILEPSY SURGERY IN CHILDREN AND ADOLESCENTS

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RATIONALE: Previous studies suggest that health related quality of life (HRQOL) of adults is improved after epilepsy surgery, but similar data are scarce in children and adolescents. We measured HRQL in operated epilepsy patients most of whom were less than 16 years old at surgery
METHODS: Two questionnaires measuring postoperative HRQOL were sent to 118 patients operated in HUCH from 1991 through 2004. 15D was used for patients over 16 years, 16D for ages 12-15 years and 17D for ages 0-11 years. Disease specific QOLIE-31 was used for all patients. Clinical data was obtained from hospital charts retrospectively
RESULTS: Forty-eight patients responded. 29 patients were under 16 years old. The mean age at surgery was 8 years (range 0.4-15.6y) in children and adolescents and 32.4 years in adults (range 17-59y). Twenty patients underwent extratemporal resections, 24 temporal resections and four callosotomy. After one year, 31 patients had Engel I outcome, seven Engel II, five Engel III and five Engel IV. The mean HRQOL follow-up after operation was 4.4 years (range 0.28 ñ12.06y). The mean overall HRQOL scores for patients under 16 years were 0.84 (16D-17D) and 70.7 (QOLIE-31), and for adults, 0.89(15D) and 71(QOLIE-31). Seizure outcome correlated with QOLIE-31 scores ($p=0.000$, $r=0.578$**) and with 16D-17D scores ($p=0.026$, $r=0.474$*) in children and adolescents. Time interval after operation did not covary with HRQOL results ($p=0.557$ for QOLIE-31 and $p=0.980$ for 15D-17D).
CONCLUSION: Good seizure outcome is associated with better quality of life by the instruments used in this study in children and adolescents after epilepsy surgery. The length of time after operation did not affect HRQOL-scores.

16.

COST-EFFECTIVENESS OF SURGERY FOR INTRACTABLE TEMPORAL LOBE EPILEPSY.

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RATIONALE: Surgery for temporal lobe epilepsy (TLE) is effective for intractable patients. The objective of this study was to determine whether TLE-surgery and drug treatment for adults with medically intractable epilepsy (MIE), is cost-effective in comparison to drug treatment only.
METHODS: 140 adult MIE patients operated for drug-resistant TLE at KUH between 1988 and 1999 were asked to participate to the study during March-April 2004. 65 patients responded. In a mirror-image design, direct treatment costs were measured before and after epilepsy surgery. Outcome measures for cost-effectiveness (CE) analysis were the number of epileptic seizures and costs related to treatment of MIE in three years before and after TLE-surgery. CE was reported as an incremental CE-ratio, CE-plane and CE-acceptability curve with and without psychiatric treatment costs.
RESULTS: With psychiatric treatment costs, the incremental cost of one avoided epileptic seizure by surgery in comparison to treatment without surgery was 98 Ä, and without psychiatric costs 86 Ä. Based on probabilistic sensitivity analysis the mean incremental effectiveness was 367 (CI 95%: 235-555) avoided epileptic seizures. The mean incremental cost was 36056 E (29497E-43498E) and excluding psychiatric costs 31669 E (26342E-37090E). TLE-surgery reduced substantially need for postoperative care for MIE. Average treatment costs for postsurgical period excluding surgery and psychiatric treatment costs were 9048 E in comparison to 17188 E in presurgical period.
CONCLUSION: Surgical together with medical treatment was more effective but more costly than drug treatment alone. If assumed that TLE-surgery in successful cases remains its effectiveness, then after 5 years TLE-surgery would be cost saving.

17.

LONG-TERM COGNITIVE OUTCOME IN 36 CHILDREN WITH ENCEPHALOPATHY WITH STATUS EPILEPTICUS DURING SLEEP (SES) OR ESES SYNDROME

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RATIONALE: Few previous studies have described the outcome of ESES syndrome (ESESS) which is characterized by focal and/or apparently generalized epileptic seizures, neuropsychological impairment and a pattern of diffuse spike wave occurring in up to 85 per cent of slow wave sleep on EEG (ESES). We report the results of long term follow-up of children with ESESS.
METHODS: Since 1991, we have prospectively followed all children with ESESS diagnosed at our unit. All diagnostic and follow-up evaluations included overnight EEG and neuropsychological examination. Primary treatment response was defined as cessation of CSWS. We included all 36 children who had been followed for at least seven years in this study.
RESULTS: The non-symptomatic group comprised twelve children with Landau-Kleffner syndrome and six with atypical Rolandic epilepsy. In the symptomatic group (N=18), twelve children had vascular etiology and five had a cortical malformation. Thirteen had a CP syndrome. Four were intellectually impaired before ESESS.
The diagnosis of ESESS was made at a mean age of 5.3 years. Response to medication was achieved in 18 children at a mean age of 7.8 years after a mean duration of 3.2 years of ESES. Eight children underwent epilepsy surgery. At latest follow-up, 12 children (33%, eight from the non-symptomatic and four from the symptomatic group) had no or subtle cognitive disturbances, 14 had mild, seven moderate and three severe intellectual impairment. Cognitive prognosis was best in children with medical treatment response and previously normal cognitive level without a clear effect of the duration of ESES.
CONCLUSIONS: Cognitive prognosis is favourable in less than half of the children with ESESS. Early surgical intervention should be offered early for medically resistant children with symptomatic etiology.

18.

INTERICTAL MAGNETOENCEPHALOGRAPHY (MEG) SPIKES REVEAL FOCAL CORTICAL DYSPLASIA TYPE 2B

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RATIONALE: Focal cortical dysplasias (FCDs) are highly epileptogenic, but challenging targets for surgery, because they may be poorly visible on MRI, and often have extra-temporal and sulcal location. We studied the sensitivity of magnetoencephalography (MEG) to identify the epileptogenic FCD2b (with balloon cells).
METHODS: We included 11 patients operated during 1999 through 2007, whose pathologico-anatomical examination revealed FCD2b and, who had been studied with MEG preoperatively. The presurgical work-up also included structural 1.5 and / or 3-Tesla magnetic resonance imaging (MRI) and long-term video-EEG. The extent of resection was based on preoperative findings and extraoperative subdural grid recordings, including direct cortical stimulation mapping. Ten patients were seizure-free after surgery during follow-up ranging from 3 months to 8 years.
RESULTS: MRI revealed FCD lesions in nine patients: four in the superior frontal sulcus, one in the medial frontal cortex, and four in the sulci adjacent to the primary sensori-motor (SM1) cortex. In eight patients, MEG spikes were generated at the epileptogenic cortex; two of these patients had normal 3-T MRI, but microscopic FCD2b in the right SM1 (one patient) and in the right temporo-parietal cortex (one patient). Three patients with MRI lesion showed no MEG spikes (one baby and two with rare spikes), and two patients generated sylvian spikes outside the epileptogenic lesion.
CONCLUSION: MEG spikes appear sensitive in localizing the epileptogenic FDC2b region, sometimes even in patients, whose FCD2b is beyond MRI resolution. This may be due to the typically sulcal location and abundant electrical activity of FCD2b.

19.

CORRELATIONS OF MYOCLONUS SEVERITY ASSESSED WITH UNIFIED MYOCLONUS RATING SCALE WITH CLINICAL PHENOTYPE CHARACTERISTICS IN PATIENTS WITH UNVERRICHT-LUNDBORG DISEASE (EPM1)

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RATIONALE: Unverricht-Lundborg disease (ULD) is an autosomal recessively inherited neurodegenerative disorder characterized by stimulus-sensitive myoclonus, and epileptic seizures. Severity and progression of ULD are known to vary from patient to patient even within the same family. We aim to provide additional characterization of the clinical disease phenotype and identify possible factors influencing patient-to-patient variation.
METHODS: Twenty three individuals homozygous for the dodecamer repeat expansion mutation and four patients carrying compound heterozygous expansion and the c.202C>T mutations in the CSTB gene were studied. Medical history was collected retrospectively from hospital records. Myoclonus severity was assessed using Unified Myoclonus Rating Scale (UMRS) test panel including Stimulus Sensitivity, Myoclonus with Action and Functional Test sections which were video-recorded and evaluated using standard protocol. Verbal (VIQ) and performance (PIQ) intellectual abilities were assessed with three verbal subtests of WAIS-R (Wechsler Adult Intelligence Scale Revised) during neuropsychological testing.
RESULTS: The Myoclonus with Action score significantly negatively correlated with the age at onset of the disease ($P < 0.01$) but not with the disease duration. In addition, intellectual abilities, especially PIQ, of the ULD patients were found to be below average and negatively correlate with myoclonus severity.
CONCLUSIONS: We present preliminary clinical results of the ongoing study carried out as a part of EPIMEC consortium which aims to unravel the disease mechanisms in EPM1. Age at onset of the disease appears to be a significant predictor of the disease progression, whereas, absence of disease duration and myoclonus severity correlation supports previous findings suggesting that the progression of the disease tends to stabilize over time. Finally, performance IQ seems to be strongly affected in the course of the disease.

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