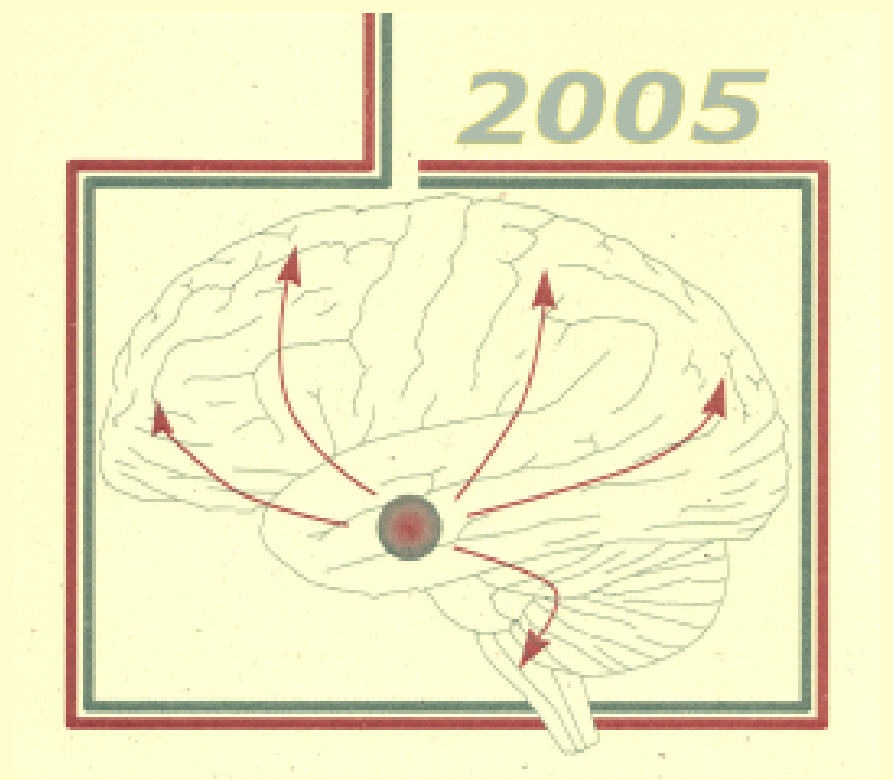
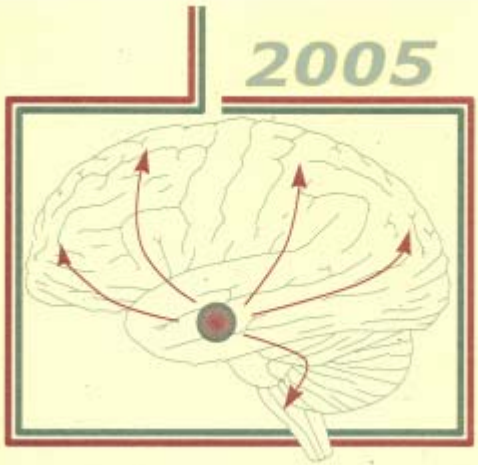
Program and Abstracts



Kuopio Epilepsy Symposium 2005



Kuopio Epilepsy Symposium 2005

Kuopio Music Centre, Kuopio, Finland

June 17-18, 2005

ORGANIZERS:
A.I.Virtanen Institute, University of Kuopio ⊙ Finnish Epilepsy Society
Department of Neurology, University of Kuopio ⊙ Finnish Epilepsy Association
UKU Neuroscience Graduate School ⊙ A.I.Virtanen Graduate School
Finnish Graduate School of Neuroscience

WELCOME TO KUOPIO

On behalf of the Finnish Epilepsy Society and the Finnish Epilepsy Association, we cordially welcome you to participate in "Kuopio Epilepsy Symposium 2005" in Kuopio, June 17-18 2005.

The meeting will be the fourth in a series of epilepsy meetings that are organized jointly by the A.I.Virtanen Institute for Molecular Sciences and the Department of Neurosciences and Neurology, University of Kuopio. We collaborate also with the Finnish Graduate School on Neuroscience.

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 Chair of the Organizing Committee

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

ORGANIZING COMMITTEE

Program Chair:
Docent
Reetta Kälviäinen
Program Co-Chair:
Professor
Asla Pitkänen
Professor
Matti Sillanpää
Mrs.
Pirkko Sormunen
Scientific Secretary:
Dr. **Leena Jutila**
Secretary:
Tuija Parsons

PROGRAM

FRIDAY, JUNE 17TH 2005

07:30 - Registration

OPENING OF THE SYMPOSIUM

08.30 - 08.45 **Rector of the University of Kuopio** Matti Uusitupa
Program Chair Dr. Reetta Kälviäinen

08.45 - 09.30 **KEY NOTE ADDRESS:**
Treatment of epilepsy today – evidence-based or not?
Prof. Emilio Perucca (Italy)

POSTTRAUMATIC EPILEPSY
Chair: Prof. Asla Pitkänen (Finland)

09.30 - 10.00 **Head trauma-induced epileptogenesis as a clinical problem**
Prof. Allen Hauser (USA)

10.00 - 10.30 **Traumatic brain injury in Finland**
Dr. Olli Tenovuo (Finland)

- Coffee -

11.00 - 11.30 **Lessons from experimental post-traumatic epilepsy - is all symptomatic epilepsy the same?**
Prof. Asla Pitkänen (Finland)

11.30 - 12.00 **Current state of the antiepileptogenic treatment after traumatic brain injury in humans**
Prof. Nancy Temkin (USA)

- Lunch -

EVOLUTION AND PROGNOSIS OF EPILEPTIC SYNDROMES
Chair: Prof. Matti Sillanpää (Finland)

13.00 - 13.45 **Epidemiology and evolution of epileptic syndromes**
Dr. Peter and Carol Camfield (Canada)

Evolution and prognosis:

13.45 - 14.15 **Infantile encephalopathies**
Dr. Marja-Liisa Granström (Finland)

14.15 - 14.45 **Are febrile seizures epileptogenic? Markers, models, mechanisms**
Prof. Tallie Z Baram (USA)

- Coffee -

15.15 - 15.45 **Idiopathic epilepsies with absence seizures**
Dr. Liisa Metsähonkala (Finland)

15.45 - 16.30 **Evolution of EEG during CNS maturation**
Dr. Perrine Plouin (France)

PREBANQUET SESSION:
INTERACTIVE EPILEPTOLOGY THROUGH CHALLENGING CASE STUDIES
Chair: Dr. Reetta Kälviäinen (Finland)

18.00 - 18.30 **Evaluating seizures and diagnosing epilepsies and syndromes**
Drs. Peter and Carol Camfield (Canada)

18.30 - 20.00 **Interesting cases**
Drs. Peter and Carol Camfield (Canada)
Interactively voted and discussed with the audience

20.00 - 22.00 **Banquet**
Kuopio Music Centre

SATURDAY, JUNE 18TH 2005

08.00 - 08.45 **KEY NOTE ADDRESS:**
Diagnosis, treatment and outcome of intracranial tumors as etiologic factor for epileptic seizures
Prof. Juha Jääskeläinen and Dr. Arto Immonen (Finland)

STATUS EPILEPTICUS
Chair: Prof. Allen Hauser (USA)

08.45 - 09.05 **Consequences of status epilepticus - developmental aspects**
Docent Hana Kubova (Czech Republic)

09.05 - 09.25 **Epidemiological data from cohort studies: Helsinki, Kuopio, Tampere**
Prof. Seppo Soinila (Finland)

09.25 - 09.45 **Treatment in adults**
Dr. Reetta Kälviäinen (Finland)

09.45 - 10.05 **Treatment in childhood**
Prof. Kai Eriksson (Finland)

- Coffee -

EPILEPSY RESEARCH GRANTS SYMPOSIUM
Chairs: Prof. H Soininen and Prof. Matti Sillanpää (Finland)

10.35 - 11.15 **Presentation of the Vaajasalo Foundation Grants**
Lecture(s) given by the awardee(s)

11.15 - 12.00 **Presentation of the Epilepsy Research Foundation Grants**
Lecture(s) given by the awardee(s)

- Lunch -

13.00 - 13.45 **PLENARY LECTURE:**
Stem cells and gene therapy – any use in the treatment of epilepsy?
Dr. Merab Kokaia (Sweden)

EPILEPSY AND PREGNANCY
Chair: Dr. Tapani Keränen (Finland)

13.45 - 14.15 **Treatment of epilepsy in women I**
Prof. Emilio Perucca (Italy)

14.15 - 14.45 **Treatment of epilepsy in women II**
Prof. Torbjörn Tomson (Sweden)

14.45 - 15.15 **Outcome of the offspring**
Dr. Eija Gaily (Finland)

15.15 - 15.30 **Closing of the Kuopio Epilepsy Symposium 2005**
Prof. Asla Pitkänen (Finland)

TREATMENT OF EPILEPSY TODAY – EVIDENCE-BASED OR NOT?

Emilio Perucca. Clinical Pharmacology Unit, University of Pavia, and Neuropharmacology Unit, Institute of Neurology IRCCS C. Mondino Foundation, Pavia, Italy.

Evidence-based therapy is the application of management decisions based on sound information about the comparative risks and benefits of available treatments. Ideally, this assessment should be based on data from randomized controlled trials (RCTs). In the last two decades, a large number of such trials have addressed a wide range of critical issues, including (i) the value of prophylactic antiepileptic drug treatment (AED) in people at high risk of developing epilepsy; (ii) the efficacy of AEDs in preventing seizure recurrence after a single seizure; (iii) the comparative efficacy and tolerability profiles of AEDs in newly diagnosed epilepsy; (iv) the efficacy and tolerability of newer generation AEDs as adjunctive therapy; (v) the relative merits of alternative monotherapy vs adjunctive therapy in patients unresponsive to a single AED; (vi) the clinical impact of therapeutic drug monitoring; (vii) the risk of seizure recurrence after AED withdrawal in seizure-free patients and (viii) the value of resective epilepsy surgery. Although these trials have been invaluable in providing information which can help in making clinical decisions, the amount and the quality of data from RCTs remains inadequate for a fully evidence-based approach to epilepsy treatment. In fact, many RCTs conducted to date have major shortcomings, such as a low statistical power, failure to account adequately for the heterogeneous nature of seizure disorders, choice of endpoints addressing regulatory concerns rather than therapeutic needs, and bias in study designs which may have favored the sponsor's product. Moreover, most trials have been focused on the treatment of partial epilepsies, and little or no RCT data are available to guide therapeutic decision in generalized epilepsy syndromes. Critical interpretation of existing data is essential for an optimal selection of the many existing treatment options.

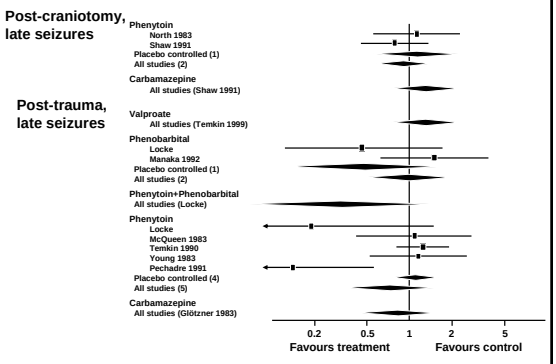
Important Issues which Can Only be Addressed by Observational Studies

- Chronic or delayed adverse effects
- Second-generation effects (including teratogenicity)
- Rare adverse effects
- Effects mimicking condition with a high background incidence (e.g., myocardial infarction)
- Certain drug interactions

Evidence-Based Medicine and Epilepsy Issues Addressed in RCTs

- Can epilepsy be prevented?
- Management after a first seizure
- Treatment of newly diagnosed epilepsy
- Treatment of refractory epilepsy
- Therapeutic drug monitoring
- Management of seizure-free patients

Clinical Studies of "Epilepsy Prevention"



N. Temkin, 2001

Treating after a First Seizure Conclusions Based on Evidence

- Treatment is effective, but does not affect long-term prognosis
- Many untreated patients will not have a recurrence anyway
- Treatment decision guided by assessment of individual risk benefit ratio
- Risk quantifiable from sound epidemiology data

RCTs of AEDs in Newly Diagnosed Epilepsy

	Partial	PGTCS	Absence	Spasms
CBZ	X	X		
VPA	X	X	X	
PHT	X	X		
PB	X	X		
ETS			X	
OXC	X	X		
VGB	X	X		X
LTG	X	X	X	
GBP	X			
TPM	X	X		

Comparative Efficacy of AEDs Conclusions Based on Evidence

- No evidence of significant differences in efficacy between AEDs active against partial or generalized TC seizures
- Most studies significantly under-powered
- Considerations other than efficacy take predominant role in AED selection
- Many trials affected by additional methodological shortcomings !

Evidence-based Medicine? Shortcomings of Many Monotherapy Trials

- Inclusion by seizure type rather than syndrome
- Heterogeneous disorders (e.g. partial and PGTCS) analyzed as if they were a single entity
- Little or no dosing flexibility, short follow-up
- Questionable endpoints (e.g., 24-week seizure freedom)
- Bias in design and analysis favoring the sponsor's product
- Most syndromes /seizure types never tested!

How Many Patients Refractory to One Drug are Controlled by an Alternative Monotherapy?

Reference	Seizure-free Rates
Hakkarainen, 1980	34%
Elkis et al, 1993	15%
Tanganelli & Regesta, 1996	44%
Kwan & Brodie, 2000	24%
Beghi et al, 2003	14%
Kaminow et al, 2004	22%

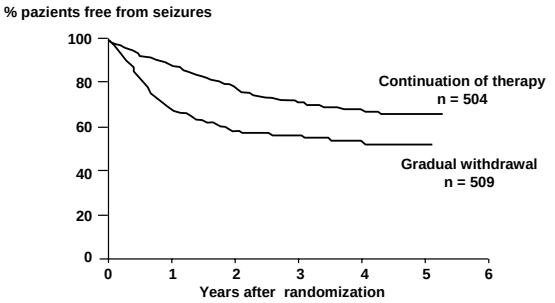
Add-on vs Alternastive Monotherapy Conclusions Based on Evidence

- No class I evidence that combination therapy is superior to alternative monotherapy
- B.A.S.E study was under-powered
- AEDs differ in mechanisms of actions and side effect profiles – not all AED combinations are the same
- Indequate evidence on the comparative value of specific AED combinations

Treating Refractory Epilepsy Conclusions Based on Evidence

- Little evidence to support superiority of combination therapy vs alternative monotherapy
- Differences in responder rates affected by trial design (dosages, titration rates, etc) and type of analysis
- Treatment decision mostly influenced by ease of use and tolerability profiles

Probability of Seizure Relapse after AED Withdrawal in seizxure-Free Patients



MRC ADWSG, The Lancet 1991; 337:1175-80.

Conclusions

- A fully evidence-based approach to epilepsy treatment remains a pipedream
- There is a great need from better designed, preferably independent, trials in many areas
- Evidence from existing randomized controlled trials is helpful, but requires critical interpretation
- Optimal management cannot disregard evidence and factors not addressed by RCTs

HEAD TRAUMA INDUCED EPILEPTOGENESIS AS A CLINICAL PROBLEM

W Allen Hauser. Columbia University, New York, New York.

The incidence of hospitalized or fatal traumatic brain injury (TBI) in the United States is to be between 180 and 220 per 100,000 population annually. Recent studies in Finland suggest the incidence of hospitalization to be about 100/100,000. With improvements in pre-hospital care and emergency room diagnosis and care of TBI, mortality rates have dropped from 50% in the early 1970's to around 30% currently. However, traumatic brain injury survivors still carry a tremendous burden of disability as a result of their injuries. Permanent disability occurs in up to 10% of mild brain injuries, 65% of moderate brain injuries and 100% of severe brain injuries. The occurrence of seizures after brain injury is a recognized complication of TBI and significantly worsens functional outcome after TBI.

Posttraumatic seizures are into three categories: "immediate" or "impact" seizures, early seizures and late seizures. The pathophysiology associated with "impact" seizures and their exact clinical significance remains in question. Early post-traumatic seizures are those occurring while the patient is still suffering from the direct effects of the brain injury. This period is commonly defined as the first week after injury although the majority of early seizures occur within 24 hours of the injury. Late posttraumatic seizures are usually defined as seizures occurring more than one week after injury.

Clinical features have been used to stratify brain injury severity. In our own studies patients have been categorized based on duration of unconsciousness or posttraumatic amnesia: "Mild" injuries were those in which no skull fracture was found and the period of loss of consciousness or posttraumatic amnesia was 30 minutes or less. "Moderate" injuries included those patients with skull fractures or with more than 30 minutes of posttraumatic amnesia or loss of consciousness who did not otherwise meet the criteria for a severe injury. "Severe" injuries were those with a documented brain contusion, an intracranial hematoma or posttraumatic amnesia or loss of consciousness of greater than 24 hours.

The incidence of early seizures ranges from 2.1 to 16.9% and, in general, the incidence is correlated with the distribution of brain injury severity regardless how measured. Early seizures occur more frequently in children than adults regardless of severity of injury.

In civilian populations, the incidence of late seizures ranges from 1.9% to over 30%. In population based studies, brain trauma accounts for 5 to 10 % of all newly diagnosed epilepsy. In survivors of military brain injury, more than half will develop post-traumatic epilepsy. Like the incidence of early posttraumatic seizures, the variability in reported frequencies of late post-traumatic epilepsy is due to variability within the patient populations being studied, especially with respect to injury severity. In general, most late posttraumatic seizures occur during the first year after injury although in people with severe injury, an increased risk for epilepsy remains for at least 15 years following the injury. There is generally a latency for the development of these late seizures of 4 to 6 months probably reflecting the time necessary to develop epileptogenic circuitry.

There are clinical markers of increased injury severity that have been shown to significantly the risk of late posttraumatic epilepsy. When severe brain injury is defined as multilobar injury (or worse) or loss of consciousness or posttraumatic amnesia lasting more than 24

hours, this measure of severity is a significant risk factor for the occurrence of late posttraumatic seizures. When injury severity is measured by brain volume loss on CT scan or by Glasgow Coma Score, the significance of the relationship disappears. Intracranial hemorrhage may confer up to 10-fold increase in risk over that among people with similar clinical severity of injury but without evidence of intracerebral blood. Subdural hematoma and intracerebral hematoma is responsible for most of this increased risk in both children and adults. The presence of a brain contusion was as strong of a predictor of late seizure occurrence as the presence of a subdural hematoma in clinical trials of prophylaxsis.

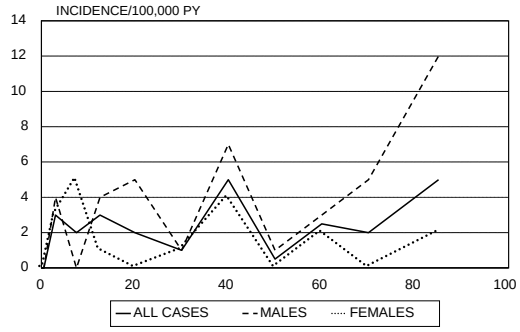
The presence of early posttraumatic seizures is also a risk factor for late posttraumatic epilepsy although this is true only in adults. Once controlling for other factors, this variable becomes less important. Early seizures seem a surrogate for severity of injury. Age greater than 65 years at the time of injury is a significant risk factor for the development of late posttraumatic seizures. This relationship is especially important in light of the fact that elderly survivors of traumatic brain injury, even without seizures, recover more slowly and are more likely to be permanently disabled as a result of their injuries than younger brain injury survivors.

Premorbid chronic alcoholism may increase the risk of the development of late posttraumatic seizures. Other risk factors for the development of late posttraumatic seizures include: metal fragment retention, skull fracture, residual cortical neurological deficits, a single CT lesion in the temporal or frontal regions and persistent focal abnormalities on EEG more than one month after injury. Family history of epilepsy is not a risk factor for posttraumatic epilepsy.

There have been a number of randomized trials with drugs such as phenytoin, valproate, and carbamezapine. These trials have demonstrated a reduction in the frequency of early posttraumatic seizures, but no decrease in the frequency of late posttraumatic epilepsy. The failure to influence the risk of post traumatic epilepsy in studies of patients with TBI are similar to findings of randomized clinical trials on seizure prevention in other conditions such as febrile seizures, cerebral malaria, craniotomy, and excessive alcohol intake. For these reasons, the prophylactic use of antiseizure medications should be short-lasting and limited to the prevention of immediate and early seizures. Chronic treatment with antiseizure medication should be considered only after a diagnosis of PTE. Appropriate interventions for prophylaxis must take into account basic mechanisms of epileptogenesis as well as the epidemiologic characteristics associated with the development of late post-traumatic epilepsy.

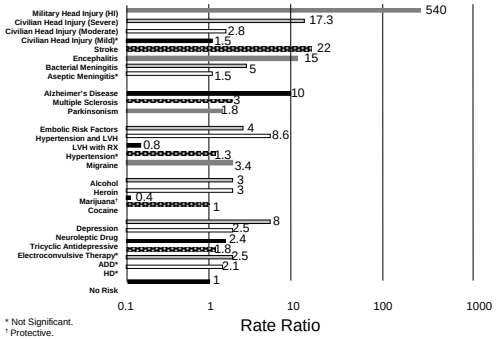
INCIDENCE OF EPILEPSY

POST TRAUMATIC



Rochester Minnesota

Risk Factors for Epilepsy



* Not Significant.
† Protective.

Gender specific Incidence

Incidence/100,000

Study Area	Male	Female	Total
Rochester	210	116	
Bronx	391	142	249
San Deigo	247	111	180
France	384	185	281

Severity of Injury

Study area	mild	moderate	severe	fatal
Rochester male	55	26	6	12
Rochester female	61	25	5	9
Bronx male				12
Bronx female				7
San Deigo	73	8	8	12
France	80	11	9	4
Johannesberg	88	9	5	

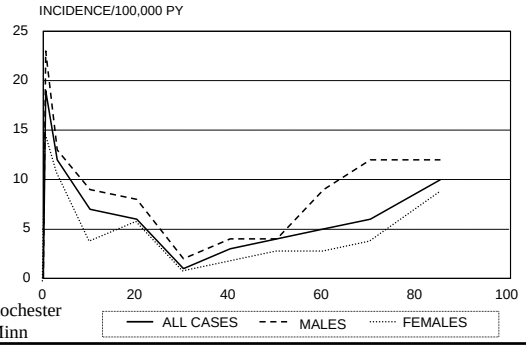
US TBI Mortality

- Overall US mortality rate for TBI in 1994 was 19.8 per 100,000
- In the elderly - 46.3 per 100,000
- Elderly TBI patients tend to die of multisystem organ failure
- Younger TBI victims usually die from irreversible brain injury
- Age 75 and older per 100,000 population
  - falls occurred in 127
  - transport related in 38
  - firearms in 13
  - assault related TBI in 2

Brain Injury Time trends

- Since 1980
  - Incidence decreasing
  - Frequency of hospitalization decreased 51%
  - In hospital deaths decreased 17%
  - Severity of hospitalized cases increased
    - Change in classification
    - More frequent use of imaging

Acute Symptomatic Seizures
head injury



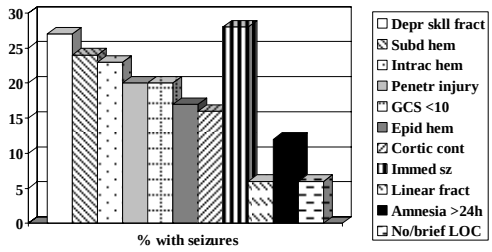
Rochester
Minn

EARLY SEIZURES
NON PENETRATING CIVILIAN INJURIES

PATHOLOGY	PERCENT	ODDS RATIO	95% CI
NONE	6.3	-----	
FRACTURE	6.5	1	0.7-1.4
SUBDURAL HEMATOMA	8.8	1.6	0.8-2.3
INTRACEREBRAL HEMATOMA	10.5	1.7	1.7-2.4

The Bronx

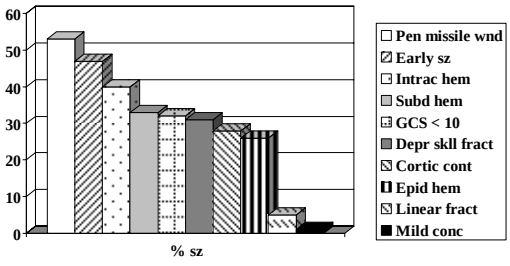
RISK FACTORS FOR EARLY POST-TRAUMATIC SZ



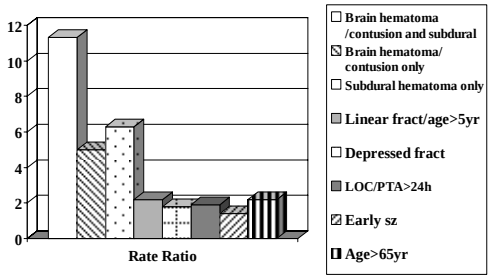
(Temkin, Neurological Surgery, 1996)

RISK FACTORS FOR LATE POST-TRAUMATIC SZ

(Temkin, Neurological Surgery, 1996)



RATE RATIOS FOR EPILEPSY AFTER TRAUMATIC BRAIN INJURY



Rochester Minnesota

MULTIVARIATE RISK FACTORS

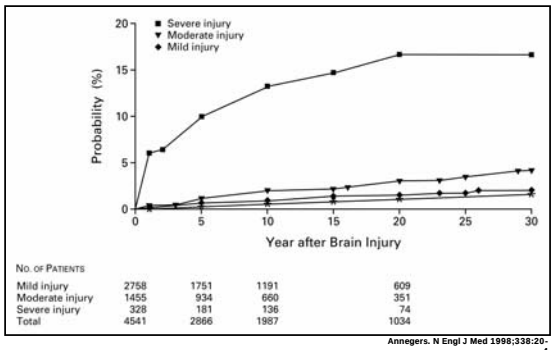
FACTORS	#	LATE SEIZURES	HAZARD RATIO	95% C.I.
Brain contusion	196	32	4.4	(2.2-8.8)
Subdural hematoma	73	17	3	(1.5-5.7)
Linear fracture, age 5+	313	17	2.2	(1.3-3.9)
Depressed fracture	214	18	1.7	(0.9-3.2)
LOC* or PTA** >=1 day	176	24	1.8	(0.9-3.5)
Early seizure	117	12	1.4	(0.7-2.8)
Age 65+	269	10	2.3	(1.2-4.6)

*loss-of-consciousness **posttraumatic amnesia

STANDARDIZED INCIDENCE RATIOS (SIR) FOR LATE POSTTRAUMATIC EPILEPSY BY SEVERITY

SEVERITY	OBSERVED	EXPECTED	SIR	95% C.I.
Mild	28	18.5	1.5	(1.0 - 2.2)
Moderate	30	10.6	2.8	(1.9 - 4.1)
Severe	39	2.3	17.3	(12.7-23.6)
Total	97	31.4	3.1	(2.5 - 3.8)

Seizure Incidence by Severity



Annegers. N Engl J Med 1998;338:20-4

Late Seizures

Group	*Rate*	*Incidence Ratio*
Mild (Annegers - 1 yr)	**<1%**	**3**
Moderate (Annegers - 1 yr)	**<1%**	**7**
Severe (Annegers - 1 yr)	**6%**	**95**
Prophylaxis studies - 2 yrs	**21%**	**241**

RISK FACTORS - I.

Univariate (crude) associations with late posttraumatic seizures:

- STRONG ASSOCIATIONS:
  - Brain contusion
  - Cerebral hematoma
  - Early seizure
  - LOC* or PTA** > 1 day
  - Depressed skull fractures
- MODEST ASSOCIATIONS:
  - Linear fractures in ages over 5
  - Basilar fractures in age 65 and older

*loss-of-consciousness **posttraumatic amnesia

RISK FACTORS - II.

Multivariate associations:

- STRONG ASSOCIATIONS:
  - Brain contusion with or without Subdural hematoma
- MODEST ASSOCIATIONS:
  - Depressed skull fractures
  - Linear skull fractures in ages over 5
  - Twofold increase for LOC* or PTA**

*loss-of-consciousness **posttraumatic amnesia

RISK FACTORS - III.

- The importance of early seizures was almost entirely explained by other risk factors.
- The increased risk among those over age 65 is the same as the effects of aging in the general population for the incidence of unprovoked seizures.

TRAUMATIC BRAIN INJURY IN FINLAND

Olli Tenovuo. Department of Neurology, University of Turku, Turku, Finland.

Detailed studies of Finnish epidemiology of traumatic brain injury (TBI) are largely lacking. Local differences in incidence and prevalence are probably marked due to several factors such as age distribution, alcohol consumption and traffic circumstances. A nationwide study covering the register of hospitalized TBI patients gave an incidence of 100 / 100 000. Studies have suggested that about 20 % of cases are not registered, about 30 % of diagnoses are missed and that about 25 % of all those seeking medical care are treated in hospital. These figures largely correspond with the clinical experience, and give a yearly incidence of 624 / 100 000. That means about 35 000 new TBI patients yearly seeking medical attendance. This is well in line with several epidemiological studies in civilized countries, which have given figures from 607 to 862 / 100 000 for yearly incidence of all those seeking medical attendance in a defined population. The number of those patients fulfilling the minimal diagnostic criteria for TBI but not seeking medical care has been estimated to be up to 75 %. The number of all TBIs per year is probably between 50 000 and 150 000 in Finland.

However, a recent comparative study in Nordic countries showed that the number of TBI deaths and acute operations for TBI is twofold in Finland compared with other Scandinavian countries. Likewise, Finland was the only Nordic country where TBI mortality had not decreased between 1987 and 2000. Moreover, studies have shown that the number of severe fall-related TBIs in the elderly has increased dramatically during the last decades, by 180 % between 1970 and 1999. A recent study of consecutive trauma patients in Oulu showed that 65 % of the head-injured patients had alcohol in their blood compared with 32 % of other traumas. The fact that especially Finnish men are twice as often intoxicated from alcohol as other Scandinavians is probably the most important contributing factor to the high number of severe TBIs in Finland. The increasing alcohol consumption raises severe concern about the real TBI burden and its development in Finland. At the present, yearly about 1150 patients die from TBI, about 4000 patients get a severe TBI, and the number of patients living with a chronic TBIs is surely over 100 000.

The acute and postacute care of TBI patients in Finland is often poorly organized and thus several patients remain without adequate follow-up or rehabilitation. This is why many chronic TBI patients live without a diagnosis for their problems, are regarded as psychiatric cases or seek for help years or decades after the trauma. The possibility of chronic TBI should be considered in patients with memory problems, fatigue, problems to manage at work, epilepsy, chronic headache or atypical psychiatric problems. A detailed trauma history and clarifying the eventual temporal connection are then essential.

The number of posttraumatic epilepsies in Finland is estimated to be about 10 000 cases (corresponding about 20 % of all epilepsies), with about 700 new cases annually.

Nationwide epidemiology based on records of in-hospital treatment

- **Yearly incidence about 100 / 100 000 (= 5500 patients)**
- **Of these 65 % from falls, 20 % from traffic accidents, 5 % from violence and 10 % from miscellaneous reasons**

Alaranta H, Koskinen S, Leppänen L, Palomäki H. Nationwide epidemiology of hospitalized patients with first-time traumatic brain injury with special reference to prevention. Wien Med Wschr 2000;150:444-8.

Estimates of TBI epidemiology

- **missing TBI-diagnoses ~ 20 %[1]**
- **misclassified TBI-diagnoses ~ 15 %[2]**
- **missed TBI-diagnoses ~ 30 %[3]**
- **unhospitalized TBI-patients ~ 75 %[4]**
- **TBI-patients not attending medical care ~ 75 %[5]**

[1]Thornhill S, Teasdale GM, Murray GD et al. Disability in young people and adults one year after head injury: prospective cohort study. BMJ 2000;320:1631-1635.

[2]Tenovuo O, Alaranta H, Kaipio M-L et al. Adult traumatic brain injuries – an evidence-based review. Duodecim 2003;119:654-81.

[3]Moss NE, Wade DT. Admission after head injury: how many occur and how many are recorded? Injury 1996;27:159-61.

[4]Sosin DM, Sniezek JE, Thurman DJ. Incidence of mild and moderate brain injury in the United States, 1991. Brain Injury 1996;10:47-54.

[5]Segalowitz SJ, Lawson S. Subtle symptoms associated with self-reported mild head injury. J Learn Disabil 1995;28:309-19.

Thus in Finland…?

5500 + 20 % = 6600 hospital diagnosed

6600 + 30 % = 8580 hospital treated

8580 x 100/25 = 34320 with medical attendance (= 624 / 100 000)

34 320 x 100/25 = 137 280 all TBIs (2496 / 100 000)

Special features of Finnish epidemiology I

- **A comparative study in Nordic countries on TBI mortality between 1987 – 2000**
- **Yearly mortality (per 100 000): Sweden 9.8, Norway 10.5, Denmark 12.8 and Finland 21.2**
- **Surgical operations for acute TBI (per 100 000): Norway 4.8, Denmark 5.1, Sweden 5.7 and Finland 10.0**
- **All countries except Finland had a significant reduction in TBI deaths during the study period**

Sundstrom T, Sollid S, Wester K. Deaths from traumatic brain injury in the Nordic countries, 1987-2000. Tidsskr Nor Laegeforen 2005;125:1310-2.

Special features of Finnish epidemiology II

The age-adjusted incidence of fall-related severe TBIs in elderly Finns (> 80 yrs) increased by 180 % between the years 1970 to 1999 (from 85 to 841 patients).[1]

The number of hospital-treated TBIs in patients over 70 yrs increased by 35.5 % from 1990-1995 to 1996-2000.[2]

[1]Kannus P, Palvanen M, Niemi S et al. Increasing number and incidence of fall-induced severe head injuries in older adults. Am J Epidemiol 1999;149:143-50.

[2]Alaranta H, Koskinen S, Turkka J. Tapaturmainen aivovaurio ei ole harvinainen. Suomen Lääkärilehti 2002;57:4801-4.

Special features of Finnish epidemiology III

- **In 385 consecutive trauma patients at an ED 65 % of the head injured patients had alcohol in their blood (vs. 32 % in other traumas)**
- **Relative risk of head injury was twofold with alcohol levels between 1.5 – 2 ‰ and fivefold with level > 2 ‰**

Savola O, Niemelä O, Hillbom M. Alcohol intake and the pattern of trauma in young adults and working aged people admitted after trauma. Alcohol Alcohol 2005; (Epub ahead of print)

Epidemiological conclusions

- **The true number of TBIs per year is unknown, but based on several sources the number of TBIs causing medical attendance is surely > 35 000**
- **All patients fulfilling minimal diagnostic criteria for TBI probably between 50 000 to 150 000**
- **About 1150 TBI deaths yearly**

- **The number of severe TBIs probably about 4000**
- **The twofold number of TBI deaths and operations suggests that at least the number of severe TBIs is clearly higher than in other Nordic countries**
- **True prevalence of chronic TBI unknown but surely more than 100 000 patients (up to 250 000?)**

Acute and postacute care of TBI patients in national health care

- **Acute care very variable in mild and moderate TBI (from medical student in remote health center to specialist in university hospital)**
- **In severe TBI a large portion treated in central hospitals without a neuro-surgeon or neuroanesthesiologist**
- **Regional trauma care systems for TBI largely still missing**

Postacute care

- **If possible, even more variable than acute care**
- **Neurosurgeons, orthopedists, general surgeons, neurologists, rehabilitation or physical medicine, general practitioners…**
- **Local systems of care very inconsistent and clear responsibility of TBI patients often missing**

How to diagnose chronic TBI in Finland?

If the patient seeks help for

- **memory problems**
- **fatigue**
- **problems to manage at work**
- **epilepsy**
- **chronic headache**
- **atypical psychiatric problems**

remember to consider the possibility of chronic TBI (detailed trauma history and temporal connection to the problems)

How many posttraumatic epilepsies in Finland?

- **About 2 % of TBI patients who seek medical attention develop epilepsy = 700 cases annually**
- **About 12 % of severe TBI patients develop epilepsy = 480 cases annually**
- **Of the 100 000 Finnish chronic TBI patients probably about 10 % has epilepsy (24 pts in a random sample of 200) → about 10 000 posttraumatic epilepsies (~20 % of all epilepsies)**

LESSONS FROM EXPERIMENTAL POST-TRAUMATIC EPILEPSY - IS ALL SYMPTOMATIC EPILEPSY THE SAME?

Asla Pitkänen. A.I. Virtanen Institute, University of Kuopio, Kuopio, Finland.

Epileptogenesis refers to a phenomenon in which brain undergoes molecular and cellular alterations after brain damaging insult which increase its excitability and eventually lead to the occurrence of recurrent spontaneous seizures. Common epileptogenic factors include traumatic brain injury, stroke, cerebral infections, and status epilepticus. Only a subpopulation of subjects with any of these brain insults, however, develops epilepsy. The great challenges are, how to identify patients at risk and how to modify the epileptogenic process to prevent the development of epilepsy. Target identification for antiepileptogenic treatments is practically impossible in humans because we are currently not able identify patients at risk of epileptogenesis that would form the target study population. Animals models of epileptogenesis are therefore necessary for progress in the field.

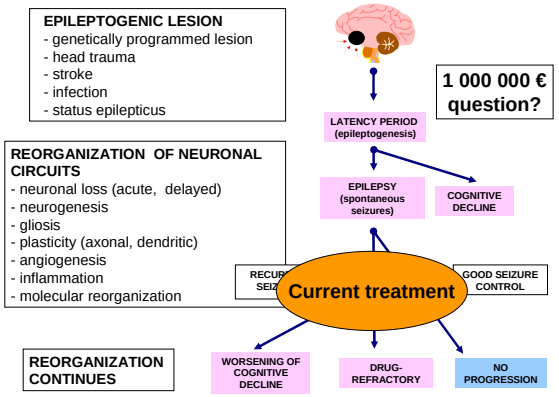
Recent advances in the development of experimental models of epileptogenesis, in which the initial brain damaging insult is followed by a latency period that eventually leads to the occurrence of spontaneous seizures have provided us tools to investigate molecular and cellular alterations, their temporal appearance, as well as the epilepsy phenotype after various clinically relevant epileptogenic etiologies, including traumatic brain injury, stroke, and status epilepticus. By studying these models we can answer to critical questions like: Do the molecular mechanisms of epileptogenesis depend on the etiology? Is the spectrum of network alterations during epileptogenesis the same after various clinically relevant etiologies? What about the temporal progression of epileptogenesis? Work is ongoing, and answers to these question will lead to identification of molecular targets for antiepileptogenic treatments, designing treatment paradigms, and deciding whether data from one etiology can be extrapolated to another.

Lessons from experimental post-traumatic epilepsy - is all symptomatic epilepsy the same?

Asla Pitkänen, MD, PhD

Epilepsy Research Laboratory
A.I.Virtanen Institute for Molecular Sciences
University of Kuopio, Kuopio
Finland
E-mail: asla.pitkanen@uku.fi

PROGRESSION OF EPILEPTIC PROCESS

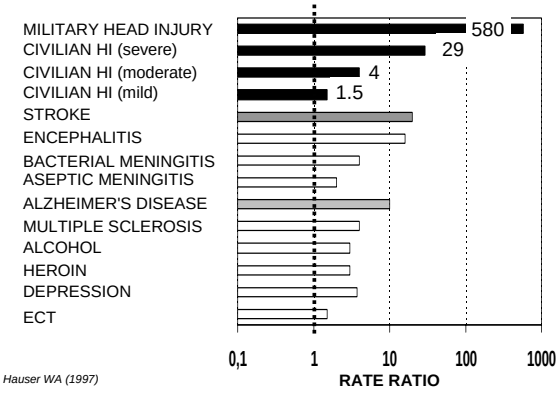


HYPOTHESIS

Understanding the molecular and cellular mechanisms that are **common** to epileptogenesis induced by different etiologies provides molecular targets that can be used to control neurobiologic alterations underlying epileptogenesis by pharmacologic or other tools

- monotherapy *vs.* polytherapy
- serial *vs.* parallel administration
- etiology-tailored treatment

POPULATIONS WITH HIGHEST RISK OF EPILEPTOGENESIS



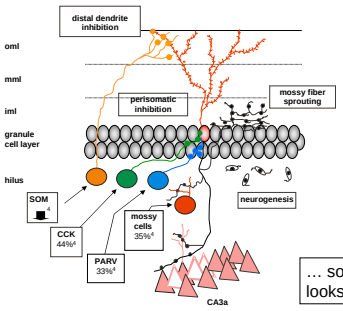
Hauser WA (1997)

POST-SE vs. POST-TRAUMATIC EPILEPSY IN RAT

Comparison of epileptogenesis and epilepsy phenotypes

	Post-SE	Post-traumatic
Spontaneous seizures:	90-100%	➡ 50%
First seizure:	< 1 mo	➡ months
Behavioral seizures:	70% SG	76% SG
Sz frequency:	up to 29 sz/day	➡ up to 1 sz/day
Mean duration of sz:	60 sec	104 sec
Day-night cycle:	57% sz lights on	no data
HC neurodegeneration:	yes	yes
Mossy fiber sprouting:	yes	yes
Behavioral impairment:	spatial memory emotional learning	spatial memory
Response to AEDs:	yes	?

REORGANIZATION OF DENTATE GYRUS AFTER TBI

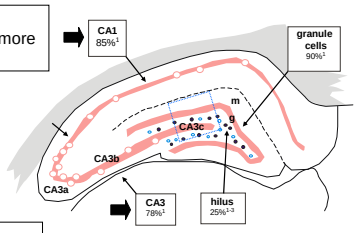


… so far, looks like after SE

Pitkänen and McIntosh, submitted

HIPPOCAMPAL NEURODEGENERATION AFTER TBI

SE models
• CA1 and CA3 more damaged



Rats with PTE
• no quantitative data

Human refractory temporal lobe PTE
All HC subfields (Mathern et al., 1994)
• 30-50% neurons remaining

[1]Grady et al. (2003)
[2]Lowenstein et al. (1992)
[3]Smith et al. (1997)
[4]Toth et al. (1997)

Pitkänen and McIntosh, submitted

CELLULAR ALTERATIONS AFTER SE AND TBI

Hippocampus

	SE	TBI (lateral FPI)
neurodegeneration	+++	+
neurogenesis	++	++
astrogliosis	+++	+++
microgliosis	++	++
	"EPILEPTOGENESIS"	**"RECOVERY"**
axonal sprouting	+++	++
axonal damage	(+)	+++
dendritic changes	+++	(+)
neovascularization	+	?

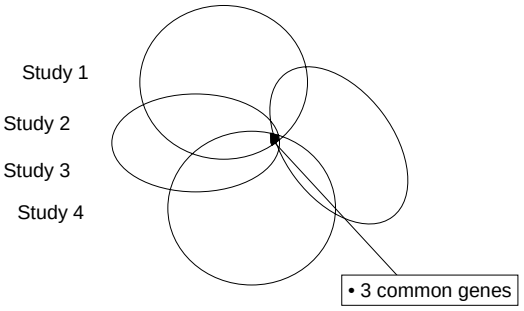
LARGE SCALE MOLECULAR PROFILING

Review by Lukasiuk and Pitkänen (2004)

	No. of regulated genes	Reference
SE models		
pilocarpine	129 of 8000	Elliot et al. (2003)
	700 of 8799	Becker et al. (2003)
kainic acid	187 of 8000	Tang et al. (2002)
amygdala stimulation	282 of 5000	Lukasiuk et al. (2003)
perforant pathway stimulation	79 (SAGE)	Hendriksen et al. (2001)
TBI models		
controlled cortical impact	525 of 8800	Matzilevich et al. (2002)
	253	Long et al. (2003)
lateral fluid percussion	266 of 3800	Natale et al. (2003)

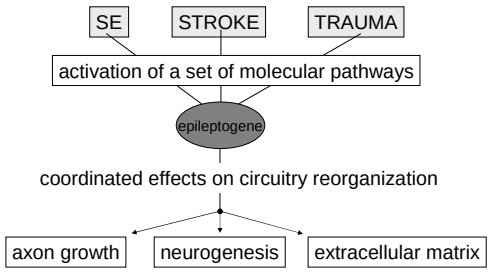
REALITY

Lukasiuk and Pitkänen (2004)



Data not available to compare different epileptogenic etiologies

ARRAY DATA PROVIDES A HYPOTHESIS



FUTURE CHALLENGES

1. Experimental studies - more attention to details
   type and location of initial insult
   • acute treatment effect
   • interanimal variability

2. Human studies - more data is needed
   etiology specific desciption of phenotype
   • etiology specific circuitry reorganization

3. New ways to look at molecular data - target identification
   coordinated effects of a set of genes
   • conceptual clarification
   recovery vs. epileptogenesis

CURRENT STATE OF ANTI-EPILEPTOGENIC TREATMENT AFTER TRAUMATIC BRAIN INJURY IN HUMANS

Nancy R Temkin. University of Washington, Seattle, WA, USA.

For antiepileptogenic treatment to be worthwhile, the risk of developing seizures needs to be high and the treatment needs to be effective in preventing the seizures. For different conditions, we review the seizure risk and the evidence for effectiveness of different anti-epileptic treatments. Provoked seizures occur during or soon after an event that disturbs the brain. Unprovoked (epileptic) seizures occur without a nearby disturbing event. For traumatic brain injury, seizures within the first week are considered provoked. Characteristics associated with at least a 20% risk include: immediate seizure, depressed skull fracture, subdural or intracerebral hematoma, penetrating brain injury, or Glasgow Coma Score 10 or below. Phenytoin and carbamazepine are effective in preventing provoked seizures after traumatic brain injury. Characteristics associated with at least a 20% risk of unprovoked seizures after traumatic brain injury include: penetrating brain injury, provoked seizure, subdural, intracerebral, or epidural hematoma, Glasgow Coma Score 10 or below, depressed skull fracture, or cortical contusion. Unfortunately, no treatment has been shown to be effective to prevent these seizures. The pattern is similar with other conditions. In many cases, prophylaxis can prevent provoked seizures. But no drugs have been shown to prevent unprovoked epileptogenesis.

Considerations for Treatment

- Risk of future seizures is high
- Treatment is effective in reducing the risk
- Benefits outweigh the costs (money, adverse effects, psychological costs)

Types of seizures

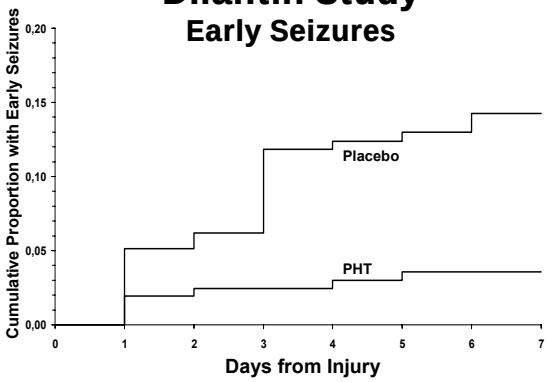
- Provoked seizures (Acute or early seizures)
  - During or soon after an event that disturbs the brain
    - Fever, alcohol withdrawal, contrast media, CNS infection
    - Soon after (usually with a week) of head trauma, craniotomy, stroke
- Unprovoked seizures (Epileptic or late seizures)
  - Remote from a precipitating event

Early Seizures after Traumatic Brain Injury

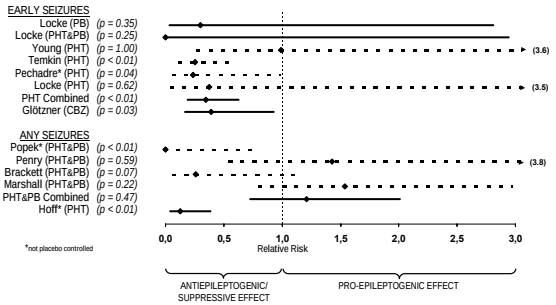
	Incidence of Early Post–Traumatic Seizures (%)
Depressed Skull Fracture	**27**
Subdural Hematoma	**24**
Intracerebral Hematoma	**23**
Penetrating Head Injury	**20**
GCS Score ≤ 10	**20**
Epidural Hematoma	**17**
Cortical Contusion	**16**
Immediate Seizures	**28**
Linear Fracture*	**6**
Post–Traumatic Amnesia > 24hrs*	**12**
No or Brief Unconsciousness*	**6**
No or Brief Unconsciousness (age < 5 yrs)*	**17**

*Jennett

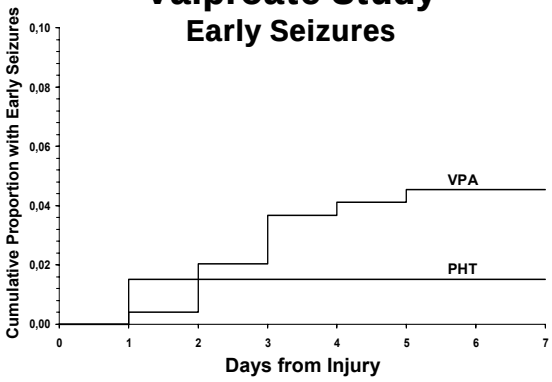
Dilantin Study
Early Seizures



Provoked Seizures after TBI



Valproate Study
Early Seizures

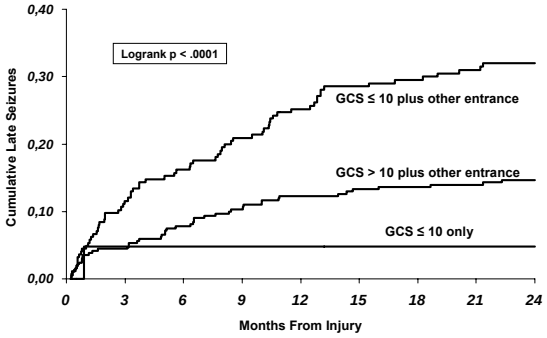


Epileptic Seizures after Traumatic Brain Injury

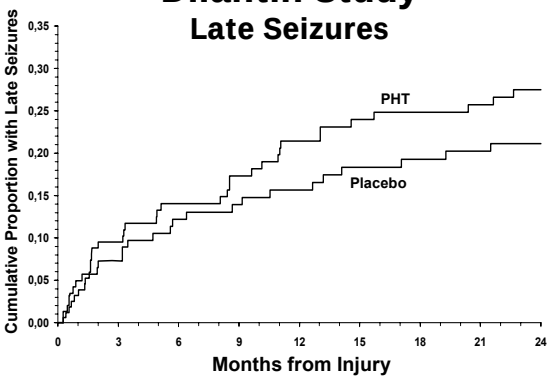
Penetrating missile wound	53%
Early seizure	47%
Intracerebral hematoma	40%
Subdural hematoma	33%
GCS ≤ 10	32%
Depressed skull fracture	31%
Cortical contusion	28%
Epidural hematoma	26%
Linear fracture	5%
Mild concussion	<1%

Source: Temkin. Post-traumatic Seizures In: Neurological Surgery (Youmans, ed) 1996

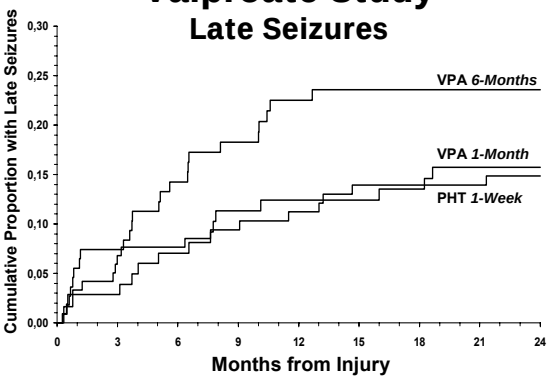
Late Seizures
Glasgow Coma Scale ≤ 10



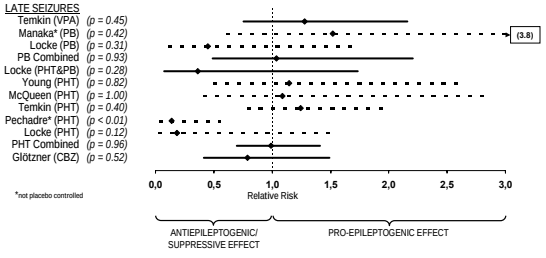
Dilantin Study
Late Seizures



Valproate Study
Late Seizures



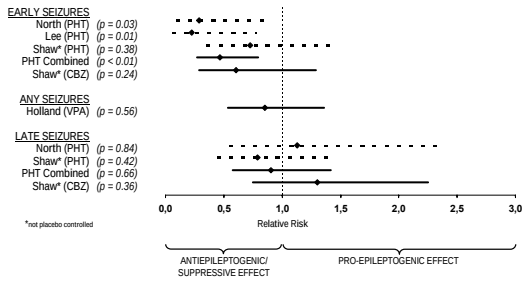
Unprovoked Seizures after TBI



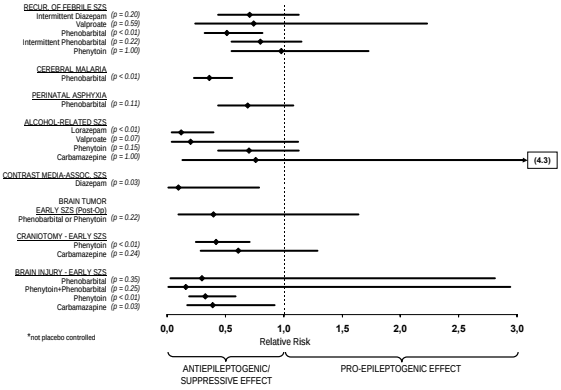
Seizures after Neurosurgery

AVM	50%
Spont. ICH	20%
Aneurysm	
Post. comm.	7.5%
Ant. cerebral	21%
Middle cerebral	38%
Meningioma	21%
Glioma	12.5%
Brain mets.	38%

Craniotomy



Provoked Seizures



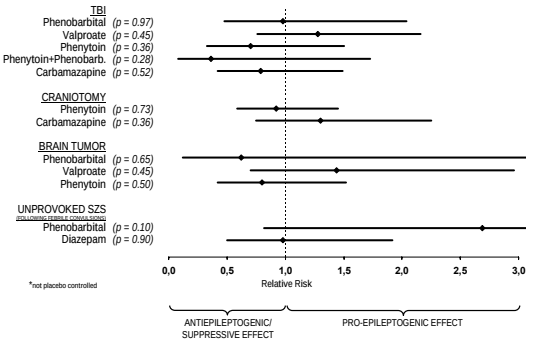
Epileptic Seizures after Febrile Seizures

Overall	7%
Complexity	
Simple	2.4%
1 complex feature*	6-8%
2 complex features*	17-22%
3 complex features	49%
*focal, prolonged, repeated	

Conditions or Procedures with High Risk of Developing Epilepsy

CONDITION OR PROCEDURE	HIGH RISK SUBGROUP	SEIZURE RATE IN HIGH RISK SUBGROUPS
Craniotomy for any reason	Supratentorial	20-50%
Traumatic brain injury	Penetrating missile wound, intracranial hematoma, cortical contusion, depressed skull fracture, immediate seizure	20-50%
Stroke	Hemorrhagic, total anterior circulation infarct, or with early seizure	20-35%
Aneurysm or arteriovenous malformation	Anterior or middle cerebral artery, any AVM	20-50%
Brain tumor	Resected	20-38%
Status epilepticus (symptomatic)		40%
CNS infection	Viral encephalitis with early seizures	22%

Unprovoked Seizures



Conclusions

- For most causes of provoked seizures, at least 1 tested drug was effective
- For different causes of unprovoked seizures,
  - Risk of seizures may be high
  - BUT, no drug has been shown to be effective
- Newer drugs, very rapid start not tested

EPIDEMIOLOGY AND EVOLUTION OF EPILEPTIC SYNDROMES

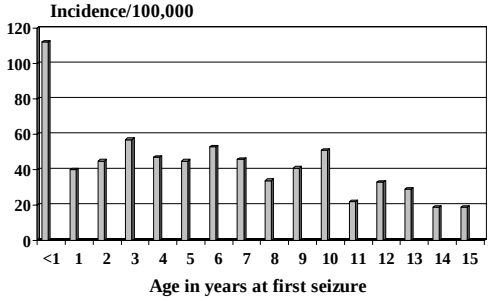
Peter and Carol Camfield. Canada.

Childhood epilepsy can be diagnosed after 2 or more unprovoked seizures, although most children with epilepsy have fewer than 10 seizures. There are many epilepsy syndromes that for epidemiology studies can be grouped into three broad categories – Partial and Convulsive Epilepsies (74%), Absence Epilepsies (14%) and Secondary Generalized Epilepsies (12%). The Nova Scotia Childhood Epilepsy study showed eventual remission in 52% of the Partial and Convulsive Epilepsies, 65% of the Absence Epilepsies but only 25% of Secondary Generalized Epilepsies. The number of seizures prior to treatment does not seem to influence the likelihood of remission. Prediction of good or poor outcome is difficult and even sophisticated statistical modeling allows a correct prediction in only 70% - about 1 of 3 will be incorrectly predicted to have/not have remission based on factors available on the day of diagnosis. Social outcome is unfavorable in about 50% of those with Partial and Convulsive Epilepsies and nearly all of those with Secondary Generalized Epilepsies. Morality in childhood epilepsy is rare, particularly SUDEP. Death is most often the result of co-morbid neurological deficits, not the epilepsy.

Epilepsy: a tendency for recurrent seizures (most have few seizures)

	Nova Scotia N=168	Bronx NY N= 407
Recurrence after First	52%	45%
Recurrence after 2nd	79%	72%
≥10 with 10 yr FU		**1st=13%** **2nd=28%**

Age of Onset



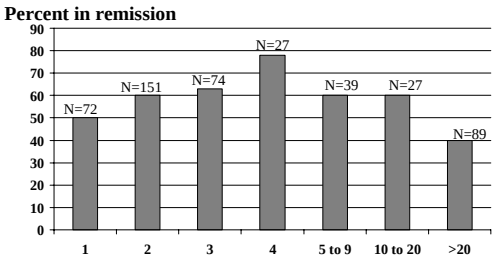
Remission – population studies, all types of epilepsy

Location	N	Followed	Remission
Oulu Finland	72 Age <2y	13 yrs	Crypt 97% Sympt 18%
Rochester	115	10 yrs	75%
Uppsala	194	12 yrs	64%
British	205	9 yrs	57%
Turku	245	20 yrs	64%
Dutch	406	2 yrs	69%
Nova Scotia	693	7-20	49%

Nova Scotia Study

Pre-Treatment seizure number

n= 486 with 7 year follow-up



Predicting Remission 20 years after day of diagnosis

Partial and Convulsive Epilepsies

Age of onset <12 years
Normal intelligence
No previous neonatal seizures
<21 seizures before treatment

Independent predictors – multivariate analysis

Remission:all good >80%
≥ 1 bad 40%
} confirmed in Turku, Finland

* Easier to predict good than bad

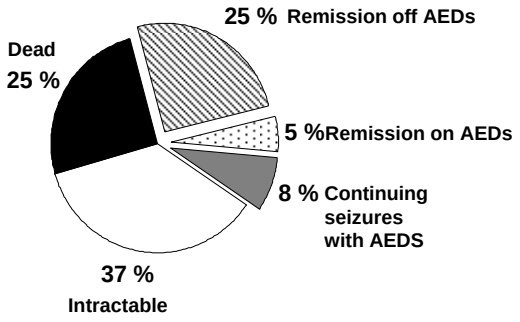
Does often does childhood absence (CAE) remit?

- 81 children with CAE – 72 (89%) contacted 14 years later (9-26 years)
- Mean age onset 5.7 yrs, follow up 20.4 yrs

Remission 65%,
No remission 35% ± medication

45% without remission had JME
15% CAE → JME

SGE outcome at the end of FU



Seizure number before treatment
Age >12 years at onset
Absence seizures
Cryptogenic generalized epilepsy
Symptomatic partial epilepsy
Neurological deficits
Mental retardation
Cryptogenic epilepsy + febrile seizures

Outcome correctly predicted = 70%

Partial and Convulsive Epilepsies: Social outcome for those with normal intelligence

F/u into school
- Grades repeated 35%
- Mental health assessment 23%
- Psychotropic medications 5%

F/u at least age 18 yrs
- Criminal 2%
- Inadvertent preg 13%
- Social isolation 16%
- Financial dependency/ unemployment 30%

	Absence	JRA
No high school grad	36%	14%
Behavior	41%	10%
Unplanned pregnancy	34%	3%
Heavy drinking	39%	16%
Psychiatric	54%	31%
Unskilled labor	53%	16%

Social outcome of 46 survivors

>18 years of age at end of F/U

- 48% unable to walk, 76% mental handicap
- 86% complete financial dependency on parents or state
- Surprisingly, only 20% were considered socially isolated by caretakers
- Desirable outcome i.e. normal intelligence, seizure-free and off AEDs, living on their own & financially independent – only 6% (n=3)

Summary

	Remit	Intract	Death	Social
Partial Convul 74%	**52%**	**8%**	**2.4%**	**~50% Poor**
Absence 14%	**65%**	**8%**	**1%**	**~50% Poor**
2nd gen 12%	**25%**	**37%**	**25%**	**93% Poor**
Total	**49%**	**~15%**	**3.8%**	**>50%**

INFANTILE EPILEPTIC ENCEPHALOPATHIES

Marja-Liisa Granström. Hospital for Children and Adolescents, Helsinki University Hospital, Helsinki, Finland.

Epileptic encephalopathies (EE) are conditions in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. It can be due to very frequent or severe seizures and/or to subcontinuous paroxysmal interictal activity which usually is generalized or multifocal. Clinically in addition of seizures the children with EE show developmental delay, arrest or deterioration. The risk for development is especially significant for EE beginning during first years of life. The target of treatment is minimizing seizure frequency and cognitive impairment by restricting ictal and interictal epileptiform activity vigorously with tolerable side-effects. Epileptic encephalopathies occur as the result of a wide variety of structural, genetic or unknown causes. Surgical treatment might still be possible if one epileptogenic area could be found for resection. Syndromes observed during the first year of life are:

- Epileptic encephalopathies with suppression bursts (Otahara syndrome and early myoclonic encephalopathy)
- Migrating focal seizures of infancy
- Infantile spasms
- Severe myoclonic epilepsy in infancy (Dravet syndrome)
- Myoclonic status in non-progressive encephalopathies

Infantile spasms (IS) is the most common of infantile epileptic encephalopathies. Incidence rate observed has varied between 2,5 and 5,1 per 10 000 live births among different studies. Various symptomatic pre-, peri- or postnatal etiologies has been observed in 70-85 % of patients. Although the list of specific diseases potentially causing infantile spasms is enormous, history and physical examination alone may identify the majority of symptomatic etiologies. MRI allows more specific classification into various etiology groups.

Between 1994 and 1999 55 infants with IS have been diagnosed and treated at the Epilepsy Unit of Hospital of Children and Adolescents, Helsinki University Hospital. The etiology was symptomatic for 44 (80%) of them. The diagnosis and treatment response was documented by video-EEG.

All children with IS received first VGB treatment (50-150 mg/kg). If spasms continued more than 2 weeks, add-on ACTH treatment was offered. Some multihandicapped infants were not treated by ACTH because of the risk of side-effects. 21 (38 %) of the infants responded to VGB within two weeks. Responses were more common among infants with cryptogenic etiology (64%) than among those with symptomatic etiology (31%). All infants with cryptogenic etiology responded to the treatment protocol, but 36% of the infants with symptomatic etiology still continued to have spasms after it. At the age of three years six (11%) infants had died and six of 49 living children showed refractory epilepsy. Etiology predicted survival as well as seizure and cognitive outcome of children. 91 % (10/11) children with cryptogenic etiology showed normal or nearly normal development. All infants with symptomatic etiology were mentally retarded. The cognitive outcome was especially poor if the infant did not respond to the treatment protocol.
None of the patients were surgical candidates.

ARE FEBRILE SEIZURES EPILEPTOGENIC? MARKERS, MODELS, MECHANISMS

Celine Dube, Amy Brewster, Roland Bender, Cristina Richichi, Tallie Z. Baram.
Anatomy/Neurobiology and Pediatrics, University of California at Irvine, CA, USA.

There is an ongoing debate in the human literature whether long febrile seizures (FS) directly cause temporal lobe epilepsy (TLE), and if so, in whom. Although strong statistical association links these two entities, most individuals with FS do not develop TLE, and a common cause of both FS and TLE will also explain the association between them. To address this issue, we developed an animal model for prolonged FS, and studied prospectively whether TLE develops (Toth et al., J Neurosci, 1998; Dube et al., Ann Neurol, 2000; Dube et al., Ann Neurol, 2005). In addition, we have set out to define markers for epileptogenesis, relying on MRI imaging (Dube et al., Ann Neurol, 2004). This talk will discuss the critical elements of FS that might be responsible for epileptogenesis, and the putative mechanisms by which a normal hippocampus becomes epileptic (Brewster et al., J Neurosci, 2002; Bender et al., J Neurosci, 2003; Brewster et al., Neurobiol. Dis. 2005). We will also discuss the role of MRI as a marker of epileptogenesis.

Are Prolonged Febrile Seizures Epileptogenic?
Markers, models, mechanisms

Tallie Z. Baram, MD, PhD
Pediatrics, Anatomy / Neurobiology, Neurology
University of California at Irvine
IRVINE, California, USA

Supported by NINDS (NS5439), AES, EFA

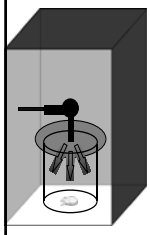
Correlation of Febrile Seizures and TLE:

Prospective: FS do not lead to TLE
Retrospective: 30-70% of TLE patients- history of early seizures / prolonged FS

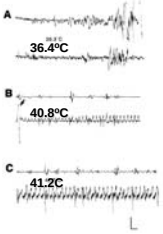
Prolonged Febrile Seizures → Epilepsy

"Cause" → Febrile seizures
"Cause" → Epilepsy

Immature rat model of prolonged (complex) Febrile Seizures



- Age appropriate*
- Physiological temps
- >98% seizure induction
- EEG validated
- Controlled seizure duration
- No mortality, morbidity



*Age of hippocampal development, Avishai-Eliner, TiNS, 2002

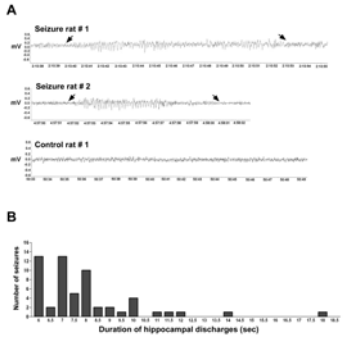
Toth et al. J Neurosci, 1998; Dube et al., Ann Neurol, 2000

Long-term Outcome

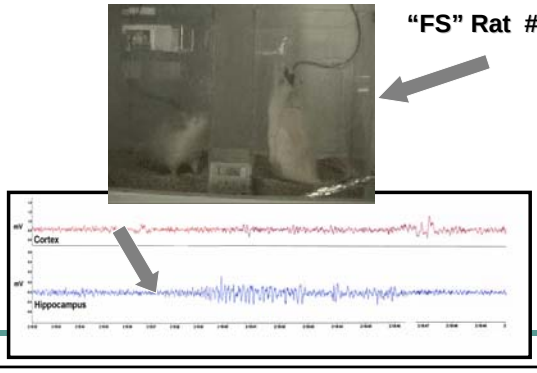
2000-2004:
Persistent hyper-excitable state;
cell injury, no death;
enduring changes in the HCN ion channels

2004: night-time chronic video-EEG
- 15/17 (88%) abnormal nocturnal EEGs
- 35% Spontaneous seizures.
- No abnormalities in controls in >300 hours

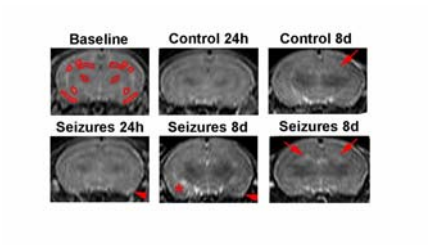
Dube et al., Ann Neurol, 2000; Dube et al., 2004



Spontaneous limbic seizure



MRI as marker of epileptogenesis



Mechanisms of Epileptogenesis

- No Cell death
- No Cell birth
- Functional changes in existing neurons
- Can we prevent them?

IDIOPATHIC EPILEPSIES WITH ABSENCE SEIZURES - PROGNOSIS AND EVOLUTION

Liisa Metsähonkala. Hospital for Children and Adolescents, Helsinki University Hospital, Helsinki, Finland.

Typical absence seizures are the predominant seizure type in clinical epilepsy syndromes such as childhood absence epilepsy and juvenile absence epilepsy. They may also occur in juvenile myoclonic epilepsy and in a few, not yet generally accepted, entities of idiopathic generalized epilepsies. Both the clinical experience and the genetic studies suggest that the boundaries of these syndromes are blurred; a factor which makes comparison of prognostic studies of these disorders difficult.

The prognosis of idiopathic epilepsies with absences is good in the sense that many of the patients either remit totally or are in remission with antiepileptic medication. However, for the clinician it is important to remember that there is considerable overlap between these syndromes and a high possibility of generalized tonic-clonic seizures in adolescence or in adulthood in patients with typical childhood absence epilepsy. There is also some evidence of social and cognitive deficiencies in this patient group in long-term follow-up.

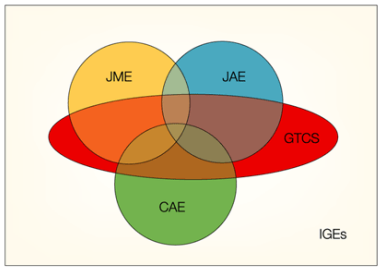
Idiopathic epilepsies with absence seizures

Prognosis and evolution

Liisa Metsähonkala

Idiopathic generalized epilepsies (IGE)

- multigenetic, multifactorial complex of disorders
- absences, myoclonias, GTCS



Nature Reviews | Neuroscience
Crunelli and Leresche 2002

Prognostic factors- clinical versus genetic approach

- CLINICAL
- seizure types
- age at onset
- EEG patterns
- response to medication

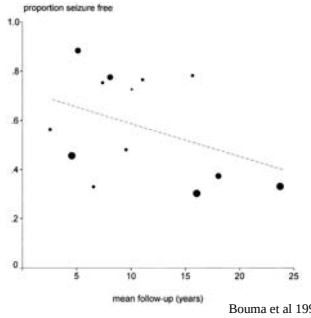
- GENETIC
- variable phenotypes
- genetic subclasses of IGE do not totally agree with the clinical syndromes

Idiopathic epilepsies with absences -clinical syndromes

- *absences predominate*
- Childhood absence epilepsy
- Juvenile absence epilepsy

- *other seizure types predominate*
- Juvenile myoclonic epilepsy
- Eye lid myoclonia with absences
- Perioral myoclonia with absences

Importance of duration of follow-up



Bouma et al 1996

Prognosis of CAE

- remission of absences up to 90%
- generalized tonic-clonic seizures in 25-40%
- JME in 15% (Wirrell et al 1996)
- poor social adaptation even in remission

Prognostic factors for CAE Wirrell et al 1996

Risk factor	Numbers with/ without	Terminal remission	RR (95% CI)
Absence status			
present	4	0%	3.2 (2.3,4.6)
absent	68	69	
Myoclonus while on AEDs			
present	12	17	3.3 (2.0,5.5)
absent	60	75	
GTC seizure while on AEDs			
present	7	14	2.9 (1.8,4.8)
absent	65	71	
EEG background slowing			
present	31	48	2.4 (1.2,4.6)
absent	41	78	
Family history of generalized seizures			
present	18	39	2.4 (1.3,4.2)
absent	54	67	
Cognitive difficulties			
present	14	43	1.9 (1.1,3.6)
absent	58	71	

RR = risk ratio; CI = confidence interval.

Prognosis of JAE

- generalized tonic-clonic seizures in 80%
- remission of absences in 50-65%

EVOLUTION OF EEG DURING CNS MATURATION

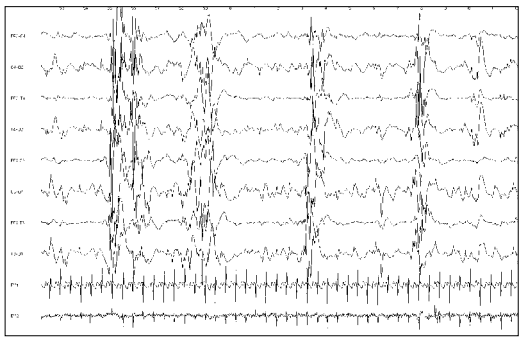
Perrine Plouin. Hôpital Necker Enfants Malades, Paris, France.

It is well known from many decades that normal EEG patterns vary from birth to adolescence, during both wakeness and sleep. Moreover the pathological EEG patterns may be comparable for a given disease at different ages (like Herpes Encephalitis), or very different for other pathological conditions such as epilepsy. Epileptic seizures and epilepsy syndromes differ among the pediatric population, according to age. Ictal and interictal EEG depend both of the maturation of CNS and of the associated pathology. We will review the different EEG presentation (ictal and interictal) in neonates, infants and young children in epilepsy syndromes, according both with idiopathic and symptomatic syndromes. In neonates the ictal-interictal EEG presentation is clearly different in idiopathic versus symptomatic cases. Suppression burst pattern of epileptic encephalopthies of that age will not be found in older children. In infancy hypsarhythmia is the typical interictal pattern of West syndrome, with some differences according to etiology; epileptic spasms occur also mainly at that age. In young children both idiopathic (ECTS) and symptomatic (Lennox Gastaut syndrome, Doose syndrome, Dravet syndrome) have specific EEG patterns. Finally we will discuss on CSWS which is also an age-dependent syndrome, present between the age of 4 and 14 probably depending on CNS maturation.

Evolution EEG in epileptic syndromes

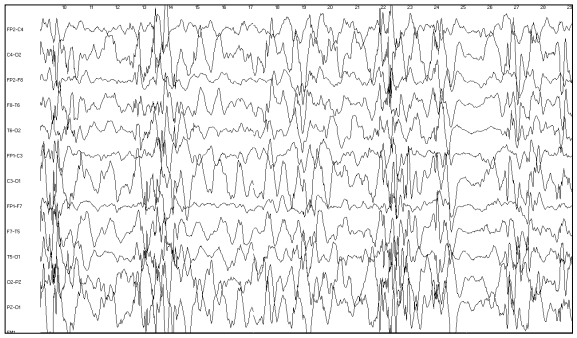
- According to age, EEg features are different from neonates to childhood
  - In epileptic encephalopathies one can recognize different interictal patterns
    - Suppression burst tracing
    - Hypsarhythmia
    - Slow SW and tonic seizures
- Although seizures may have or not the same EEG component

Suppression Burst Tracing



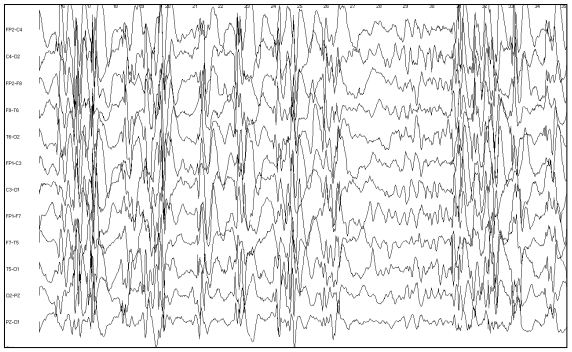
GOT..2 m

Hypsarhythmia sleep 6 m



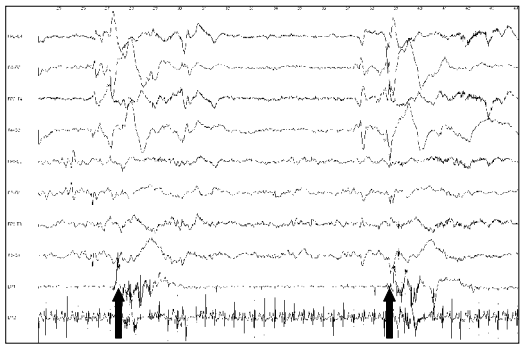
Bro… 6 months SVP

Lennox Gastaut syndrome



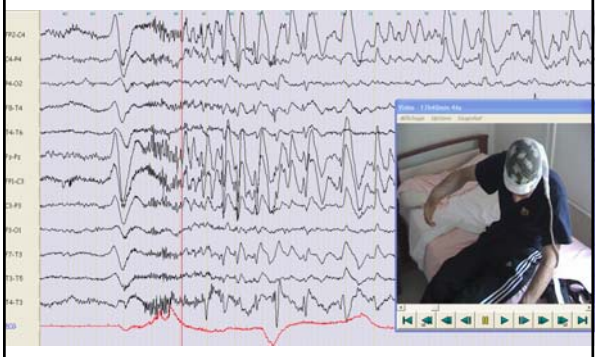
Benjamin L 7 ans

Epileptic Spasms



HAM… D14

Lennox Gastaut –tonic seizure



Leb…Guillaume 22 ans NEM

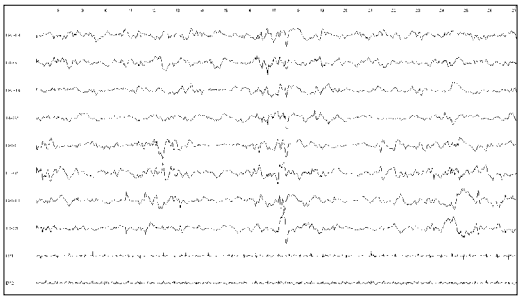
Evolution EEG in epileptic syndromes

– In benign epilepsies the electro-clinical presentation of seizures differ in
  - BFNS in neonates
  - BIS and BFS in infancy
  - BECTS and BEOS in childhood
– The interictal EEG may also present differently in these 3 age groups, concerning the focus of spikes.

Evolution EEG in epileptic syndromes

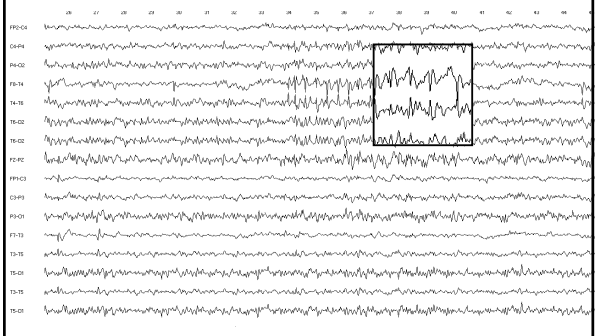
– In benign epilepsies the electro-clinical presentation of seizures differ in
  - BFNS in neonates
  - BIS and BFS in infancy
  - BECTS and BEOS in childhood
– The interictal EEG may also present differently in these 3 age groups, concerning the focus of spikes.

BFNC interictal sleep



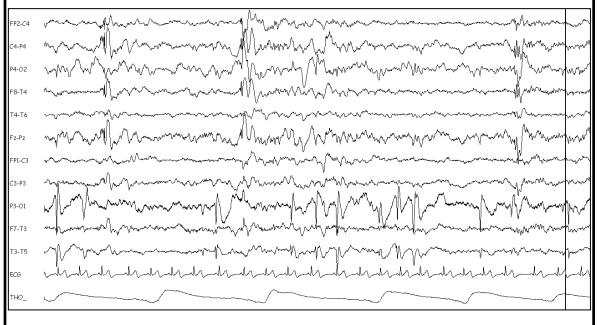
ELG..D8 **SVP**

ECTS



Pus.. 10 years **SVP**

Panayiotopoulos syndrome



Other situations

- Migrating Partial Seizures in Infancy
- CSWS
- Myoclonic status epilepticus in non progressive encephalopathies
- Ring chromosome 20 epilepsy
- Focal cortical dysplasia

EVALUATING SEIZURES AND DIAGNOSING EPILEPSY AND SYNDROMES

Peter and Carol Camfield. Canada.

The diagnosis of a first seizure may be complex and involve a long differential diagnosis. An extensive literature indicates that experts often disagree about seizure diagnosis. One strategy is to wait for a second attack in ambiguous cases. Syndrome diagnosis is also complex. In about 25% of cases, experts disagree about specific syndromes and in 15% of cases the syndrome diagnosis changes over time. We will use three cases to illustrate these concepts. Based on an extensive literature review, there is evidence that a specific syndrome diagnosis rarely yields an accurate prognosis.

Ideas

1. There is considerable variation in diagnostic accuracy – seizure and syndrome.
2. There are many syndromes that have an uncertain prognosis.

Dutch expert panel: 3 child neurologists reviewed history *presented by a neurologist*

(Van Donsellar Neurology 1989;39:267-71)

- 207 with first seizure, 156 "definite" 54 (35%) "disputable" – all followed for a year.
- 46% of "definite" had recurrence – 54% were "definite" but it was not confirmed (no second seizure). *I said it was a seizure, therefore it was.*
- 5 (10%) of "disputables" had "definite" seizure recurrence, 9 (17%) had non-epileptic recurrence.
- 8/54 "disputables" had spikes on first EEG
  3/8 recurred, 5/8 did not.

What type of seizure was it?

- 30 video seizures shown to relatives and physicians with 15 point check list – lots of discrepancies, especially in convulsive szs.
  (Rugg-Gunn Epilepsy Res 2001;43:193-9)
- 500 written descriptions of seizures shown to 3 neuro residents compared with the professor – kappa 0.12-0.90 depending on seizure type.
  (Bodensteiner Epilepsia 1988;29:123-8)
- Kappa - "almost perfect" >0.80, "substantial" 0.80-0.61, "moderate" 0.60-0.41, "fair" 0.40-0.21, "slight" 0.20-0.00, and "poor" <0

What type of seizure was it?

- 3 neurologists viewed videos of 138 seizures – kappa for seizure type = 0.41 (moderate to fair) (Parra Epilepsia 2001:42;476)
- 3 child neurologists read 100 written descriptions of febrile seizures
  – kappa for focality = 0.58 (moderate)
  (Berg Epilepsia 1992;33:661-6)

Does syndrome diagnosis change over time ?

- Connecticut consensus diagnosis 2 years later – changed in 13.5% (Berg Epilepsia 2000;41:1269-75)
- Dutch – 108 children presented at <6 yrs. with idiopathic or cryptogenic generalized epilepsy - followed 2-5 years – changed in 16%
  (Middeldorp Epilepsia 2002;43:734-9)
- New York – 407 first seizure, 182 (45%) had a 2nd seizure (syndrome diagnosis), 9 year f/u, syndrome changed in 18%
  (Shinnar Ann Neurol 2000;48:140-7)

Syndrome diagnosis – how well do we agree?

- **Italian** - easy to use, explicit algorithm to lead clinicians through ILAE syndrome classification – 37 cases (19 children) (Rinaldi Epilepsy Res 2000;41:223-34)
  "an algorithm of the ILAE classification is a fairly reliable instrument only for making a broad syndromic classification of epilepsy at the time of diagnosis."
- **Connecticut** – 613 newly diagnosed children, 3 child neurologists reviewed for syndrome – 26% disagreement, 10% at first level – localization related versus generalized versus other. Consensus achievable.
  (Berg Epilepsia 1999;40;439-444)

Syndromes with a definite prognosis

- Benign rolandic
- Panayiotopoulos
- Rasmussen
- Autosomal dominant nocturnal frontal lobe epilepsy
- Lennox Gastaut
- Dravet syndrome

DIAGNOSIS, TREATMENT AND OUTCOME OF INTRACRANIAL TUMORS AS ETIOLOGIC FACTOR FOR EPILEPTIC SEIZURES

Juha Jääskeläinen and Arto Immonen. Department of Neurosurgery, Kuopio University Hospital and University of Kuopio, Kuopio, Finland.

CONSEQUENCES OF STATUS EPILEPTICUS - DEVELOPMENTAL ASPECTS

Hana Kubova. Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic.

Data on long-term functional outcome after status epilepticus (SE) in developing animals are controversial. Resistance as well as sensitivity of immature brain to SE-induced adverse effects was reported. The results suggest that long-term outcomes of SE are highly age- and model-dependent. In addition, possible effects of the insult on brain development are usually not studied.

Status epilepticus was induced by LiCl-pilocarpine in normally developing immature rats (at the age of 12 or 25 days - P12 or P25). Previously published developmental studies suggest that rats 12 and 25 days old correspond to early postnatal and preschool or early school age in infants and children, respectively). SE had no major effect on body growth, however, animals of both age groups gained less weight within the first 24 h after SE compared to age-matched controls. No difference in weight gain was observed at later intervals. In P12 rats, SE did not induce delay of eye opening and basic motor abilities. On the other hand, SE at P12 delayed habituation in the open field suggesting developmental delay of non-associative learning.

SE induced memory impairment in both age groups 5 mo after SE. Rats of P25 group were not able to learn the Morris water maze task. Rats with SE at P12 exhibited much less severe but still significant impairment in this test. Based on cumulative escape latencies (Σ D3-D5 escape latencies), 17% of animals with SE at P12 exhibited severe memory impairment in this test.

Video-electroencephalographic monitoring 5 mo after SE demonstrated that almost 50% of rats in the P12 and 80% in P25 group developed spontaneous seizures. Seizure frequency tended to be in animals with P25 compared to P12 group. Also average seizure duration was longer in P25 than in P12 group (26 ± 5 *vs* 11 ± 2 s). Total seizure duration assessed as time spent in seizures per 24 h was about 9 times higher in P25 than in P12 group. Only nonconvulsive seizures (ictal activity mainly in hippocampus accompanied by automatisms) were recorded in P12 group whereas rats in P25 group exhibited clonic convulsions.

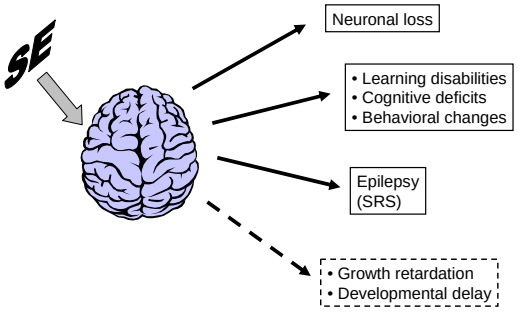
The present findings indicate that SE is harmful to the immature brain and that severity of functional impairment increases with age at SE. Importantly, functional sequelae of SE can be detected only in a subpopulation of animals in adulthood.

The present study was financially supported by Grant No 304/05/2582 of the Grant Agency of the Czech Republic.

Consequences of status epilepticus - developmental aspects

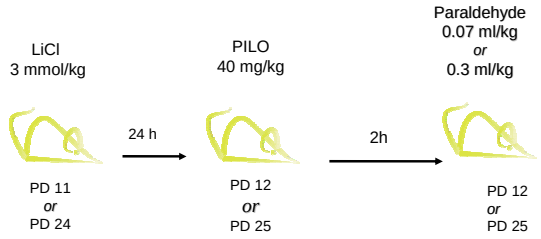
Hana Kubova,
Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic

Consequences of SE in the immature brain

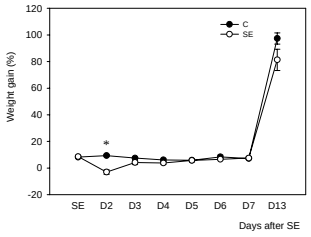


Methods

P12 *(comparable to human infants)*
P25 *(comparable to early school age)*

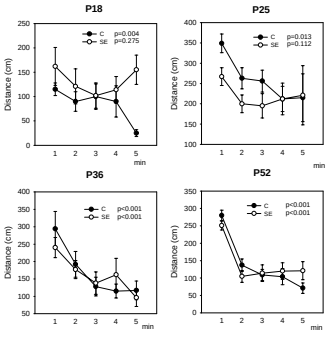


Effects of SE at P12 on body weight gain and other developmental milestones

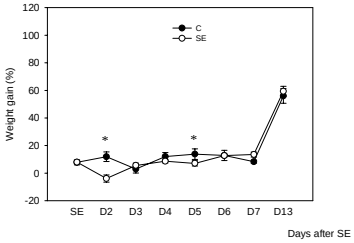


Eye opening
PD13-14

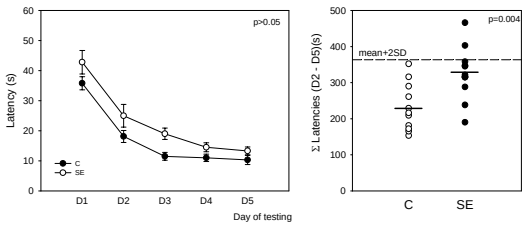
Delay of habituation in animals with SE at P12



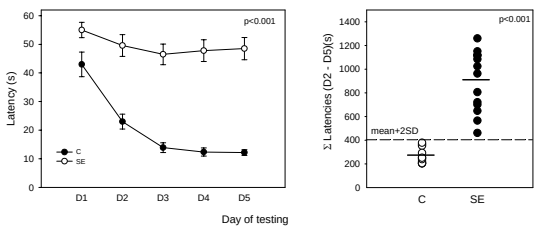
Effects of SE at P25 on body weight gain



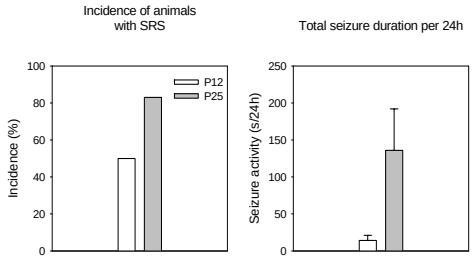
Effects of SE at P12 on cognitive functions (5 mo after SE)



Effects of SE at P25 on cognitive functions (5 mo after SE)



Incidence of epilepsy and seizure characteristics 5 mo after SE



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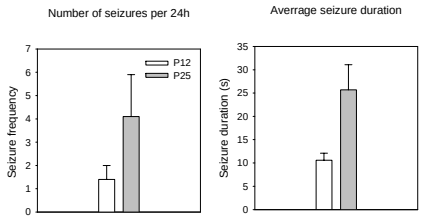


Conclusions

- SE leads to permanent functional changes even in P12 rats. The functional impairment as well as epilepsy are however detectable only in the subpopulation of animals.
- Pattern as well as severity of functional impairment are highly related to the age at SE.
- The contribution of SE-induced developmental delay or retardation to long-term outcome cannot be excluded and it remains to be studied

STATUS EPILEPTICUS – EPIDEMIOLOGICAL DATA FROM COHORT STUDIES: HELSINKI, KUOPIO, TAMPERE.

Seppo Soinila, Reetta Kälviäinen, Kai Eriksson. Department of Neurology, Helsinki University Hospital, Helsinki, Finland; Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland. Pediatric Research Centre, Medical School, University of Tampere, Tampere, Finland.

We summarize recent data obtained from three university hospitals on status epilepticus (SE) in children and adults. SE is considered as a continuum from premonitory stage (seizures lasting over 5 min) through established SE (seizures > 30 min) to refractory SE (seizures > 60 min).

Prognosis of prolonged convulsive seizures in children
57 % of prolonged (> 5 minute) seizure episodes lead to established SE. 42 % of episodes were febrile seizures, 28 % remote symptomatic, 4 % acute symptomatic and 26 % were of unknown etiology. None of the cases were fatal due to SE. Permanent and non-permanent neurological sequelae were rare (2.2 %, 3.2 %, respectively) and did not correlate with the duration of convulsions.

Progression of prolonged convulsive seizures to refractory SE in adults
16 % of the episodes of premonitory SE were stopped with benzodiazepine, while 59 % required second line anticonvulsive therapy. 25 % progressed into refractory SE. Mortality of this group was 31 % and overall mortality in the whole population was 38/252 (15 %) episodes.

Delay of treatment response in SE of adults
Mean time from onset to burst-suppression was 34 h. Mean time from onset to retained consciousness was 95 h. Mortality of SE was 11 %. Long delay did not correlate with death or slow recovery of consciousness.

We conclude that SE remains a life-threatening emergency in adults, which requires early, aggressive treatment with continuous EEG monitoring.

Definitions for Status Epilepticus

- Prolonged seizure – Premonitory stage
  - Seizure duration > 5 minutes
  - Over 90% of epileptic seizure end spontaneously within 4 minutes
- Early status epilepticus – First stage
  - Seizure duration 5 – 30 minutes
  - Seizures lasting over 5 minutes have over 90% probability of lasting over 30 minutes

Definitions for Status Epilepticus

- Established status epilepticus – Second stage
  - Seizure duration > 30 minutes or recurrence without regaining of consciousness
  - Criteria used for SE in epidemiological studies
- Refractory status epilepticus – Third stage
  - Seizure duration > 60 minutes
  - Persistent seizure activity despite first- and second line treatment

THE DURATION OF CONVULSIVE SEIZURES AND STATUS EPILEPTICUS IN CHILDREN – TAMPERE COHORT 1993-1999 –
Metsäranta et al., 2004

- Population based, retrospective
  - pop. 444 000, children <16 years: 85 000
- Study population
  - all patients <16 yrs admitted into pediatric ER/PICU due to acute convulsive disorder of any etiology
  - duration of convulsive seizure over 5 min
  - 186 patients, 279 seizure episodes
- Follow up: mean 2.1 yrs (range 0.1 - 7.7 yrs)
- Structured review of all medical charts and records; paramed & ICU notes and diaries

Outcome after prolonged convulsive seizures in 186 children: low morbidity, no mortality.
Metsäranta P, Koivikko M, Peltola J, Eriksson K. *Dev Med Child Neurol 2004*

- Febrile 42 %, remote symptomatic 28 %, acute symptomatic 4 %, idiopathic 26 %
- Mean duration 42 min. (range 5 - 330 min)
- 9.7 % stopped spontaneously
- Diazepam effective in 52 %
- Second line anticonvulsants needed in 33 %
- Thiopentone anesthesia in 6.8 %

Barbiturate anestesia as a treatment for convulsive seizures lasting over 30 minutes (age < 16 yrs)

Year	BA +	Major neur seq	Minor neur seq	Onset of epilepsy
1980-1992 (Eriksson et al. 1997)	25/65 (38%)	4/25 (16%)	3/25 (12%)	6/24 (25%)
1993-1999 (Metsäranta et al. 2004)	19/160 (13%)	0/19 (0%)	0/19 (0%)	6/19 (32%)
Total 1980-1999	44/225 (20%)	4/44 (9%)	3/44 (7%)	12/44 (27%)

Outcome after prolonged convulsive seizures in 186 children: low morbidity, no mortality.
Metsäranta P, Koivikko M, Peltola J, Eriksson K. *Dev Med Child Neurol 2004*

- No mortality related to prolonged seizures
- Permanent neurological sequelae in 2.2 %
  - new epilepsy (22 %)
  - developmental delay (1 pt)
  - hemiplegia (3 pts)
- Non-permanent (< 6 mo) sequelae in 3.2 %
  - motor dysfunction
  - cognitive impairment

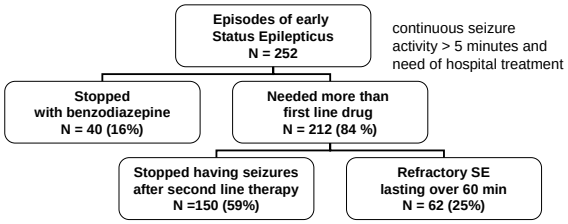
Outcome after prolonged convulsive seizures in 186 children: low morbidity, no mortality.
Metsäranta P, Koivikko M, Peltola J, Eriksson K. *Dev Med Child Neurol 2004*

CONCLUSIONS:

- Prognosis of prolonged convulsive seizures in children is good
- Permanent neurological sequelae are related to aetiological factors rather than duration of convulsions

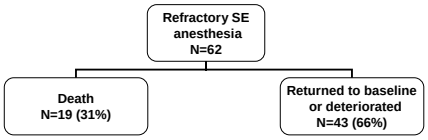
Status Epilepticus Adults – Kuopio cohort 1999 – 2003

Kälviäinen et al., unpublished



Refractory Status Epilepticus – Adults – Kuopio cohort 1999 – 2003

Kälviäinen et al., unpublished



-moreover 19 pts, who were not treated with anesthesia, died

- overall mortality 38/252 episodes = **15%**

Refractory Status Epilepticus – Adults – Helsinki cohort 2000 – 2003

Ritvanen et al., unpublished

- Population 1,4 million
- Total 248 episodes, avg. 59 episodes/year
- Preliminary data on 57 cases in 2002-2003
  - Epilepsy diagnosed prior to SE in 61 %
  - Mean age 54.4 yrs (range 17-85 yrs)
  - Intracranial 38 %, extracranial 39 %, alcoholism 23 %

Refractory Status Epilepticus – Adults – Helsinki cohort 2000 – 2003

Ritvanen et al., unpublished

- 91 % convulsive
- 44 % EEG-monitored
  - burst-suppression obtained in 72 %
- Mean time to return of consciousness 95 h
- Mean delay of treatment response 34 h
  - onset to burst-suppression
- Mortality 11 %
- PVS 4,5 %

Conclusions

- In adult patients, SE continues to be a life-threatening emergency
- Long delay in treatment response does not correlate with slow recovery or death.
- SE bears a significant risk of neurological sequelae. How about long-time outcome of survivors?

STATUS EPILEPTICUS – TREATMENT IN ADULTS AND CHILDREN

Reetta Kälviäinen, Kai Eriksson. Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland. Pediatric Research Centre, Medical School, University of Tampere, Tampere, Finland.

Status epilepticus is a neurological emergency that requires prompt recognition and aggressive drug treatment. An organized, systematic approach for the treatment makes the treatment more effective. It is essential for each emergency unit and intensive care unit to have algorithm for the treatment of status epilepticus. This presentation focuses on generalized convulsive status epilepticus, which is the most common form of the disorder.

The goal of the treatment of status epilepticus is to terminate both the clinical and electrical seizure activity. Once the diagnosis of the early status epilepticus is done, appropriate antiepileptic drug (AED) treatment should be started immediately. Response of status epilepticus to treatment has been shown to decline from 80% in those patients whose treatment began within 30 minutes from the onset of seizures, to less than 40% when treatment was initiated 2 hours or later from seizure onset. The outcome of status to a great extent depends on the etiology, and the urgent treatment of causal factors is vital.

Benzodiazepines are initial drug therapy because they are potent and have rapid onset of action. The efficacy of first line treatment (benzodiazepines either rectally or intravenously) for prolonged (over 5 minutes) convulsive seizures in children was in a retrospective population based study 58% and in adults in a prospective, randomized, double-blind study the efficacy of intravenous lorazepam was 65%. Phenytoin/fosphenytoin in patients of all ages and phenobarbital ín children are established second-line intravenous drugs. In a retrospective population based study in children 9% and in a retrospective cohort study of adults 31% the status epilepticus episodes could be regarded as refractory status epilepticus.

The drug treatment for refractory status epilepticus is general anaesthesia with continuous intravenous anaesthetics given in doses, which abolishes all clinical and electrographic epileptic activity. This requires often sedation to the point of burst suppression in the EEG and the patients have to be managed in an intensive care unit setting because artificial ventilation and hemodynamic support are required. EEG monitoring is essential to evaluate the electrophysiological treatment response and the depth of anaesthesia.

Barbiturates, propofol and midazolam have all been used as intravenous drugs for this purpose but barbiturates probably remain the only agent to ensure the termination of both clinical and electrographic seizure activity with minimal risk of breakthrough seizures (problem with midazolam) or immediate relapse after drug withdrawal or severe adverse reactions especially in children (problems with propofol).

During anaesthetic therapy intravenous fosphenytoin/valproate administration should also be continued to be able to gain a baseline medication before withdrawal of the anaesthetic therapy in order to prevent the recurrence of status epilepticus. Earlier AED therapy is continued. If additional medication is needed, the best AEDs to be started quickly in this setting are wide-spectrum AEDs, e.g. levetiracetam or topiramate.

Drug treatment, general measures and emergency investigations of convulsive status epilepticus as function of time from the onset of the seizure

Prolonged epileptic seizure
Premonitory stage / Out-of-hospital (non-medical persons)

Time	Drug Treatment		General measures	Emergency investigations
5 min.	***Adults***: Diazepam 10 mg rectally	***Children***: Diazepam 0,5 mg/kg rectally	Airway Breathing Circulation	Glucose (glucometer)
	Repeat once if necessary			

If seizure continues, proceed

Early status epilepticus
First stage / Out-of or in-hospital (medical personel)

Time	Drug Treatment		General Measures	Emergency investigations
5 - 30 min.	***Adults***: Lorazepam i.v. 4 mg ***or*** Diazepam i.v. 10 mg	***Children***: Lorazepam i.v. 0,1 mg/kg ***or*** Diazepam i.v. 0,3 mg/kg	Airway; oxygen Cardiorespiratory function and regular monitoring; ECG, blood pressure, SpO_2 Intravenous access; i.v. thiamine (adults), pyridoxine (children) Treat acidosis, hypoglycaemia	Glucose, Na, K, Ca, CRP, Astrup Levels of AEDs Toxicology screening Kidney and liver function tests
	Repeat after 5 min. if necessary			

If seizure continues, proceed

Established status epilepticus
Second stage / Emergency department

Time	Drug Treatment	General Measures	Emergency investigations
30 - 60 min.	Fosphenytoin i.v. 15-18 mgPE/kg at max. rate of 150 mgPE/min ***or*** Phenytoin i.v. 15-18 mg/kg at max. rate of 50 mg/min ***or in children***: Phenobarbital i.v. 15-20 mg/kg at max. rate of 100 mg/min	Cardiorespiratory function and monitoring; ECG, blood pressure, SpO_2, use pressors if needed Seek signs for increased intracranial pressure Identify and treat medical complications	CT scan for etiology CSF for CNS infection EEG for pseudostatus

If seizure continues, proceed

Refractory status epilepticus
Third stage / Intensive care unit

Time	Drug Treatment	General measures	Emergency investigations
>60 min.	General anaesthesia; Thiopental; 3-5 mg/kg bolus, then 3-5 mg/kg/h ***or*** Pentobarbital 10-15 mg/kg, then 0,5-1 mg/kg/h ***or*** Midazolam; 0,2 mg/kg boluses max. 2 mg/kg, then 0.05-2 mg/kg/h ***or in adults:*** Propofol; 1-2 mg/kg boluses, max. 10 mg/kg, then 2-4 mg/kg/h	Intensive care; ventilatory and hemodynamic treatment Increased intracranial pressure; measure and treat when exist Anaesthesia continued for 12-24 hours after last clinical or electrographic seizure Optimize maintenance AED treatment	Continuous EEG monitoring; electrographic seizures, depth of anaesthesia (burst-suppression) Monitor; Astrup, K, Na, glucose, lactate, levels of AEDs

STEM CELLS AND GENE THERAPY – ANY USE IN THE TREATMENT OF EPILEPSY?

Merab Kokaia. Sweden.

In-vivo and *ex-vivo* gene therapies are emerging as new treatment strategies in different animal models of neurological diseases. In this regard, epilepsy is not an exception. About 30% of temporal lobe epilepsy cases remain refractory to a pharmacological treatment, and are surgically inoperable, providing an urge for alternative treatment strategies. Accumulating experimental evidence indicates that *in-vivo* viral vector-based transfer of genes for adenosine and neuropeptides can modulate seizure activity in the hippocampus of experimental animals. Our preliminary data indicate that such a transfer for NPY gene could also compromise activity-dependent potentiation of synaptic strength (LTP) in the CA1 area, which is considered as a synaptic correlate of learning and memory in the hippocampus.

Ex-vivo gene transfer strategies using neural stem cell lines could serve as an alternative route of gene product delivery. In addition, these cells can migrate into the seizure-damaged areas of the brain, differentiate into neurons and integrate into the circuitry, thus replacing lost host neurons. We have shown that such immortalized neural stem cell line (RN33B) can successfully differentiate into the cortical and hippocampal principal neurons, and synaptically integrate into the circuitry of newborn rats. Moreover, these cells are also capable of integrating into the circuitry of seizure-damaged hippocampus after electrically induced status epilepticus model of epilepsy.

Taken together, experimental data indicate that cell and gene therapies in epilepsy based on overexpression of neuropeptides and other active molecules could be a feasible approach but much research is still required to unveil the underlying cellular and synaptic mechanisms of such treatment.

TREATMENT OF EPILEPSY IN WOMEN I

Emilio Perucca. Clinical Pharmacology Unit, University of Pavia, and Neuropharmacology Unit, Institute of Neurology IRCCS C. Mondino Foundation, Pavia, Italy.

The optimal management of epilepsy in women must take into consideration a number of issues, including (i) potential gender-related peculiarities of seizure disorders, including changes in seizure threshold associated with the menstrual cycle, pregnancy and hormonal status, (ii) implications for the female gender of certain adverse effects of AEDs , with special reference to cosmetic effects, endocrine effects and effects on reproductive organs; (iii) the impact of epilepsy and its treatment on fertility; (iv) interactions between antiepileptic drugs (AEDs) and oral contraceptives or other drugs which are used predominantly in females; (v) gender-related changes in pharmacokinetics of AEDs, with special reference to those occurring during pregnancy; (vi) effects of maternal AEDs, seizures and other risk factors on fetal development, and on postnatal development; (vii) inplications of AED treatment with respect to breast-feeding; (vi) optimal monitoring tools to protect maternal and fetal health. This presentation will provide a general introduction to the theme, appraise the evidence linking AEDs to gender-related adverse effects, review drug interactions of special relevance for women, discuss gender-specific pharmacokinetic issues, and summarize current recommendations for the optimal management of epilepsy in women.

Issues with AED Treatment in Women

- Gender – related differences in pharmacokinetics
- Adverse effects of special relevance to female gender
- Interaction with gender-specific drugs (e.g. steroid oral contraceptives)
- Issues related with conception and pregnancy

Endocrine Reproductive Disturbances in WWE

- Reduced libido
- Reduced fertility
- Hypothalamic amenorrhea (without hyperandrogenism)
- Early menopause
- Functional hyperprolactinemia
- Menstrual disturbances
- Polycystic Ovary Syndrome

Bauer et al J Neurol Neurosurg Psych 2002;73:121-5

AEDs as a Cause of Endocrine Reproductive Disturbances

- Direct effects on the endocrine glands
- Effects on hormone metabolism
- Effects secondary to weight changes and insulin resistance

AEDs and Reproductive Hormones Metabolism

- **Enzyme inducing AEDs**
  - Reduced testosterone and estradiol levels
  - Increased levels of sex hormones binding globulin
- **Enzyme inhibiting AEDs**
  - Increased androgen levels

Fertility

- Most studies (but not all) report lower fertility in WWE than in women without epilepsy
- Hypofertility less prominent in WWE than in men with epilepsy
- Causes probably multifactorial (psychosocial, epilepsy-related factors, AED-related factors)

Webber et al., *Epilepsia* 1986; Olafsson et al., *Neurology* 1998, Tettemborn et al., *Epileptic Disord* 2002, Artama et al. *Am J Epidemiol* 2004

Polycystic Ovary Syndrome (PCOs) and AEDs Methodological Issues

- Definition criteria for PCOS
- Availability of ultrasonographic data
- Duration of follow up
- Sample size
- Availability of appropriate controls (untreated WWE)
- Lack of randomised allocation to treatment

Polycystic Ovary

- ❖ Genetic predisdposition
- ❖ Follicular subcapsular ovaric cysts
- ❖ Menstrual disorders
- ❖ High testosterone levels observed inconsistently

Prevalence in the general population: 20-30% (17-33%) of premenopausal women

Bauer et al J Neurol Neurosurg Psych 2002;73:121-5

Polycystic Ovary Syndrome

Associated Disorders

- Spontaneous abortions
- Reduced tolerance to carbohydrates, hyperinsulinemia and insulin resistance
- Cardiovascular disorders
- Altered blood lipids
- Obesity

Polycystic Ovary Syndrome

Diagnostic criteria (NIH Consensus conference)

1. Menstrual disorders (amenorrhea, oligomenorrhea, or polymenorrhea)
2. Laboratory and clinical evidence of hyperandrogenism (hirsutism, acne, obesity, androgenic alopecia)
3. Exclusion of other endocrine disorders

Prevalence in the general population: 4-7% (up to 11%) and up to 45% in WWE on medication

Diagnosis not excluded by absence of ovaric cysts

Polycystic Ovary Syndrome: Conclusions

- ❖ Present in up to 10% of the general population
- ❖ Increased incidence in WWE irrespective of presence /absence of treatment
- ❖ More commonly associated with VPA (most studies) – age of treatment probably critical
- ❖ Pathogenesis unclear (direct drug effects, indirect effects, secondary to obesity)
- ❖ Needs to be recognized and investigated

Clinical Implications

- ❖ Use most appropriate AED for seizure control
- ❖ Inform patient about risk of menstrual/endocrine disorders
- ❖ Check for potential infertility, anovulation, menstrual disorders, clinical signs of hyperandrogenism, weight changes

Interactions of AEDs with Oral Contraceptives

Benzodiazepines	No interaction	Mattson,1986
Carbamazepine	↑ steroid metabolism	Crawford,1990
Phenobarbital	↑ steroid metabolism	Back, 1980
Phenytoin	↑ steroid metabolism	Crawford,1990
Primidone	↑ steroid metabolism	Coulam,1979
Valproic acid	No interaction	Crawford,1986
Felbamate	↑ steroid metabolism	Saano, 1995
Gabapentin	No interaction	Eldon, 1993
Lamotrigine	↑ LTG and steroid metabolism	Holdich, 1991 Sabers 2003 Sidhu, 2004
Levetiracetam	No interaction	Raguenau-Majlessi, 2002
Oxcarbazepine	↑ steroid metabolism	Fattore, 1999
Pregabalin	No interaction	Brockbrader, 2004
Tiagabine	No interaction	Mengel, 1994
Topiramate*	↑ steroid metabolism*	Doose, 2003
Vigabatrin	No interaction	Bartoli,1995
Zonisamide	No interaction	Mather, 2002

* at doses ≥ 200 mg/d

Issues with AED Treatment in Pregnancy

- Changes in drug disposition and response
- Teratogenic risks
- Other risks to mother – newborn
- Nursing

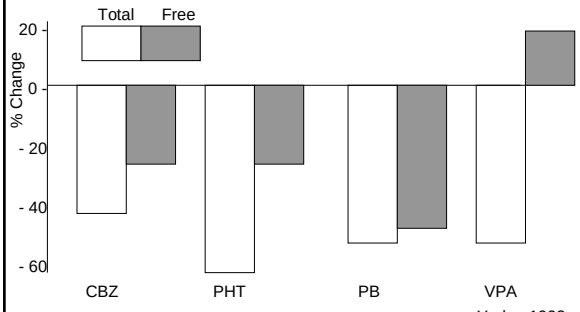
Relevance of Pharmacokinetic Changes during Pregnancy and Puerperium

- May affect maternal seizure control and susceptibility to adverse effects, and possible need for dosage adjustments
- May affect fetal drug exposure through the fetoplacental circulation
- Have implications for infant's drug intake through breastmilk

Pharmacokinetic Changes during Pregnancy Experience with Older AEDs

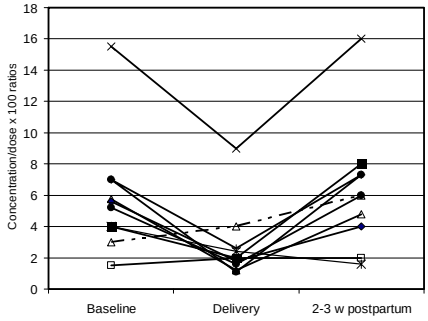
- Plasma concentrations of most conventional AEDs decrease during pregnancy
- Plasma protein binding of most highly bound drugs (VPA, PHT, DZP) also decreases
- Free AED concentrations tend to decrease, but to a lesser extent compared with total concentrations

Percentage Change in Total and Free Serum Concentrations of AEDs during Pregnancy



Yerby, 1992

Lamotrigine concentration/dose ratios at baseline, at delivery, and during nursing two-three weeks postpartum (Ohman et al, 2000)



Conclusions

- Use of AEDs in women involves many issues
- Female gender implies special considerations for drug choice and patient's monitoring
- Seizure control, avoidance of adverse effects and patient's counselling are of paramount importance
- Pregnancy is an especially sensitive issue, and teratogenesis is not the only concern

TREATMENT OF EPILEPSY IN WOMEN II: PREGNANCY

Torbjörn Tomson. Department of Clinical Neuroscience, Karolinska institutet, Stockholm, Sweden.

Optimal medical management during pregnancy is one of the most important treatment issues for women with epilepsy and their physicians. Potential adverse effects of antiepileptic drugs (AEDs) on the foetus need to be weighed against the foetal and maternal risks associated with uncontrolled seizures. The prevailing treatment strategy is based on the assumption that seizures, especially convulsive seizures, are more harmful to the mother and to the foetus than are the drugs. Although this assumption rests on circumstantial evidence, recent reports indicate increased maternal mortality in women with epilepsy and that this might be related to abrupt withdrawal of AEDs during pregnancy due to fear of teratogenic effects of the drugs. The objective of the treatment should be to maintain control of seizures, in particular tonic-clonic seizures, throughout pregnancy by using AEDs in a way, which minimizes adverse effects to the mother and the foetus. Physicians are generally advised to optimise treatment before conception, to choose the drug that is most effective for the seizure type or syndrome and to prescribe it as monotherapy at the lowest effective dosage. A major problem has been the lack conclusive data comparing different AEDs with respective human developmental toxicity. This is due to methodological shortcomings and in particular insufficient power in previous studies. This presentation will discuss data from more recent large-scale studies and pregnancy registries on the relative risks of major congenital malformations with different AEDs and in particular the emerging data suggesting higher malformation rates with valproate exposure.

Basis for treatment strategy in pregnancy

- Uncontrolled tonic-clonic seizures are more harmful than antiepileptic drugs (AEDs) to the mother and the foetus
- Objective is to control seizures with minimized risks to the mother, the foetus, the newborn and the nursed child
- AEDs are indicated during pregnancy if necessary to control tonic-clonic seizures

Epilepsy & Pregnancy Maternal risks

Maternal deaths in UK 1985-1999

Maternities	11.26 million
Direct & indirect deaths	1199
Deaths/Maternities	0.01%
Deaths in epilepsy	46
Deaths in epilepsy/All deaths	3.8%

Adab et al., JNNP 2004

Alterations in seizure control during pregnancy

	Unchanged	Improved	Worse
Bardy,1982 SF	54%	14%	32%
Gjerde, 1988 N	67%	17%	17%
Tomson, 1994 S	61%	34%	15%
Sabers, 1998 DK	66%	13%	21%

AEDs are Teratogenic

AED exposure vs. healthy controls

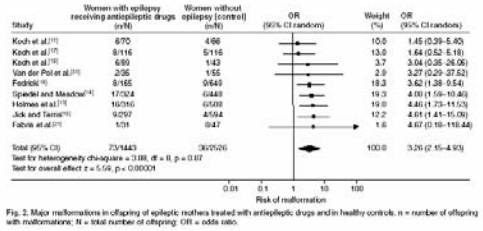


Fig. 2. Major malformations in offspring of epileptic mothers treated with antiepileptic drugs and in healthy controls. n = number of offspring with malformations; N = total number of offspring; OR = odds ratio.

Fried et al Drug Safety 27:197-202, 2004

C. Reduce polytherapy

- Polytherapy consistently associated with higher malformations rates

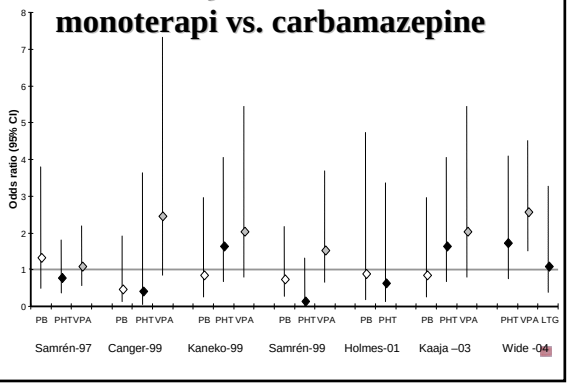
  Olafsson et al 1998, Samrén et al 1999, Kaneko et al 1999, Holmes et al 2001, Kaaja et al 2003, Wide et al 2004

- Altered treatment strategy (from poly- to monotherapy) associated with reduced malformation rates

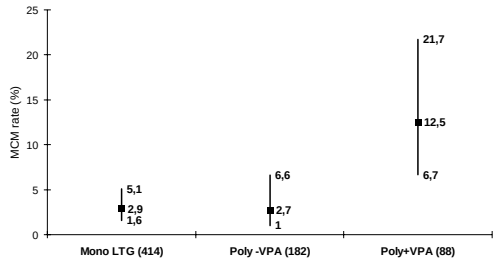
  Lindhout el al Neurology, 1992, Kaneko et al Neurology, 1992

- Are some combinations more harmful than others?

Risk for major malformations in monoterapi vs. carbamazepine



Lamotrigine Pregnancy Registry



Cunnington et al Neurology 2005;64:955-960

North American Registry >3,700 enrolled, 63% prospective

	N	MCM (%)
Phenobarbital	77	5 (6.5%)
		RR (95% CI)
PB vs. unexposed*		4.2 (1.5-9.4)
PB vs. 3 other AEDs**		2.0 (0.9-4.5)

*Relative to background rate (1.62%) among unexposed historical controls
**Three other unspecified monotherapies from NAREP

[1]Holmes et al., Arch Neurol 2004;61:673

North American Registry >3,700 enrolled, 63% prospective

	N	MCM (%)
Valproate	149	16 (10.7%)
		RR (95% CI)
VPA vs. unexposed*		7.3 (4.4-12.2)
VPA vs. all other AEDs**		4.0 (2.1-7.4)

*Relative to background rate (1.62%) among unexposed historical controls
**All other monotherapies from NAREP (n=1048)

Wyszynski et al., Neurology 2005;64:961-965

Observations from the UK Registry n=2050 prospective monotherapy

AED	N	Malformation rate (95% CI)
None	194	4.1% (2.1-7.9)
Carbamazepine	777	2.1% (1.3-3.3)
Lamotrigine	390	3.5% (2.2-5.5)
Valproate	572	6.1% (4.5-8.3)
Phenytoin	74	4.1% (1.4-11.3)

Russell et al Abstract AES 2004

Valproate exposure & malformations

- VPA appears to be associated with a particularly high malformation rate
  - -causal relationship or due to confounders?
- Difference demonstrated vs. CBZ. How about other AEDs with similar spectrum of efficacy as VPA?
- How do low VPA dosages compare with other AEDs with respect to teratogenicity?

Treatment strategy in women with epilepsy planning pregnancy

- All major changes in therapy should be accomplished before pregnancy
- Use lowest effective dose of suitable AED as monotherapy
- Valproate not first choice and best avoided if other suitable treatment options available
- If valproate needed for seizure control, strive for doses <800-1000 mg/day

EPILEPSY AND PREGNANCY: OUTCOME IN THE OFFSPRING

Eija Gaily. Hospital for Children and Adolescents, Helsinki University Hospital, Helsinki, Finland

Studies looking at postnatal cognitive development in children with prenatal antiepileptic drug (AED) exposure are challenged by several potential confounders that are difficult to control for. Choice of antiepileptic drug treatment and risk of genetic or acquired cognitive dysfunction in the mother are associated with epilepsy syndrome. Environmental epilepsy-related factors such as maternal seizures during pregnancy or postnatal psychosocial disadvantage may also affect development in the offspring.

Reliable assessment of the risk of cognitive impairment in the offspring requires follow-up extending to at least 5-6 years and prospective, controlled, preferably population-based design. Four such studies (U.S., Finland, Sweden) have reported intelligence (WPPSI, WISC) or developmental (Griffiths) scores in altogether 549 children of mothers with epilepsy at age 4-11 years. Four studies compared results between AED-exposed children and control children of mothers without epilepsy, and three also included nonexposed children of mothers with epilepsy. The main drugs studied were phenytoin (PHT, approximately 100 monotherapy) and carbamazepine (CBZ, 139 monotherapy). Most other children had been exposed to various forms of polytherapy, and 85 were nonexposed. The results suggest that PHT and CBZ monotherapy may be relatively safe for cognitive development. Polytherapy may be more harmful than monotherapy (based on one study). The results obtained in a very small group of valproate (VPA) -exposed children (13 mono-, 17 polytherapy) raised a suspicion that prenatal VPA exposure may impair verbal intelligence. This has recently been supported by the results of a retrospective survey (U.K.) containing 41 children exposed to VPA monotherapy. At present it is not possible, however, to rule out confounding by other epilepsy-related factors in the VPA group. Further prospective studies containing larger numbers of children exposed to VPA and other monotherapies are urgently needed.

Epilepsy and Pregnancy: Outcome in the offspring

Eija Gaily
Hospital for Children and Adolescents
Helsinki University Hospital

Kuopio Epilepsy Symposium 2005

Studies looking at postnatal cognitive development in children with prenatal AED exposure: challenges

- Population-based studies give the most reliable data but are very laborious to carry out,
- Prospective clinic-based studies and retrospective studies may be seriously biased,
- All major AEDs need to be evaluated separately in monotherapy and combinations,
- Cognitive defects milder than (moderate?) mental deficiency cannot be reliably assessed before age 5-6 yrs,
- Long follow-up periods increase the number of children lost to follow-up,
- The evaluation of cognitive abilities is time-consuming,
- There are many confounding factors difficult to control for.

The effect of AEDs: Confounding factors

- Drug choice depends on epilepsy type / syndrome
  - Genetic traits associated with susceptibility to developmental disorders may co-vary with epilepsy syndrome
- Other genetic effects
  - Epilepsy may limit partner choice -> increased risk of hereditary cognitive dysfunction from the paternal side
- Environmental effects
  - Maternal seizures during pregnancy may cause fetal distress
  - Active epilepsy may reduce maternal capacity for care giving
    - Seizures, AED side effects
  - Socioeconomic factors

Population-based prospective controlled studies

Study (Main drugs)	*% * of pop. included (N)*	*Outcome (method)*	*Controls*
Shapiro 1976 (PHT + PB)	45-50? (180)	IQ (?)	No AED No epilepsy
Gaily 1988 (PHT)	60-75 (148)	IQ, MR prev. (WPPSI)	No AED No epilepsy
Wide 2002 (CBZ)	45-54 (66)	DQ (Griffiths)	- No epilepsy
Gaily 2004 (CBZ)	42-57 (182)	IQ, MR prev. (WPPSI, WISC)	No AED No epilepsy

PHT = phenytoin, PB = phenobarbitone, CBZ = carbamazepine. MR prev. = prevalence of mental retardation. * Percentage of population included (N= number of children of mothers with epilepsy)

Fetal exposure	*Number of children*	*IQ at 4 yrs mean (SEM)*
PHT + PB	90	95.9 (1.7)
PHT	35	91.1 (2.7)
PB	27	96.4 (3.1)
neither	28	95.2 (3.0)
controls	27 832	97.0 (0.09)

Shapiro et al. Lancet 1976; i: 272-275
(SES, ethnic group, hospital accounted for in covariance analysis)

Fetal exposure	*N (mono-therapy)*	*Verbal IQ WPPSI 5.5yrs mean(SEM)*	*Nonverbal LIPS 5.5 yrs mean(SEM)*
PHT	80 (46)	111.4 (1.7)	109.8 (1.3)
CBZ	35 (18)	107.7 (3.8)	106.3 (3.6)
PB	19 (0)	111.1 (3.5)	109.1 (3.1)
None	12	111.6 (5.3)	104.7 (3.8)
Controls	104	114.5 (1.3)	113.2 (1.3)

Gaily et al. J Pediatr 1988; 113: 677-684
(SES/Maternal education accounted for in ANOVA)

Griffiths at 2-8 yrs, subtest **Exposure** (N)	*Loco-motor f.* mean	*Hearing speech* mean	*Practical reasoning* mean	*Total score* mean
CBZ (35)	104	105	101	618
PHT (15)	98*	111	110	635
Other (7)	102	97	97	612
Poly (9)	104	104	107	633
Controls (66)	106	107	108	641

Wide et al.Acta Paediatr 2002; 93: 174-176
(Maternal education and number of siblings accounted for in regression analysis,
* p <0.05 vs controls)

Group **(age 5-11 yrs)**	*Verbal IQ WPPSI/WISC-R mean (SEM)*	*Nonverbal IQ WPPSI/WISC-R mean (SEM)*
Children of mothers w/ epilepsy, N =182	92.8 (1.3)	96.0 (1.2)
Controls, N=141	94.9 (1.2)	97.6 (1.4)

Gaily et al. Neurology 2004; 62: 28-32.

Exposure (N)	*Verbal IQ mean (SEM)*	*Nonverbal IQ mean (SEM)*
Monotherapy (107)	94.4 (1.7)	101.9 (1.4)
CBZ (86)	96.2 (1.9)	103.1 (1.5)
VPA (13)	83.5 (3.8)	96.3 (4.8)
Other (8)	91.1 (6.4)	96.9 (4.6)
Polytherapy (30)	84.9 (2.5)*	97.1 (2.9)
VPA comb (17)	81.5 (2.8)	96.1 (3.7)
No AED (45)	94.3 (2.6)	95.6 (2.8)

Gaily et al. Neurology 2004; 62: 28-32
* F = 5.2, p = 0.02 vs monotherapy, with maternal education and test as covariants

Prevalence of mental deficiency

Combined prospective population-based data from 1975-79# and 1989-1994##, age 5+ years:

Children of mothers w/ epilepsy: 6/330 = 1.8%
Controls (no epilepsy): 3/246 = 1.2%
RR 1.5 (95%CI 0.4-5.9)

Birth cohort of 12 000 children in Northern Finland (Rantakallio & von Wendt 1986): 1.2%

Gaily et al. J Pediatr 1988; 113: 677-684,
Gaily et al. Neurology 2004; 62: 28-32

What can we say at present about the effect of prenatal AED exposure on cognitive development?

- PHT or CBZ monotherapy below toxic range seem to be relatively safe for cognitive development at least in the populations studied so far,
- Polytherapy may be more harmful than monotherapy,
- Valproate monotherapy may impair verbal intelligence but the effect of other epilepsy-associated factors cannot be ruled out- further large prospective studies are needed,
- No prospective data are available on other antiepileptic drugs in monotherapy.

SCIENTIFIC ABSTRACTS

Poster presentations

1.

SURGICAL OUTCOME OF MRI- NEGATIVE PATIENTS IN TEMPORAL LOBE EPILEPSY EVALUATED WITH INTRACRANIAL INVASIVE MONITORING

A Immonen, L Jutila, A Muraja-Murro, R Vanninen, E Mervaala, R Kälviäinen, M Vapalahti. Departments of Neurosurgery, Neurology, Clinical Neurophysiology, and Clinical Radiology, Kuopio University Hospital, Kuopio, Finland; Departments of Neurosurgery and Neurology, University of Kuopio, Kuopio, Finland.

RATIONALE: The aim of the study was to assess the surgical outcome with those MRI- negative temporal lobe epilepsy patients who underwent preoperative evaluation with invasive intracranial electrodes. **METHODS:** Since 1988 Kuopio University Hospital has served as a national center for adult epilepsy surgery in Finland (population 5.3 million). From January 1990 to October 2003 altogether 132 patients with medically refractory epilepsy has been evaluated with intracranial EEG monitoring, and 120 of them had suspected temporal lobe epilepsy. Of the 120 patients, 60 had normal MRI findings and 39 of them were operated determined by the results of invasive monitoring. The surgical outcome in these 39 patients was assessed according to Engel's classification at one year postoperative follow-up. The reasons for not to proceed to operative treatment was analysed among those 21 patients who were considered inoperable. **RESULTS:** Twelve patients (30.8 %) were seizure free at 1- year follow-up (Engel's class I) and three patients (7.7 %) had rare seizures (Engel's class II). Nine patients (23.1 %) had worthwhile improvement (Engel's class III) and fifteen patients (38.5 %) did not benefit from the surgery (Engel's class IV). Of those 21 inoperable patients, 7 patients (33.3 %) had inadequately localised extratemporal onset of the seizures and 5 patients (23.8 %) had bitemporal onset of the seizures. Two patients (9.5 %) had seizure onset near Wernicke's area and with two patients (9.5 %) the frontotemporal differential diagnostics was not possible to demonstrate. The other five patients (23.9 %) did not either get seizures during monitoring, were seizure free after registration or had generalised epilepsy. **CONCLUSIONS:** It is possible to achieve satisfactory surgical outcome with this diagnostically challenging subgroup of MRI negative patients with temporal lobe epilepsy who underwent intracranial monitoring. On the other hand, with those patients who did not benefit from surgical treatment, the predicting factors for outcome need to be further analysed.

2.

ENDOTHELIN-1 INDUCED MIDDLE CEREBRAL ARTERY OCCLUSION LEADS TO EARLY-ONSET SEIZURES AND TRANSIENT SENSORIMOTOR DEFICIT IN RATS

H Karhunen, J Nissinen, J Sivenius, J Jolkkonen, A Pitkänen. A.I. Virtanen Institute for Molecular Sciences and Department of Neuroscience and Neurology, University of Kuopio, Kuopio, Finland.

RATIONALE: Stroke is one of the most common causes of epilepsy in adulthood. In the present study endothelin-1 (ET) induced middle cerebral artery occlusion (MCAo) was used to model human stroke in Spraque-Dawley rats. We aimed to answer the following questions: 1) Does ET-induced MCAo lead to spontaneous seizures and 2) do ET-induced MCAo and seizures have an effect on sensorimotor and memory functions? **METHODS:** Ischemia was induced with ET-injection (120 pmol) under halothane anaesthesia. Sham group was operated but ET was not applied. Video-EEG was recorded within 2 h and at 2, 4, 6, and 12 months after ischemia induction (each 2 wk, 24h/d). Sensorimotor function was tested with running wheel test. At the end of the experiment spatial and emotional learning and memory were tested with water maze and fear conditioning. Timm's silver staining was used for the mossy fiber sprouting. **RESULTS:** Early-onset seizures occurred in 43.8% of ischemic rats, but only one rat developed epilepsy. The epileptic rat did not have mossy fiber sprouting. Ischemic rats also had transient sensorimotor deficit, but memory impairment was not observed. Seizures did not have any effect on behavioural recovery. **CONCLUSIONS:** ET-induced MCAo in rats produced early-onset seizures and transient sensorimotor deficit. In the ischemic group 9.1% of animals developed epilepsy.

3.

ASSOCIATION OF HIPPOCAMPAL DAMAGE WITH THE SEVERITY OF EPILEPSY INDUCED BY FLUID PERCUSSION INJURY IN RAT

I Kharatishvili, J Nissinen, A Pitkänen. Epilepsy Research Laboratory, A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland.

RATIONALE: Traumatic brain injury (TBI) is a major risk factor for subsequent development of epilepsy. The mechanism by which trauma to the brain tissue leads to recurrent seizures is unknown. The contribution of hippocampal damage to the generation of chronic spontaneous seizures is under dispute. Here, we addressed this controversial question by examining whether severity of neuronal loss and density of mossy fiber sprouting correlate with the seizure frequency.
METHODS: The recently developed rat model for post-traumatic epilepsy was used in the study. Epileptogenesis was induced in 18 rats by lateral fluid percussion injury (FPI). After FPI long term video-electroencephalographic monitoring was performed for 10 months to prove development of post-traumatic epilepsy (PTE) and follow seizure frequency. The density of mossy fiber sprouting was analyzed from Timm-stained sections. The loss of hippocampal neurons was assessed by stereological cell counts. **RESULTS:** Nine out of 18 (50%) animals with head trauma developed epilepsy. Mean seizure frequency was 0.3±0.14 sz/day. In the PTE animals there was a correlation between seizure frequency and overall mossy fiber sprouting (mean score from septal + temporal ends of the dentate gyrus) both ipsilaterally and contralaterally to FPI. Further, in the septal end of the dentate gyrus there was a clear correlation between hilar cell loss and seizure frequency both ipsi- and contralaterally to the injury site. **CONCLUSIONS:** Our data indicate that the overall neuronal damage in the hippocampus after fluid percussion injury in rat can contribute to the occurrence of chronic spontaneous seizures and the severity of post-traumatic epilepsy.

4.

A LONG-TERM MRI ASSESSMENT OF HEAD TRAUMA INDUCED TISSUE DAMAGE IN RAT BRAIN

RJ Koskinen, I Kharatishvili, HI Gröhn, A Pitkänen, OHJ Gröhn. Departments of Biomedical NMR and Neurobiology, A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland.

RATIONALE: The MRI investigation of spatio-temporal changes in morphology and tissue water-homeostasis in traumatic brain injury (TBI) may clarify the mechanisms of TBI and provide an insight into long-term consequences leading to e.g. development of epilepsy in ~50 % of patients with penetrating head trauma. Non-invasive detection of surrogate markers that predict the prognosis of TBI would be of value for development of treatments. **METHODS:** TBI was induced to 14 rats by fluid percussion [1]. 6-months MRI follow-up was performed in 4.7T. Volumetric changes were detected using T_2-wt adiabatic spin-echo multi-slice. T_2, $T_{1\rho}$ and the diffusion (D_{av}) were quantified from single slice using a fast-spin-echo. Gradient-echo detected intracerebral hemorrhages. 6months after TBI the functional outcome was evaluated by Morris water-maze. **RESULTS:** In acute phase, the initial diffusion drop and intracerebral haemorrhage, as detected by T_2^*, seem to best predict the severity of the subsequent lesion. Elevated diffusion and $T_{1\rho}$ reveal progressive changes, continuing even after 6 months. Dav, T1ρ and T2 in hippocampus already 3hours or 3days after TBI correlated with the long-term functional outcome (water-maze latency changes). The extent of atrophy also correlated with the functional outcome. **CONCLUSIONS:** Present data show that TBI-animals develop cortical and/or hippocampal damage that continues to progress several months after TBI and is detectable with quantitative MRI. Quantitative MRI may help to predict the long term functional outcome. It remains to be studied whether quantitative MRI may also predict the histologically determined cellular damage. References: [1] McIntosh, T.K., Neuroscience, 28(1): 233-44, 1989.

5.

NOVEL TOOLS FOR EPILEPSY CARE AND RESEACRH (EpilCare)

R Kälviäinen, T Mäenpää, E Gaily, T Keränen, E Herrgård, L Jutila, K Eriksson. Kuopio Epilepsy Center, Department of Neurology and Pediatric Neurology, Kuopio University Hospital, Kuopio, Finland; Marimedical Ltd, Finland; Hospital for Children and Adolescents, Helsinki University Hospital, Helsinki, Finland; Department of Neurology, Tampere University Hospital, Tampere, Finland; Pediatric Research Center, Medical School, University of Tampere, Tampere, Finland.

RATIONALE: The purpose of this of this research is to create specialized computer application and clinical database for epilepsy (EpilCare), which is used as a tool for supporting the daily registration and storage of clinical events in epilepsy (seizures and changes of medication). Traditionally, paper-based records have been used for these purposes. **METHODS:** The collection of patient-specific clinical data forms the patient database. The database contains structured terminology of seizure types, syndromes, epilepsy type, etiology, description of the impairment(s) caused by the epilepsy and diagnostic evaluations and treatments. We have used the new 2001 ILAE diagnostic scheme consisting of five axis as the basis of describing individual data in each patient. **RESULTS:** The EpilCare application is built by MariMedical Ltd which is also responsible for the maintenance of the database. Adult and pediatric epileptologists have provided the knowledge of diagnostics and treatment of epilepsy for the basis of the application. The personnel and patients at Kuopio University Hospital Epilepsy Center are going to perform the pilot testing of EpilCare. EpilCare will utilize the latest Internet technologies and contain an advanced graphical user interface. **CONCLUSIONS:** EpilCare is a novel method for collecting and storing clinically relevant data from patients with epilepsy. EpilCare allows a fast review of data during the clinical visit or during phonecall. The application improves the flow of information within the hospital information system. The clinical database of EpilCare allows the standardization of patients' data, and a better organization of the patient management process. It can also be used for quality management purposes, for medical research and as an information exchange channel.

6.

UPREGULATION OF UROKINASE-TYPE PLASMINOGEN ACTIVATOR IN THE RAT BRAIN DURING EPILEPTOGENESIS

L Lahtinen, K Lukasiuk, A Pitkänen. Epilepsy Research Laboratory, A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland; The Nencki Institute of Experimental Biology, Department of Cellular Biochemistry, Warsaw, Poland.

RATIONALE: The epileptic process typically develops in three phases: initial brain damaging insult, latency period (epileptogenesis) and recurrent seizures (epilepsy). Involvement of the plasminogen system has been highly implicated in different diseases affecting the brain. cDNA array studies indicated urokinase-type plasminogen activator (uPA), to be one of the genes upregulated during epileptogenesis. The aim of this work was to further study the expression of uPA during the epileptogenic process. **METHODS:** Epileptogenesis was triggered by inducing status epilepticus (SE) with electrical stimulation of the amygdala in rats. Continuous video-EEG recordings were used to monitor the development of SE and spontaneous seizures. Animals were sacrificed 1d, 4d or 14d after stimulation and brains were processed for histology or protein extraction. Localization of uPA in the brain was studied with immunohistochemistry. Enzymatic activity of uPA was measured using zymography. **RESULTS:** In rats undergoing epileptogenesis, there was a marked increase in uPA immunoreactivity in the hippocampus and temporal lobe compared to controls. Most prominent expression was observed 1d and 4d after SE in astrocytes and pyramidal neurons. Accordingly, enzymatic activity of uPA was increased in the hippocampus and temporal lobe in epileptogenic animals. **CONCLUSIONS:** These results suggest a possible role for uPA in the reorganization of cellular networks during epileptogenesis.

7.

$GABA_A$ RECEPTOR SUBUNIT MRNA AND PROTEIN EXPRESSION ALTERATIONS IN THE DEVELOPING RAT BRAIN AFTER KAINIC ACID-INDUCED STATUS EPILEPTICUS

HB Laurén, FR Lopez-Picon, ER Korpi, IE Holopainen. Department of Pharmacology and Clinical Pharmacology, University of Turku, Turku, Finland; Institute of Biomedicine, Pharmacology, University of Helsinki, Helsinki, Finland.

RATIONALE: Impaired $GABA_A$ receptor function can contribute to seizure generation in epilepsy, but it is not known if the subunit expression and the pharmacological properties are modulated by seizures in the developing brain. **METHODS:** Kainic acid (KA)-induced status epilepticus (SE) was elicited in immature, 9-day old rats. *In situ* hybridization was used to compare the acute and sub-acute changes in the $GABA_A$ receptor subunit mRNA expression in different brain regions and immunocytochemistry was applied to detect subunit proteins. **RESULTS:** There was increased expression with age of α1 and α4 subunit mRNA in the control rats, whereas those of α2, β3, and γ2 subunits decreased, in hippocampal subregions. The KA treatment caused alterations in the normal developmental expression variations of α1, α2 and β3 subunit mRNAs. **CONCLUSIONS:** Our results suggest that SE-induced changes in the normal expression pattern of $GABA_A$ receptor subunit mRNAs in the brain, during the sensitive postnatal phase of development, can seriously disturb the normal development and lead to expression of receptors with altered pharmacological profile. Acknowledgements: The Foundation of University of Turku, the Finnish Graduate School of Neuroscience, the Research and Science Foundation of Farmos, the Sigrid Juselius Foundation, the Special State Grant for Clinical Research (EVO), the Svenska Kulturfonden.

8.

INFLUENCE OF AETIOLOGY ON SEIZURE FREQUENCY IN LOCALISATION-RELATED REFRACTORY EPILEPSY IN ADULT PATIENTS

S Liimatainen, M Kaartinen, J Peltola. Department of Neurology and Rehabilitation, Tampere University Hospital, Tampere, Finland; Tampere University Medical School, Tampere, Finland.

RATIONALE: Earlier studies have shown that aetiology makes a difference in the outcome of epilepsy, but most studies are paediatric. **METHODS:** We retrospectively investigated the cause of epilepsy in 131 adult patients with localisation-related refractory epilepsy followed-up in our centre and evaluated the influence of aetiology, number of antiepileptic drugs (AEDs) and the duration of epilepsy on seizure frequency in a two-year follow-up. **RESULTS:** Most of the patients had persistent seizures while the remaining previously uncontrolled patients achieved at least six months seizure-freedom. The most common epilepsy type was temporal lobe epilepsy (TLE). The most common aetiologies were hippocampal sclerosis (HS) and brain trauma. Those with cortical dysplasia (CD), vascular malformation and dual pathology were most refractory, none being seizure-free. **CONCLUSIONS:** In this group of refractory patients there was no specific aetiology with an especially good outcome and no difference in the outcome of remote symptomatic and cryptogenic aetiologies. All patients had undergone many AEDs trials and most were still on at least dual therapy. There was a small group of patients achieving remission after multiple AED regimens. Duration of disease did not influence the seizure frequency.

9.

REGULATION OF NEUROFILAMENTS DEGRADATION BY GLUTAMATE RECEPTORS AND CALPAIN PROTEASES IN KAINIC ACID-TREATED IMMATURE HIPPOCAMPAL SLICE CULTURES

F Lopez-Picon, T Kukko-Lukjanov, IE Holopainen. Department of Pharmacology and Clinical Pharmacology, University of Turku, Turku, Finland.

RATIONALE: Although neurofilaments (NFs) constitute the main cytoskeletal network in neurons, their stability in neuronal death in the immature brain has remained unknown. We have now studied whether a calpain inhibitor and glutamate receptor antagonists effect the KA-induced NF degradation and neuronal damage in immature hippocampal slice cultures. **METHODS:** Cultures where treated for 24 h with KA (5 μM) alone or in combination with calpain inhibitor MDL-28170 (0.5 μM), AMPA/KA receptor antagonist (CNQX, 10 μM), and NMDA receptor antagonist MK-801 (0.5 μM). Western blotting and immunocytochemistry where used to asses the changes in NF proteins, and Fluoro-Jade B and thionin stainings to study neuronal damage. **RESULTS:** KA treatment significantly decreased the levels of NF proteins in Western blotting, and decreased NF immunoreactivity. These changes were decreased in the presence of MDL-28170 and CNQX, which also even enhanced NF-L and NF-H immunoreactivity in CA3 pyramidal cell bodies, and reduced KA-induced CA3 neuronal damage. **CONCLUSIONS:** Our results suggest that the stability of NF proteins is of crucial importance for neuronal survival during KA-induced excitotoxic injury, and both calpain inhibitors and specific AMPA/KA receptor antagonists seem have neuroprotective effect in immature cultures. Acknowledgements: This work was supported by the Finnish Graduate School of Neuroscience, the EVO Grant, and Arvo and Lea Ylppö Foundation.

10.

CHANGES IN GENE EXPRESSION PATTERN IN THE BASOLATERAL AMYGDALA INDUCED BY PAVLOVIAN FEAR CONDITIONING IN RATS UNDERGOING EPILEPTOGENESIS.

K Majak, A Pitkänen. Epilepsy Research Laboratory, Department of Neurobiology, A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland; Department of Anatomy and Neurobiology, Medical University of Gdańsk, Gdańsk, Poland; Department of Neurology, Kuopio University Hospital, Kuopio, Finland.

RATIONALE: Several studies implicated that the lateral and basal nuclei of the amygdala play critical role in the emotional learning. It has been also shown that during development of temporal lobe epilepsy (epileptogenesis) the lateral and basal nuclei of the amygdala are damaged. So the aim of the study was to reveal the differences in gene expression pattern during emotional learning in rats undergoing epileptogenesis and controls. **METHODS:** Epileptogenesis was induced in 8 rats by stimulation of the left lateral amygdala (8 controls were not stimulated). Fife days later animals were habituated to fear conditioning apparatus for 3 days. Next, control and epileptic animals received training session composed of either two times paired or unpaired tone and footshock presentation. 3h later the animals were sacrificed and the lateral and basal nuclei of the amygdala were microdissected using Leica AS LMD Laser System. Then 30ng of total RNA from each animal underwent 2 rounds of amplification. Finally the aRNAs from 4 experimental groups: epileptic paired (EP), epileptic unpaired (EU), control paired (CP) and control unpaired (CU) were pooled (2 animals per group) and hybridized to GeneChip® Rat Genome 230 2.0 Array (Affymetrix). **RESULTS AND CONCLUSIONS:** Comparisons of genes differently expressed in basolateral amygdala among experimental groups revealed the candidate genes related to epileptogenesis, tone and footshock presentation as well as emotional learning.

11.

ACUTE PROLONGED CONVULSIVE SEIZURES IN CHILDREN - ETIOLOGY, TREAMENT AND OUTCOME

P Metsäranta, K Eriksson. Pediatric Research Center, Medical School, University of Tampere, Tampere, Finland.

RATIONALE: Prolonged convulsive seizures are a common neurological emergency and a potential cause for neuronal damage and functional sequel. Factors contributing to the duration of a single convulsive seizure are of great interest due to the possibility to reduce this risk. **METHODS:** We retrospectively reviewed children (aged 1 month to 16 years) who had been admitted to the Pediatric Emergency Department of Tampere University Hospital, from January 1993 to December 1999, due to acute convulsive disorder. Seizures lasting over 5 minutes were included into the analysis. Patients had been followed up afterwards on individual basis (mean follow-up time 2.1 years, range 0.1 to 7.7 years). All data of the initial seizure episode and clinical follow-up was analyzed retrospectively through medical records. **RESULTS:** There were 279 separate seizure episodes lasting over 5 minutes in 186 children (mean age 4.4 years; range 0.1-15.25 years). The etiology of the seizure was idiopathic in 26.5%, febrile in 42.3%, remote symptomatic in 27.6% and acute symptomatic in 5.7% of the episodes. The mean duration of all seizure episodes was 42.5 minutes. It correlated with the etiology: shortest in the febrile group (35.4 minutes), longest in the acute symptomatic group (88.6 minutes) ($p<0.001$). There were no deaths directly related to these acute seizure episodes. The most common sequel was onset of epilepsy in 40 children (22%). Other, permanent neurological sequel was noted only in four patients (2.2%) and nonpermanent sequel in six patients (3.2%). Further analyses on treatment delay were made on patients having their first convulsive seizure during to study period (n=157). It showed that acute anticonvulsive medication (usually rectal diazepam) was rapidly induced in most patients: 84.7% of the patients received their first medication within 30 minutes after onset of the seizure. Rapid treatment (< 30 min.) also seemed to reduce the risk of poor treatment response. **CONCLUSIONS:** Neurological sequelae in children after prolonged convulsions were rare and often related to etiological factors. Contribution of rapid treatment in these patients remains unclear due to retrospective and uncontrolled methods. Treatment was rapidly and effectively induced in this study population. The risk of poor treatment response seems to increase as the seizure endures.

12.

DEPTH-RECORDED MISMATCH NEGATIVITY FROM HUMAN HIPPOCAMPUS AND AMYGDALA

A Muraja-Murro, A Pääkkönen, S Määttä, L Jutila, A Immonen, R Kälviäinen, E Mervaala.
Departments of Clinical Neurophysiology, Neurology, and Neurosurgery, Kuopio University Hospital, Kuopio, Finland.

RATIONALE: Mismatch negativity (MMN) is an event-related potential (ERP) produced by a deviant auditory stimulus occurring infrequently mixed among many physically constant standard stimuli. The MMN is thought to reflect activation of an automatic change-detector system that compares each new auditory input with a memory trace of the previous stimuli. MMN is composed of several subcomponents, which according to previous studies are all generated in different cortical sites. Even though hippocampus and amygdala are important structures for learning and memory, MMN has not been recorded from these structures in humans. **METHODS:** We studied mismatch negativity in four adult patients undergoing preoperative depth electrode recordings aiming at epilepsy surgery. The deepest contacts of stereotactically inserted electrodes were aimed at the amygdalo-hippocampal complex. A total of 6 hippocampi and 5 amygdala were recorded. The waveforms from the deepest contacts were used to analyze the differences between the responses to deviant and standard tones in the MMN latency range of 120-250 ms. **RESULTS AND CONCLUSIONS:** Significant differences between the responses to standard and deviant tones (i.e. MMN) in at least one temporomesial derivation was observed in three of our four patients. In the MMN latency range we found differences in 4/6 hippocampal structures and in 3/5 amygdala structures. Our study implicates that mismatch detection also activates temporomesial structures in addition to previously described several cortical areas.

13.

MANGANESE ENHANCED MRI (MEMRI) FOR DETECTION OF EPILEPTOGENESIS-RELATED MOSSY FIBRE PLASTICITY IN RAT

J Nairismägi, A Pitkänen, S Narkilahti, J Huttunen, RA Kauppinen, OHJ Gröhn. Department of Biomedical NMR, Epilepsy Research Laboratory, and Department of Cognitive Neurobiology, A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland; School of Sport & Exercise Sciences, University of Birmingham, UK.

RATIONALE: Mn^{2+} behaves analogously to Ca^{2+} in many biological systems and it can be detected by MRI due to its paramagnetic properties. The present study was designed to investigate anatomical and functional changes of the mossy fiber pathway, in vivo, after kainic acid (KA) induced status epilepticus (SE) by using manganese enhanced MRI (MEMRI). **METHODS:** Epileptogenesis was induced by KA injection (3mmol/ml/kg, ip). Two weeks later, epileptic (n=14) and control rats (n=6) received 40nL injection of 1M $MnCl_2$ into entorhinal cortex to label the perforant pathway that conveys information to the granule cells of dentate gyrus as well as to pyramidal cells of the CA3-CA1 of the hippocampus. Animals underwent 3D T1-wt MRI, at 4.7 T, 3 and 5 days after Mn-injection. Mossy fiber sprouting was assessed from Timm stained histological slices. **RESULTS:** Enhanced MEMRI signal was detected in CA3 and dentate gyrus of hippocampus allowing in vivo visualization of the 3D-structure of mossy fiber pathway. Epileptic rats demonstrated increased Mn^{2+}-contrast and significant correlation between Mn^{2+}-enhanced MRI signal and histologically determined mossy fiber sprouting. **CONCLUSIONS:** Present data show that MEMRI is able to detect cellular level changes in mossy fibers after KA injection induced SE in vivo. These alterations are attributed to either increased activity or axonal sprouting and are thus associated either functional or structural plasticity during epileptogenesis in hippocampus. As mossy fiber sprouting can be detected before occurrence of spontaneous seizures MEMRI provides a potential surrogate marker for developing epilepsy.

14.

EFFECTS OF ANTIEPILEPTIC DRUG IN A MODEL OF SPONTANEOUS SEIZURES IN RATS

J Nissinen, A Pitkänen. Department of Neurobiology, A.I.Virtanen Institute, University of Kuopio, Kuopio, Finland.

RATIONALE: Pre-clinical efficacy of antiepileptic drugs (AEDs) is assessed in experimental models, where seizures are evoked electrically or chemically. Ideal model of human temporal lobe epilepsy (TLE), should present spontaneous seizures, with electrographic and behavioral characteristics resembling human TLE. Here, we tested the effect of antiepileptic drugs in an experimental model of TLE, in which status epilepticus (SE) is followed by a latency period, and spontaneous seizures. **METHODS:** SE was induced by electrical stimulation of amygdala. Three months after SE, 1 week video-EEG monitoring was performed to detect spontaneous seizures, and to establish baseline seizure frequency and duration. Thereafter, carbamazepine (CBZ, 120 mg/kg/d), valproic acid (VPA, 600 mg/kg/d), ethosuximide (ESM, 400 mg/kg/d), lamotrigine (LTG, 20 mg/kg/d) or vigabatrin (VGB 75 mg/kg/d., 250 mg/kg/d) were administered for 9-11 days. Antiepileptic effect was monitored electrographically. **RESULTS:** In all animals, LTG, VPA and VGB250 reduced mean seizure frequency by 84% ($p<0.05$), 77% ($p<0.05$) and 60%, respectively. No such effect was found in CBZ or ETX treated rats. Over 50% reduction in seizure frequency was found in 100% of VPA, 88% of LTG, 83% of VGB250 treated animals. A significant decrease in seizure duration was found in VPA (from 46 to 18 sec, $p<0.05$) and ETX treated rats (from 57 to 41 sec, $p<0.05$). **CONCLUSIONS:** In epileptic rats, temporal lobe seizures are controlled by the same AEDs as in patients with TLE. This model offers a tool to predict the clinical efficacy of compounds in chronic study designs similar to clinical trials in humans.

15.

THE EFFECTIVENESS AND EFFICIENCY OF EPILEPSY SURGERY

P Putkonen, L Jutila, M Granström, E Gaily, R Kälviäinen. Laboratory of Biomedical Engineering, Helsinki University of Technology, Helsinki, Finland; Department of Health Policy and Management, University of Kuopio, Kuopio, Finland; Department of Neurology, Kuopio University Hospital (KUH), Kuopio, Finland; Hospital for Children and Adolescents, Helsinki University Hospital (HUCH), Helsinki, Finland.

RATIONALE: Approximately 20 % of all epilepsy patients are drug resistant and may benefit from surgical treatment. The direct treatment cost change and the change of quality of life are measured both retrospectively and prospectively for Finnish patients with epilepsy who are evaluated for surgical treatment. **METHODS:** The retrospective research group I includes 141 adult TLE-epilepsy patients from KUH and between 1991 and 2003 operated 133 children, adolescents and adults from HUCH operated during the 1990`s. Patients have been enrolled to the prospective group II from April 2004; this group includes all patients referred for surgical evaluation. Until June 2, 2005, 47 prospective patients have been enrolled. The direct treatment cost counting includes all hospital treatments related to epilepsy in primary and special health care (outpatient visits and hospital admissions), AED-treatment and other costs such as the use of medical technology. The count- period covers at least two years before and two years after surgery. The change of quality of life is measured three times with 15D and with disease specific QOLIE-31; before, 6 months after and one years after epilepsy surgery in patient group II and immediately in group I. Markov modeling is used to count the probabilities for change in costs and quality of life for longer time period by patient types. **RESULTS AND CONCLUSIONS:** Preliminary estimation of cost changes in the retrospective research group suggests a very significant decrease in post-surgical treatment costs, especially in outpatient visits of both children and adults. Warning: the final calculation will include also HILMO (the Finnish register for treatment announcements) results.

16.

FERTILITY IN WOMEN WITH ACTIVE EPILEPSY

K Viinikainen, S Heinonen, R Kälviäinen. Department of Neurology and Department of Obstetrics and Gynaecology, Kuopio University Hospital, Kuopio, Finland.

RATIONALE: Studies suggest that fertility among women with epilepsy is decreased. Purpose of this study was to assess fertility in women with active epilepsy (WWAE) with emphasis on effects related to valproate (VPA) treatment. **METHODS:** We identified from the prospective, population based pregnancy registry of Kuopio University Hospital (pop. 250000) all women who had given birth between 1989 and 2000 and had active epilepsy (N=79). Altogether 20 women were on VPA monotherapy during pregnancy. We compared fertility related factors of these women with the healthy pregnant population (n=16599) during the same time period. **RESULTS:** Altogether 4.7 per 1000 pregnancies involved WWAE. The average number of children was equal in WWAE compared to controls (2.1±1.1 vs. 2.2±1.2). The time needed to conceive did not differ between all WWAE (5.0±6.8 months), women using VPA (6.4±6.2) and controls (5.4±9.4). Women using VPA had higher body mass index than controls (24.9±5.3 vs. 22.8±4.0, $p=0.09$) but did not have more menstrual disturbances than controls. None of the women using VPA had needed infertility treatments. Delivery was induced in 55% of women using VPA and in 17% of controls, $p<0.0001$. **CONCLUSIONS:** The number of children is equal in WWAE and controls. Valproate does not seem to increase difficulties in becoming pregnant in WWAE. According to the epidemiological data from our area, the prevalence of epilepsy in fertile aged women is 0.58%. In our population 4.7 out of 1000 (0.47%) pregnancies involve active epilepsy, which means that if we only exclude patients with severe comorbidity, fertility in WWAE is not decreased.

17.

HISTAMINERGIC INNERVATION PROTECTS HIPPOCAMPAL NEURONS FROM KAINIC ACID-INDUCED DAMAGE IN AN ORGANOTYPIC CO-CULTURE SYSTEM

T Kukko-Lukjanov, SL Soini, KA Michelsen, P Panula, IE Holopainen. Departments of Pharmacology and Clinical Pharmacology, University of Turku, Turku, Finland; Department of Biology, Åbo Akademi University, Turku, Finland; Neuroscience Center, Institute of Biomedicine/ Anatomy, University of Helsinki, Helsinki, Finland.

RATIONALE: Histamine inhibits epileptic seizures through histamine 1 (H_1) and 3 (H_3) receptors. However, it is not known whether central histaminergic neurons have any neuroprotective effect on seizure-induced cell damage. **METHODS:** We have used an organotypic co-culture system to examine whether histaminergic neurons can ameliorate kainic acid (KA)-induced neuronal death, which was verified with Fluoro-Jade B staining. **RESULTS:** KA-induced (5 μM, 12 h) CA3 neuronal damage was significantly decreased in co-cultures composed of hippocampus with the posterior hypothalamic slice containing histaminergic neurons (HI+HY, POST), when compared to the hippocampus cultured alone (HI). α-fluoromethylhistidine, an inhibitor of histamine synthesis, abolished the neuroprotective effect of histamine in KA-treated HI+HY, POST. In the CA1 subregion, spontaneous electrical activity after the 6-h KA treatment exhibited significantly less burst activity in HI+HY, POST than in HI. **CONCLUSION:** Our results indicate that histaminergic innervation protects the immature hippocampus from KA-induced neuronal damage, regulation of neuronal survival being at least partly mediated through H_1 and H_3 receptors.Acknowledgements: Supported by the Sigrid Juselius Foundation, the Special State Grant for Clinical Research, the Foundation of University of Turku, the Finnish Cultural Foundation, the Finnish Society of Sciences and Letters, Research and the Science Foundation of Farmos.