KUOPIO EPILEPSY SYMPOSIUM
March 15-16, 2002
Kuopio Music Center
Kuopio, Finland

PROCEEDINGS

Saturday March 16th 2002

Abstracts (pdf file)
Poster abstacts (pdf file)

On behalf of the Finnish Epilepsy Society and the Finnish Epilepsy Association, we cordially welcome you to participate in "Kuopio Epilepsy Symposium 2002" in Kuopio, March 15-16 2002.

The meeting will be third in a series of epilepsy meetings that are organized jointly by the A.I.Virtanen Institute for Molecular Sciences and the Department

Friday, March 15th 2002

Opening of the Symposium

Rector of the University of Kuopio *Matti Uusitupa*
Program Chair Prof. *Asla Pitkänen*

Key note address: **Prevalence and predictors of refractory seizures: can early detection improve treatment options?**
Prof. *Martin Brodie* (Scotland) Key slides (pdf file)

Epileptology after human genome project
Chair: Prof. Asla Pitkänen (Finland)

Molecular basis of epileptogenesis in experimental models
Prof. *Asla Pitkänen* (Finland) Key slides (pdf file)

Molecular profiling of human temporal lobe epilepsy
Prof. *Albert Becker* (Germany)

Channelopathies: How does the understanding of molecular change alter the diagnosis, treatment practice or does it?
Prof. *Giuliano Avanzini* (Italy)

Pharmacogenomics: can we predict and prevent the side effects of AEDs with profiling
Dr. *Michael Johnson* (UK) Key slides (pdf file)

Neurobiological basis of drug-refractory partial epilepsy
Chair: Prof. Matti Sillanpää (Finland)

Natural course of untreated partial epilepsy - lessons learnt from developing countries Prof. *J.W.A.S Sander* (UK) Key slides (pdf file)

of Neuroscience and Neurology, University of Kuopio.

The objective of the meeting is to present up-to-date knowledge of selected topics related to epilepsy. Both experimental and clinical data will be presented.

We hope to bring together people working on 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.

Asla Pitkänen
Professor
Chairperson of
the Organizing Committee

Reetta Kälviäinen
Docent
Co-chairperson of
the Organizing Committee

Spectrum of brain pathologic lesions associated with drug-refractory temporal lobe epilepsy
Prof. *Gary Mathern* (USA) Key slides (pdf file)

Molecular basis of drug-refractoriness
Prof. *H. Potschka* (Germany) Key slides pdf file)

Association of imaging findings with clinical outcome
Dr. *Tuuli Salmenperä* (Finland) Key slides (pdf file)

Treatment of drug-refractory partial epilepsy
Prof. *Jacqueline French* (USA) Key slides (pdf file)

History and surgical outcome of drug-refractory patients with TLE
Dr. *Leena Jutila* (Finland) Key slides (pdf file)

Interactive epileptology through challencing case studies

Chair: Dr. Reetta Kälviäinen

Matching the treatment with epilepsy syndrome and seizure type
Dr. *Reetta Kälviäinen* (Finland) Key slides (pdf file)

Case studies
Dr. Leena Jutila, Dr. Aarne Ylinen, Professor Juhani Partanen
- Commented by special guests (Dr. Marja-Liisa Granström, Professor Tapani Keränen, Professor Martin Brodie, Professor J.W.A.S. Sander and the audience)

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Key note address: Do febrile seizures cause temporal lobe epilepsy ?

Prof. *Tallie Z. Baram* (USA) Key slides (pdf file)

Evidence based treatment of newly diagnosed epilepsy at special ages
Chair: *Dr. Aarne Ylinen* (Finland)

In infancy Dr. Eija Gaily (Finland) Key slides (pdf file)
In childhood Dr. *Kai Eriksson* (Finland) Key slides (pdf file)
In puberty Dr. *Leena Vainionpää* (Finland) Key slides (pdf file)
In elderly Dr. *Tapani Keränen* (Finland) Key slides (pdf file)

Update of epilepsy research in Finland: selected abstracts
Chair: Prof. Hilkka Soininen

Click here for abstracts of oral presentations (pdf file)

Oral presentation I
THE LEVELS OF IL-6 AND ITS SOLUBLE RECEPTORS IN CEREBROSPINAL FLUID AND SERUM AFTER SEIZURES
KA Lehtimäki, J Palmio, J Ollikainen, J Honkaniemi, H Huhtala, T Keränen, J Peltola.

Oral presentation II

UPREGULATION OF CYSTATIN C IN THE RAT HIPPOCAMPUS DURING EPILEPTOGENESIS
TJ Pirttilä, K Lukasiuk, A Pitkänen. A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, P.O.B. 1627, 70211 Kuopio, Finland.

Oral presentation III

SEVEN FINNISH FAMILIES WITH GENETIC EPILEPSY
A Sirén, H Rantala, A Nuutila, O Saarenpää-Heikkilä, K Eriksson, M Koivikko, M Pandolfo. Department of Neurology, Erasmus Hospital, Brussels, Belgium; Department of Pediatrics, University Hospital of Tampere, Finland; Department of Pediatrics, University Hospital of Oulu, Finland; Department of Pediatrics, Central Hospital of Etelä-Pohjanmaa, Finland.

of Neuroscience and Neurology, University of Kuopio.

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Oral presentation IV

REPRODUCTIVE ENDOCRINE DISORDERS IN YOUNG WOMEN WITH EPILEPSY
KH Ruotsalainen, LK Vainionpää, JS Tapanainen, I Järvelä, JI Isojärvi. Departments of Pediatrics, Neurology and Gynecology, University of Oulu, Oulu, Finland.

Oral presentation V

MULTIPARAMETRIC MRI ANALYSIS OF DRUG-RESISTANT TLE
PM Goncalves Pereira, M Forjaz Secca, A Leal, C Ribeiro, P Evangelista, P Rosado. Neuroradiology Dept, H. Egas Moniz, Lisbon, Portugal; Physics Dept. New University of Lisbon, Portugal; Neurology Dept, H.Fernado Fonseca, Lisbon, Portugal; Caselas Magnetic Resonance Center, Lisbon, Portugal; Neurology Dept, H.Egas Moniz, Lisbon, Portugal.

Plenary lecture

MEG signs of normal and abnormal brain function in neurological patients
Dr. *Jyrki Mäkelä* (Finland) Key slides (pdf file)

Vaajasalo Foundation Young Investigator Award

Vagus nerve stimulation in the treatment of epilepsy

Chair: Dr. Jouko Isojärvi (Finland)

Critical overview
Prof. *Elinor Ben-Menachem* (Sweden) Key slides (pdf file)

Finnish experience
Dr. *Jouko Isojärvi* (Finland) Key slides (pdf file)

Panel discussion:

Place of vagus nerve stimulation in the treatment of epilepsy
(Invited Panel: Dr. *Mervi Kotila*, Dr. *Elina Liukkonen*, Prof. *Matti Vapalahti* and the audience)

Closing of the Kuopio Epilepsy 2000 Symposium
Prof. A*sla Pitkänen*

ORAL PRESENTATIONS I-V Saturday 16.03.2002 10.35-11.50

I

THE LEVELS OF IL-6 AND ITS SOLUBLE RECEPTORS IN CEREBROSPINAL FLUID AND SERUM AFTER SEIZURES

KA Lehtimäki, J Palmio, J Ollikainen, J Honkaniemi, H Huhtala, T Keränen, J Peltola.

RATIONALE: Using kainic acid animal model, we have shown that IL-6 is induced in the rat brain concomitantly with its receptors IL-6R and Gp130 after status epilepticus. **METHODS:** Here we determined the levels of IL-6 and the soluble forms of IL-6R and Gp130 (sIL-6R and sGp130) in cerebrospinal fluid (CSF) and serum samples from healthy controls and from patients with a single tonic-clonic seizure, recurrent tonic-clonic seizures and prolonged partial seizures. **RESULTS:** After seizures, IL-6 levels were increased in CSF or serum samples in all patient groups when compared to controls, with simultanous decrease in CSF or serum sIL-6R levels. These changes were more prominent after recurrent tonic-clonic seizures when compared to a single tonic-clonic seizure. In addition, more robust changes were evident after recurrent tonic-clonic seizures than prolonged partial seizures. CSF levels of sGp130 were unaffected after seizures, but after single tonic-clonic seizure, serum sGp130 levels were increased. **CONCLUSIONS:** In general, these results indicate that CSF and serum levels of IL-6 and its soluble receptors are affected by seizures. Increase in IL-6 levels is associated to decrease in CSF and serum sIL-6R levels. This increase in IL-6 levels is also dependent on recurrence and generalization of seizures, indicating that IL-6 production is affected by duration and distribution of seizure activity.

II

UPREGULATION OF CYSTATIN C IN THE RAT HIPPOCAMPUS DURING EPILEPTOGENESIS

TJ Pirttilä, K Lukasiuk, A Pitkänen. A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, P.O.B. 1627, 70211 Kuopio, Finland.

RATIONALE: A brain trauma like status epilepticus often causes epileptogenesis that is followed by appearance of seizures. Our previous cDNA array findings showed several SE induced changes in gene expression. One of the upregulated genes was cystatin C. Here we studied the distribution and cellular localization of cystatin C protein in normal and epileptogenic rats. **METHODS:** Status epilepticus induced epileptogenesis was triggered by electrically stimulating the left amygdala for 20 to 30 min. Rats were perfused and processed for histology at 24h, 4d, 1wk and 2wk after stimulation. Cresyl violet staining and immunohistochemistry with cystatin C-antibody were performed. Cellular localization of cystatin C was investigated from double-immunostained sections. **RESULTS:** Cystatin C immunoreactivity was already present in normal hippocampus. However, in rats undergoing epileptogenesis, there was a marked increase in cystatin C immunoreactivity, which was predominantly localized in activated microglia. Also, the increase of cystatin C-positive microglial cells was more prominent in rats with severe pyramidal cell damage in the hippocampus. The increased cystatin C levels were seen already 24 h after SSSE, but the increase was more substantial 4 d after SSSE and it persisted for at least 2 wk. **CONCLUSIONS:** Cystatin C upregulation in microglial cells during the epileptogenesis seems to be associated with the severity of the damage. Cystatin C may be related to recovery from SE induced damage.

III

SEVEN FINNISH FAMILIES WITH GENETIC EPILEPSY

A Sirén, H Rantala, A Nuutila, O Saarenpää-Heikkilä, K Eriksson, M Koivikko, M Pandolfo. Department of Neurology, Erasmus Hospital, Brussels, Belgium; Department of Pediatrics, University Hospital of Tampere, Finland; Department of Pediatrics, University Hospital of Oulu, Finland; Department of Pediatrics, Central Hospital of Etelä-Pohjanmaa, Finland.

RATIONALE: To identify families with genetic epilepsy, especially with febrile seizures (FS). Background: We had earlier identified a new epilepsy locus on chromosome 5 in two Finnish families with generalized epilepsy and FS. As a consequence of the population history of Finland it is possible that new families with identical phenotype could be linked to chromosome 5 locus as well. **METHODS:** Pediatric neurologists in two university hospitals and one central hospital were asked to recognize epilepsy patients with one or more relatives with febrile seizure or epilepsy. The index patient and his/her parents were informed of the study. If they agreed they were first contacted by telephone and later a field trip was performed to interview and collect the blood samples. All information including medical files was reviewed to classify the epilepsy syndromes. **RESULTS:** Seven families were identified. All together 141 individuals were interviewed and blood samples were collected. The families varied in size from a four-member nuclear family to two big three-generation families. Altogether there were 52 affected individuals (mean 7.5, range 2-18 in each family). Following seizure types or epilepsy syndromes were observed: 27 individuals had FS, 18 had primary generalized epilepsy, eight had partial epilepsy, three had neonatal convulsions, two had status epilepticus, one had primary generalized epilepsy and also partial epilepsy. Mode of inheritance was dominant with reduced penetrance in six families. In two families a bilinear inheritance with probably digenic influence is possible. One of the smallest family consisted of two affected daughters and unaffected parents. No other individuals in this family were known to be affected. **CONCLUSIONS:** FS is a prominent seizure type. In big families variable phenotypes were observed. Supported by: The Arvo and Lea Ylppö Foundation, Finland (AS), The Medical Research Fund of Tampere University Hospital, Finland (AS), Fonds National Recherche Scientifique (FNRS), Belgium, (AS).

IV

REPRODUCTIVE ENDOCRINE DISORDERS IN YOUNG WOMEN WITH EPILEPSY

KH Ruotsalainen, LK Vainionpää, JS Tapanainen, I Järvelä, JI Isojärvi. Departments of Pediatrics, Neurology and Gynecology, University of Oulu, Oulu, Finland.

RATIONALE: The purpose of this study was to evaluate whether epilepsy during childhood or adolescence is related to later reproductive endocrine disorders. **METHODS:** A previously identified cohort of 65 girls and young women with epilepsy (initially aged 8-18.5 years, now 12.5-25.8 years) and 41 healthy control girls of similar age and pubertal stage participated in this study. 34 of the girls with epilepsy were initially taking valproate (VPA), 15 carbamazepine (CBZ) and 16 oxcarbazepine (OXC) as monotherapy. Body mass index (BMI) was calculated, menstrual history was obtained and ovarian ultrasonography was performed in each subject in this study. **RESULTS:** 57 % of the patients were off medication, while 43 % of the girls were still under medication. The mean increase in BMI was higher in patients (3.3 kg/m^2, from 19.4 to 22.7) than in control subjects (2.0 kg/m^2, from 18.5 to 20.5; p=0.016). This was especially evident in girls initially taking VPA (3.7 kg/m^2, from 20.1 to 23.9; p=0.009). Polycystic ovaries (PCO) were found in 34 % of patients and 25 % of controls (p=0.36). However, PCO were more common among patients, who were still on medication (58 %) than among controls (p=0.009). The frequency of menstrual disorders was 44 % in the patients and 39 % in the controls. PCO with menstrual disorders were found in 18 % of patients and 14 % of control subjects. **CONCLUSIONS:** Epilepsy during childhood or adolescence may be associated with increased prevalence of weight gain and reproductive endocrine disorders later in life in young women with epilepsy, especially if they remain on medication until adulthood.

V

MULTIPARAMETRIC MRI ANALYSIS OF DRUG-RESISTANT TLE

PM Goncalves Pereira, M Forjaz Secca, A Leal, C Ribeiro, P Evangelista, P Rosado. Neuroradiology Dept, H. Egas Moniz, Lisbon, Portugal; Physics Dept. New University of Lisbon, Portugal; Neurology Dept, H.Fernado Fonseca, Lisbon, Portugal; Caselas Magnetic Resonance Center, Lisbon, Portugal; Neurology Dept, H.Egas Moniz, Lisbon, Portugal.

RATIONALE: Quantitative MRI is a valuable non-invasive tool in the diagnosis of sclerotic lesions located in the medial portion of the temporal lobe in patients with drug-resistant TLE. The most commonly used techniques (volumetry, T2 relaxometry and spectroscopy) have been applied successfully in the evaluation of candidates to amygdalo-hippocampectomy procedures. In the clinical setting, these techniques are used to complement the conventional image examinations, since a full MR advanced protocol is time-consuming and can challenge the collaboration of the patients. At our center, we are performing, in all the subjects with cryptogenic TLE under pre-surgical evaluation, a full compreensive multimodal MRI evaluation in order to analyse the potential added value of this combination of sequences to detect damage in the mesio-temporal structures. **METHODS:** 35 patients with chronic TLE and 31 age-matched controls were enrolled. All underwent MR investigations including a whole brain coronal T1-weighted 3D-dataset and T2 relaxometry (T2-r), and axial ^{1}H multi-voxel spectroscopy (mv-S). Lateralization of the seizure focus was obtained by means of long-term video-EEG recordings. Values for the hippocampal and amygdala volumetry and T2-r, and hippocampal mv-S (NAA/(Cho+Cre) were correlated with the EEG data and the neuropsychological evaluations. All examinations were blind studies. Pathological values were considered if they differed more than 3SD (2.5 in mv-S). **RESULTS:** 17 patients had a right seizure focus and another 18 lateralized on the left. 74% (26/35) of the patients had ipsilateral pathological values and were classified as MTS, 42% of which (11/26) had lesions in the hippocampus and the amygdala, 23% (6/35) had only hippocampal lesions with a significant mv-S and 34% (9/35) had hippocampal lesions without mv-S. Of the remaining 9/35 patients, 44% (4/9) failed to show any pathology, 33% (3/9) had bilateral atrophy/asymmetry/T2-r with ipsilateral mv-S and 22% (2/9) showed ipsilateral mv-S. Analysis of the neuropsychological data is ongoing. **CONCLUSIONS:** Multiparametric MRI analysis yield consistent results in the detection of MTS. Pathological values showed a better correlation between the volumetry and T2-r analysis. These results suggest that mv-S has a different substrate of disease than structural volumetry/T2-r. Funding supported by: Fundação para a Ciência e a Tecnologia BD 18498/98, Subprograma Ciência e Tecnologia do 2° Quadro Comunitário de Apoio" and "Fundação Grünenthal".

POSTER PRESENTATIONS **Authors present on Saturday 16.03.2002 10.05-10.35**

1.

TRANSGENIC RATS OVEREXPRESSING CYSTATIN B, THE GENE MUTATED IN PROGRESSIVE MYOCLONUS EPILEPSY (EPM1)

J Arbatova, L Alhonen, A Kalda, A Zharkovsky, C Ekdahl, Z Kokaia, J Jolkkonen, M Reeben. Department of Neuroscience and Neurolology, A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, and Kuopio University Hospital, Finland; Department of Pharmacology, University of Tartu, Estonia; Wallenberg Neuroscience Center, Lund University Hospital, Sweden.

RATIONALE: Defects in a cysteine proteinase inhibitor of cathepsins, cystatin B (CSTB) gene are responsible for progressive myoclonus epilepsy of Unverricht-Lundborg type (EPM1) - an autosomal recessive neurodegenerative disease. The mechanisms how lack of CSTB causes the disease phenotype are still poorly understood. CSTB-deficient mice, the mouse model of EPM1 (Pennacchio et. al., Nature Genetics, 20, 251-8, 1998) provided evidence that CSTB could have a role in preventing neuronal apoptosis. **METHODS AND RESULTS:** We have produced transgenic rats that overexpress human CSTB in the nervous system under the control of the rat light neurofilament gene regulatory regions. CSTB was over-expressed primarily in the hippocampus, e. g. the dentate hilus, CA1 and CA3. Some cells were also scattered in motor and sensory cortical regions, cerebellum, and some brain stem nuclei. We demonstrated that cerebellar granule cells from transgenic rats were slightly more sensitive to the neurotoxic effects of glutamate and colchicine as compared with wild-type littermates. When these rats were exposed to transient focal cerebral ischemia by occluding the middle cerebral artery for 120 min, transgenic rats showed a trend towards a more severe cortical damage measured on day 22 after ischemia and a more severe impairment in sensorimotor functions as assessed by the limb-placing test. **CONCLUSIONS:** These results demonstrate that overexpression of CSTB has no significant neuroprotective role in the present transgenic rat model. An explanation for these results could be that in this model overexpression of CSTB is limited to a small number of neurons. Supported by: Academy of Finland and European Commission QLG3-CT-2000-01405.

2.

EPILEPSY IN 100 SEVERELY MENTALLY RETARDED FINNS

M Arvio, V Oksanen, L Valanne, M Peippo. Pääjärvi Centre, Lammi, Finland; Kanta-Häme Central Hospital, Hämeenlinna, Finland; Department of Neurology, Helsinki University Hospital, Helsinki, Finland; The Family Federation, Helsinki, Finland.

RATIONALE: To define epilepsies and epileptic syndromes according to the ILAE 1989 classification and find the etiology of disability among mentally retarded people. **METHODS:** One hundred consecutive mentally retarded (IQ<50) patients aged 0.5 to 65 years from the Pääjärvi Center were evaluated by a medical team. Each patient underwent a clinical examination, a video EEG, and then either brain MRI (93 patients) or CT (7 patients). Etiological studies were performed as considered necessary by individual evaluation in each case. **RESULTS:** The disability was related to CNS malformation in 29, to acquired disorder in 29, to genetic factors in 26, and was idiopathic in 16 (syndromic in 10 and nonsyndromic in 6) patients. Ninety-two had symptomatic and three cryptogenic intractable epilepsy or epileptic syndrome. The seizures of five patients were non-epileptic. Forty-three had localization-related, and 41 generalized epilepsy or epileptic syndrome. Eight had epilepsy with generalized and focal features, and three a special syndrome. **CONCLUSIONS:** The background of intractable epilepsy in these severely mentally retarded patients involved either a disease affecting the brain or a congenital structural brain anomaly. In most cases the seizures had appeared early in childhood (62%) except in patients with a slowly progressive syndrome, in whom seizure onset usually occurred in adulthood. The epileptic syndromes with a poor outcome, such as Lennox-Gastaut and the syndrome with continuous spike-waves during sleep (CSWSS) were common, representing 28% and 8.5% of the study group.

3.

COGNITIVE PERFORMANCE OF NEWLY DIAGNOSED PATIENTS WITH EPILEPSY AFTER 15-YEARS FOLLOW-UP

O Kaarre , R Varis, M Äikiä , R Kälviäinen. Department of Neurology, Kuopio University Hospital and University of Kuopio, Kuopio, Finland.

RATIONALE: Aim of the study was to prospectively follow up the cognitive performance of newly diagnosed patients with epilepsy with test interval long enough to provide an estimation of the effects of seizures over the lifetime of an adult. **METHODS:** Altogether 25 patients with cryptogenic epilepsy participated. The first comprehensive neuropsychological testing was performed at the time diagnosis of epilepsy before the start of drug treatment and again after 15 years. **RESULTS:** After the follow-up 16 of the patients (mean age at start 31.3 ± 11.9) were still using antiepileptic drugs (AEDs) and 9 of the patients (mean age at start 30.9 ± 12.0) had been withdrawn from their treatment mean 8.9 ± 0.6 years earlier. In the drug treated group 3 patients were on polytherapy and 13 on monotherapy. During the 15 years follow-up 3 patients of the drug treated group had been seizure-free, 8 had had satisfactory seizure-control and 5 were refractory. At the time of diagnosis cognitive performance was similar in both groups. After 15 years in memory tasks the mean cognitive performance was mostly the same in both study groups, as only the percent retention of the words in the list learning task was better at 15 years in drug withdrawal group than in drug treated group ($p=0.02$). In tasks requiring psychomotor and mental speed mild impairment was found in Trail making B ($p=0.03$) and in Symbol digit modalities test ($p=0.00$) in the drug treated group. In symbol digit task the worsening was greater in the drug group than in the withdrawal group ($p=0.004$). In letter fluency task change was different between the groups ($p=0.001$), the mean performance in non-drug group improved, but remained the same in the drug treated group. **CONCLUSIONS:** The cognitive performance of newly diagnosed patients show only mild changes across longer follow-up period and therefore adult-onset epilepsy seems not to be always associated with losses in mental abilities. However, poorer seizure outcome and use of AED treatment seems to have some adverse effects on the long-term cognitive outcome of the patients.

4.

FREEZING TO TONE IS PRESERVED IN EXPERIMENTAL TEMPORAL LOBE EPILEPSY

S Kemppainen, J Nissinen, A Pitkänen. Epilepsy Research Laboratory, Department of Neurobiology, A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, P.O.Box 1627, FIN-70211, Kuopio, Finland.

RATIONALE: Learning and expression of fear conditioning is known to involve the amygdala that is damaged in temporal lobe epilepsy (TLE). In the present study we investigated whether rats with spontaneous recurrent seizures had deficits in fear conditioning in two different *status epilepticus*-models of TLE. **METHODS:** *Status epilepticus* was induced either by the electrical stimulation of the amygdala (n=13, 15 unstimulated controls) or by the injection of kainic acid (i.p., n=20, 10 saline injected controls). Fear conditioning was trained and tested shortly after the first spontaneous seizures in stimulated rats and two months after induction of *status epilepticus* in kainic acid injected rats. Rats were trained either 4 or 6 times by pairing a tone (20 s, 10 kHz, 75 dB) with an electric foot shock (0.5 s, 0.5 mA) delivered at the end of the tone. Freezing of rats was measured throughout the training and testing periods. The neuronal damage was assessed in the lateral, basal, and central nuclei of the amygdala in kainic acid treated rats. **RESULTS:** Our data show that in both models of TLE rats freeze less to the first foot shock than the control rats. Also, freezing to context measured at the beginning of the second training day was decreased in TLE rats. Freezing to test tone was, however, equal between the TLE and control groups. Interestingly, after the cessation of test tone the control rats continued to freeze whereas TLE rats began to move within few seconds. Cell damage was the most severe in the caudal half of the medial division of the lateral nucleus and in the parvicellular division of the basal nucleus. Damage to the central nucleus was mild. **CONCLUSIONS:** Our present study suggests that rats with TLE are able to learn and express fear conditioning to tone. Data also implies that freezing to contextual cues is impaired in TLE. Analysis of amygdaloid lesions shows that the most rostral parts of the lateral and basal nuclei of the amygdala are sufficient to associate and relay acoustic and somatic information to the central nucleus for fear conditioning in TLE rats.

5.

ANALYSIS OF CHANGES IN GENE EXPRESSION FOLLOWING THE AMYGDALA STIMULATION INDUCED STATUS EPILEPTICUS IN THE RAT MODEL OF TEMPORAL LOBE EPILEPSY USING CDNA ARRAYS

K Lukasiuk, A Pitkänen. A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland.

RATIONALE: Epilepsy frequently develops as a result of brain insult and the epileptic process can be divided into tree phases: initial insult, latency period (epileptogenesis) and epilepsy. In the present study we aimed at identification of genes that change their expression following initial insult, and therefore can be involved in the epileptogenesis. **METHODS:** We used an amygdala stimulation model of the temporal lobe epilepsy, in which status epilepticus (SE) is followed by a latency period preceding the appearance of the first spontaneous seizures. Rats were sacrificed 1d, 4d, or 14d after induction of SE. RNA isolated from the hippocampi or temporal lobe was used for hybridization with cDNA arrays. **RESULTS:** Altogether changes in the level of expression were observed for 61. One day after SE, alteration in expression was observed for 38 genes, at 4d for 14 genes, at 14d in animals without seizures for 17 genes and at 14 d in animals with seizures for 12 genes. **CONCLUSIONS:** This report provides evidence for dynamic changes in gene expression during the process of epileptogenesis. Further characterization of expression of genes involved in process of epileptogenesis may lead to development of rational antiepileptogenic therapy in the future.

6.

EFFECT OF ALTERED BDNF SIGNALLING IN EPILEPTOGENESIS

S Lähteinen, A Pitkänen, E Castrén. A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, P.O.B. 1627, FIN-70211 Kuopio, Finland.

RATIONALE: Brain-derived neurotrophic factor (BDNF) is involved in neuronal plasticity and connectivity and is regulated activity-dependently. However, results about BDNF in epileptogenesis are controversial, demonstrating as well protective as noxious effects. **METHODS:** We studied the effects of reduced and increased BDNF signalling to epileptogenesis. As models we used adult wild type mice and two transgenic mice lines, one overexpressing truncated trkB receptor (TK-; decreased signalling) and the other overexpressing full-length trkB receptor (TK+; increased signalling). Kainate (29-35 mg/kg) model of temporal lobe epilepsy was used and the development of spontaneous seizures was monitored up to 20 weeks with combined video-EEG system. Histological analyses were performed to assess cellular changes. **RESULTS:** Reduced epileptogenesis was observed in TK- mice with decreased BDNF signalling. Fewer transgenic mice developed epilepsy and interictal spiking in epileptic animals was less frequent compared to wild type mice. Furthermore, the frequency of spontaneous seizures tended to be lower and the seizures appeared to be shorter and milder. However, no changes were found in cellular level. TK+ mice had a reduced seizure threshold. However, no differences in epileptogenesis between genotypes were observed. Moreover, histology was identical in both genotypes. **CONCLUSIONS:** These results suggest that decrease in BDNF signalling inhibits epileptogenesis. Although increase in BDNF signalling does not affect to the development of epilepsy, neurotrophin signalling might be a possible target of drug development in the future.

7.

THE AMYGDALO-ENTORHINAL PATHWAY IS INVOLVED IN FEAR CONDITIONING

K Majak, A Pitkänen. Epilepsy Research Laboratory, A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland.

RATIONALE: The aim of the present study was to investigate whether the amygdalo-entorhinal pathway is activated in the fear conditioning procedure. **METHODS:** We iontophoresed retrograde tracer, Fluoro-Gold (FG), to the entorhinal cortex of 9 rats. Rats were habituated to the fear-conditioning apparatus for 5 consecutive days. Thereafter, 5 rats were conditioned by a single tone-footshock pairing (trained group) and 4 received another habituation session (control group). One hour later the animals were scarified and the brains were processed for double immunohistochemistry for c-Fos and GAD67 (activation of interneurons) or c-Fos and FG (activation of projecting neurons). The labeled neurons were plotted and calculated in each division of the lateral and basal nuclei. **RESULTS:** The training increased number of c-Fos immunoreactive nuclei by 2.6-fold compare to controls ($p<0.05$) in the medial division of the lateral nucleus. The highest density of FG-positive neurons was found in the medial division of the lateral nucleus and 7.9% of the FG positive neurons were also c-Fos positive that was significantly more than in control group ($p<0.05$). In c-Fos/GAD67 preparations, only an occasional double-labeled neuron was found. **CONCLUSIONS**: Associative learning of novel stimuli is accompanied by the significant increase of c-Fos immunoreactivity in the projection neurons of the medial division of the lateral nucleus, some of which project to the entorhinal cortex.

8.

Withdrawn

9.

ABSENCE EPILEPSY IN THE WAG/RIJ RATS CORRELATES WITH CHANGES IN BRAIN MONOAMINERGIC SYSTEMS

IS Midzyanovskaya, L Tuomisto, GD Kuznetsova, E MacDonald. Department of Pharmacology and Toxicology, Kuopio University, Kuopio, Finland; IHNA & NPh of RAS, Moscow, Russia.

RATIONALE: the study was aimed to study possible involvement of the brain histamine-, 5-hydroxytryptamine- and catecholaminergic systems in pathogenesis of absence epilepsy and audiogenic convulsions in rats. **METHODS:** male rats of the WAG/Rij (N=10) and Wistar (N=10) strains were used in the study. 5 rats of each strain demonstrated susceptibility to audiogenic convulsions. Thus, 4 experimental groups were formed: rats with absence, audiogenic, mixed (absence + audiogenic) epilepsies, and non-epileptic rats. Stainless steel screws were implanted epidurally, under chloral hydrate narcosis and procaine anaesthesia. EEGs were registered 10 days post-surgery; percentage of time occupied by the spike-wave activity (SWI) was calculated for each animal. 10-14 days after recording sessions, animals were decapitated, brains removed and dissected on ice. Histamine was assayed, as described by Yamatodani (1985, 1991). Catecholamines were assayed as described by Mefford (1981). The Kruskall-Wallis U-test and Spearman method of rank correlation were used for statistical analyzis. $P<0.05$ was accepted as minimal for significance. **RESULTS:** SWI was found to correlate negatively with the tissue concentrations of: histamine (in the neocortex, hypothalamus, striatum), 5HIAA (in medulla, thalamus); positive correlations were obtained between SWI and noradrenaline (in striatum). Metabolic rates of dopamine (HVA/DA ratio) in frontal cortex, striatum, medulla, thalamus negatively correlated with SWI. No correlation was found for the scores of audiogenic seizures. **CONCLUSIONS:** The spike-wave activity in EEG is the main indicator of absence epilepsy. We conclude, that this kind of epilepsy may be influenced by the dopaminergic, histaminergic and serotoninergic systems.

10.
MORPHOLOGICAL CHANGES DURING EPILEPTOGENESIS AS DETECTED BY MULTIPARAMETRIC MRI

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RATIONALE: We have investigated anatomical distribution and progression of brain damage and histological abnormalities during epileptogenesis, induced by status epilepticus (STE), using a rat model of temporal lobe epilepsy. **METHODS**: Multiparametric and quantitative MRI (T_2, D_{av}, T_1) were sequentially acquired during six month follow-up period. Thickness of tissue and relaxation times in various brain structures (amygdala, piriform cortex, thalamus and hippocampus) and seizure frequency by video-EEG, were determined. Histology by Timm and Nissl stainings was assessed at 8 months. **RESULTS**: MRI relaxation times increased by 2 days after induction of STE in all areas analyzed. In the later time points, the values were close to control. MRI showed neuronal damage in hippocampi also later. All signs of damage were more extensive in the stimulation side. MRI of the hippocampi was not correlated with cell damage and mossy fiber sprouting. **CONCLUSIONS**: Reversibility of the MRI relaxation times in amygdala and piriform cortex shows that this structure can recover from the initial insult, yet atrophy develops over the time. Furthermore, hippocampi seem to become secondarily damaged. Our results indicate that MRI-positive events in the early epileptogenesis may not predict severity of becoming epilepsy.

11.
CASPASE 3 PROTEIN EXPRESSION AFTER STATUS EPILEPTICUS IN RAT BRAIN

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RATIONALE: Status epilepticus (SE) causes neurodegeneration, which is mostly necrotic. It is under dispute whether caspase-mediated programmed cell death is activated by SE and whether caspase inhibitors would be rational targets for development of neuroprotective treatments for SE. The aim of this study was to investigate the expression and activity of caspase 3 protein after SE. **METHODS:** SE was induced in adult male Wistar rats (n=6) with kainic acid (10mg/kg, i.p.). After a 2-d or 7-d survival, rats were sacrificed and the block containing the hippocampus or the thalamus, or the amygdala, piriform and entorhinal cortices were dissected from each hemisphere. Samples from one hemisphere were processed for Western blotting. Tissue from the other hemisphere was reserved for enzyme assay. **RESULTS:** In controls, constitutive expression of the 32-kDA procaspase 3 protein was detected in all brain regions analyzed. After SE, the expression of procaspase 3 was elevated by about 1.5-fold in all brain areas both at 2 d and 7 d after SE. The cleaved (presumably activated) 17-kDA fragment of caspase 3 was, however, detected only in samples that were collected from the hippocampus or the amygdala, piriform and entorhinal cortices 7 d after SE. **CONCLUSIONS:** These data suggest that caspase 3 mediated programmed cell death contributes to SE-induced neurodegeneration.

12.

DIAZEPAM TREATMENT HAS A DISEASE MODIFYING EFFECT ON THE DEVELOPMENT OF EPILEPSY AFTER STATUS EPILEPTICUS IN RAT

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RATIONALE: Status epilepticus (SE) is associated with an elevated risk of epilepsy and cognitive decline later in life. A question is: (1) does the treatment of SE have any antiepileptogenic effects and (2) if the epilepsy develops, is the disease as severe as without treatment. **METHODS:** Self-sustained status epilepticus (SSSE) was induced by stimulating the amygdala of adult Spraque-Dawley rats (n=73) electrically for 20-40 min. Thirty-seven of the animals were allowed to recover from SSSE spontaneously. In another group of rats (n=36), SSSE was stopped with diazepam (DZP, 20 mg/kg , i.p.) 2-3 hours after the induction of SE (an additional dose 5-10 mg/kg was given 6 hours later). SSSE and the development of spontaneous seizures were monitored with continuous video-EEG monitoring (24 h/day, at least for 7 days) 7-9 weeks after SSSE. **RESULTS:** In the DZP group, the number of animals that developed epilepsy was lower than in the untreated group (51% (19/37) *vs.* 83% (30/36), p=0.006, Pearson chi-square test). The percentage of epileptic animals with mild epilepsy (seizure frequence <1/day) was 53% (10/19) in the DZP group and 37% (11/30) in the untreated group (no difference). Percentage of animals with no epilepsy or mild epilepsy was 76% (28/37) in the DZP group and 47% (17/36) in the untreated group (p=0.017, Pearson chi-square test). The duration of spontaneous seizures did not differ between the DZP and untreated groups (p>0.05, Mann-Whitney *U*-test). **CONCLUSIONS:** Administration of DZP at about 3 h after the beginning of SE disrupts epileptogenesis in a subgroup of animals. Further, a significantly lower proportion of DZP treated animals develop severe epilepsy (>1 seizures/day). Taken together, our data suggest that discontinuation of SE with DZP has a disease modifying effect on the developing epilepsy.

13.

PLATELETS AS A MODEL FOR GABA AND GLUTAMATE DYSFUNCTION IN EPILEPTIC PATIENTS

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RATIONALE: Both the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and the excitatory amino acid glutamate (GLU) are involved in various processes related to epilepsy. Platelets have been used as a peripheral model for disorders of GABA and GLU in humans. We assessed the uptake of GABA and GLU in platelets in different epileptic syndromes. **METHODS:** We studied two groups of patients with juvenile myoclonic epilepsy (JME, N = 14 and 20), 20 patients with either refractory localization related epilepsies (RLE) or temporal lobe epilepsy with hippocampal sclerosis (TLE+HS) and 20 healthy volunteers. The patients and volunteers were matched for age and sex. GLU uptake was assessed with tritium-labeled GLU, GABA uptake with tritium-labaled GABA as a tracer and GABA-T activity with carbon labeled GABA. **RESULTS:** The activity of platelet GABA-T was significantly higher in the JME patients than in patients with RLE and healthy volunteers. RLE patients did not differ from the healthy subjects. GABA uptake was slowest in the JME group and fastest in healthy volunteers. The uptake of GLU was fastest in the TLE+HS patients. JME patients did not differ from volunteers. **CONCLUSIONS:** Marked differences in platelet GABA uptake and activity of the catabolic enzyme GABA-T seem to exist between patients with generalized and localization related epilepsies. The observed peripheral alterations may indicate impairment in GABAergic functions in the brain. Altered GLU uptake in patients with TLE+HS may indicate deranged extracellular levels of GLU within the CNS.

14.

PREVALENCE AND PROGNOSIS OF VIGABATRIN-ASSOCIATED VISUAL FIELD DEFECTS

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RATIONALE: To evaluate prevalence, prognosis and risk factors of vigabatrin-associated concentric visual field defects. **METHODS:** Sixty patients with partial epilepsy, 35 treated with vigabatrin monotherapy and 25 with add-on therapy, were examined with the kinetic Goldmann perimeter. A follow-up examination was performed after 4 to 38 months (mean 15 ±7) in 55 patients, 29 of whom had discontinued vigabatrin treatment. **RESULTS:** The duration of therapy varied between 29 to 120 months (mean 70 ± 30) in monotherapy group and between 7 to 168 months (mean 49 ± 36) in add-on group. The cumulative doses were 2-19 kg (mean 6 ± 4 kg) and 0,4-18 kg (mean 4 ± 4 kg), respectively. At the first examination, bilateral concentric visual field constriction was found in 24 of 60 patients (40%); severe in eight patients (13%) and mild in 16 patients (27%). The prevalence in men was 11 of 25 (44%), and in women 13 of 35 (37%) (chi-square test, p =0.118). One add-on patient with mildly constricted visual fields in the first evaluation, had normal visual fields in the follow-up examination after stopping the drug. For the group, the mean change in the cardinal meridians during the follow-up varied from narrowing by only 1° to widening by only 2°. There was no significant difference between the patients who continued or discontinued vigabatrin treatment. The age, body weight, duration of vigabatrin therapy or cumulative vigabatrin dose did not correlate with the visual field extents. **CONCLUSIONS**: Vigabatrin-associated visual field defects are neither reversible after cessation of the drug nor progressive with continued therapy.

15.

EPILEPSY AND PREGNANCY: OUTCOME OF A RETROSPECTIVE COHORT OF 179 SINGLETON PREGNANCIES

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RATIONALE: Women with epilepsy are considered to be at high risk in pregnancy. Attention has mostly been given to teratogenicity of antiepileptic drugs (AEDs), increased risk of preterm delivery and intrauterine growth restriction. **METHODS**: Altogether 179 singleton pregnancies of women with epilepsy were registered during January 1989 and October 2000: 127 had used AEDs during pregnancy (women with active epilepsy, WWAE) and 52 women had not. The control group comprised of 25.000 women without epilepsy. **RESULTS**: The age of the WWAE (28.6 ± 4.7 years) was the same as with controls (28.9 ± 5.4 years). Prepregnant BMI was in WWAE 24.3±5.0 kg/m^2 and 23.4±4.5 kg/m^2. Altogether 82% had monotherapy during pregnancy (72 carbamazepine, 28 valproate, 2 oxcarbazepine and 2 phenytoin). Altogether 16% had duotherapy and 2 % had polytherapy with three AEDs. During the pregnancy 58% of the WWAE were seizure-free. Caesarean section was performed equally often in both groups (15.6% vs. 16.7%). The birth weight was the same as was also the duration of the pregnancy. Apgar points at 1 minute were below 7 in 10% of the children of WWAE and only 5% of children of controls ($p< 0.05$). The risk of small for gestational age was increased in WWAE (17% vs. 9%, $p<0.01$). More children of WWAE were treated in the intensive care unit (14% vs. 7%, $p<0.01$. The frequency of all malformations was 7.1% and of all major malformations was 2.4%. Patients without AEDs resembled the control group. **CONCLUSIONS**: Malformation rate was according to literature. Need of intensive care after birth and higher risk for being small for gestational age may have impact for the long-term cognitive and overall outcome of these children.

PREVALENCE AND PREDICTORS OF REFRACTORY SEIZURES: CAN EARLY DETECTION IMPROVE TREATMENT OPTIONS?

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The natural history of treated epilepsy has substantial relevance to its pharmacological and surgical management. In our centre, 525 unselected, untreated patients were given a diagnosis of epilepsy, commenced on antiepileptic drug (AED) therapy and followed for a median of five years. Sixty three percent had been seizure-free for at least the previous year. Patients with symptomatic or cryptogenic epilepsy were more likely to remain uncontrolled. Those with a high number of pre-treatment seizures, especially over 20, were also less likely to become seizure-free. Forty seven percent of 470 previously drug-naïve patients responded to their first AED, mostly at modest or moderate dosage. Thirteen percent were seizure-free on the second, and 1% on the third monotherapy choice. Prognosis in patients whose epilepsy did not respond to the first AED was strongly associated with reason for failure. Only 11% of patients with inadequate control on the first well-tolerated AED later became seizure-free. In a parallel study of 550 patients with localisation-related epilepsy, patients with mesial temporal sclerosis were more likely to be uncontrolled than other aetiological groups. Nevertheless, 42% remained seizure-free, some off AED therapy.

These results suggest that patients with epilepsy comprise two distinct populations. Around 60% will control on monotherapy, usually with the first or second AED chosen. The remaining 30-40% will be difficult-to-control from the outset. A management plan should be formulated for each patient when initiating treatment. Strategies for combining drugs should involve individual assessment of patient-related factors, including seizure and syndrome classification, married with an understanding of the mechanisms of action, side-effects and interaction profiles of the AEDs. Epilepsy surgery should be considered after failure of two well-tolerated treatment regimens whether as monotherapy or with one monotherapy and the first combination. The prevention of refractory epilepsy should be the goal of treatment when prescribing the first AED since a range of deleterious changes in brain structure and function may be a consequence of recurrent seizures. A staged approach to the pharmacological management, and, when appropriate, surgical work-up for each epilepsy syndrome will optimise the chance of perfect seizure control.

MOLECULAR BASIS OF EPILEPTOGENESIS IN EXPERIMENTAL MODELS

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OBJECTIVE: Symptomatic human temporal lobe epilepsy frequently develops as a result of brain insult and the epileptic process can be divided into three phases: 1) initial insult, 2) latency period (epileptogenesis) and 3) recurrent seizures (epilepsy). The lack of available strategy to prevent the development of epilepsy is due to our limited understanding of events taking place during the latency period.

METHODS: During past years, we have focused on identification of epileptogenesis related genes. We have taken advantage of the amygdala stimulation model of temporal lobe epilepsy developed in our laboratory. In this model, status epilepticus (SE) is evoked by an electrical stimulation of the lateral nucleus of the amygdala. SE is followed by a latency period lasting for about 1 month, after which, spontaneous seizures appear (Nissinen et al., Epilepsy Res 2000:38:177-205). To verify the disease stage, animals are continuously followed-up with a video-EEG monitoring. During epileptogenesis (14 d after induction of SE) rats were sacrificed and RNA from the hippocampus was extracted. Reverse transcription was used to synthesize radioactive cDNA probe from total RNA from control (unstimulated) rats and rats undergoing epileptogenesis. cDNA probes were hybridized to commercially available high density cDNA arrays containing over 5000 gene probes. Densitometric analysis followed by careful visual inspection of arrays revealed that the expression of majority of genes did not change.

RESULTS: Genes with changed expression levels could be divided on the basis of the function of their protein products into following classes: lipid metabolism, protein metabolism, regulation of transcription, cell-cell interactions, and synaptic function (Lukasiuk and Pitkänen, unpublished). Twenty seven of "candidate epileptogenesis genes" have been previously shown to be expressed in the brain, role in the epilepsy or seizures has been implicated for 7, and role in other pathological conditions for 16. Changes in the expression of selected genes were confirmed by RT-PCR.

CONCLUSIONS: These data provide insight into molecular changes occurring during epileptogenesis and will hopefully open new avenues for the development of rational antiepileptogenic therapies.

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MOLECULAR PROFILING OF HUMAN TEMPORAL LOBE EPILEPSY

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The comprehensive analysis of disease-related gene transcripts becomes increasingly important for further understanding the molecular basis of human diseases. Here, we report on results of microarray-based expression profile analyses in the hippocampus of individuals suffering from temporal lobe epilepsy (TLE). Human temporal lobe epilepsy usually presents with seizure onset during early childhood, whereas spontaneous seizure activity manifests in adolescence. At the end stage of the disease, histological alterations include Ammon's horn sclerosis, i.e. segmental hippocampal cell loss in CA1 and CA4, whereas dentate gyrus (DG) granule cells and CA2 pyramidal neurons are more resistant. Using high-density oligonucleotide arrays we attempted to identify molecular pathways involved in region specific hippocampal epileptogenesis. Since AHS in hippocampal biopsy specimens from pharmacoresistant TLE patients frequently resembles the end stage of the disease it is necessary to compare data obtained from human tissue samples with those from animal models.

480 out of approx. 1200 genes were differentially expressed during hippocampal epileptogenesis and in the chronic epileptic stage. Our preliminary analysis revealed three major patterns: (i) in the early epileptogenesis stage, upregulation of genes was linked to stress and cell damage associated signaling cascades; (ii) those genes preceeding initiation of chronic seizures include transcription factors, neurotransmitter receptors, calcium-signaling or structure related molecules; (iii) significantly more genes were differentially expressed in CA1 than in DG. These data provide a systematic analysis of region-specific gene expression during hippocampal epileptogenesis and in the chronic epileptic stage. The identification of signaling pathways preceding chronic seizure manifestation, i.e. neurotransmitter receptor reorganization, may offer potential targets for novel, site-specific therapeutic strategies.

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CHANNELOPATHIES: HOW DOES THE UNDERSTANDING OF MOLECULAR CHANGE ALTER THE DIAGNOSIS, TREATMENT PRACTISE, OR DOES IT?

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PHARMACOGENOMICS: CAN WE PREDICT AND PREVENT THE SIDE EFFECTS OF AEDS WITH PROFILING?

Michael Johnson

THE PROGNOSIS OF EPILEPSY: LESSONS FROM THE DEVELOPING COUNTRIES

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In developing countries, patients may have had epilepsy for long periods. If these patients never remit, prevalence rates in developing countries should be higher than in the developed world. Indeed some studies in developing countries have reported higher prevalence for epilepsy. However, these were small studies of selected populations that may have high rates of CNS degenerative diseases, parasitic diseases or specific syndromes. Large-scale prevalence rates in largely untreated populations in developing countries have reported rates similar to those found in developed countries despite higher incidence rates. One explanation is that epilepsy has a higher mortality rate, but this is unlikely to account for the whole difference. Another possible explanation is that case ascertainment for active seizures was not optimal. However, cases in remission are more likely to be missed than active seizures in such studies. A more plausible explanation would be that some patients enter spontaneous remission. Two small retrospective studies, one in Finland and the other in India, seem to support this explanation: both reported a remission rate of 50% in untreated patients. Observations on the efficacy of treatment in patients with chronic epilepsy who had not previously received AED treatment have been made in three different studies from developing countries. These studies have found that neither the duration of the condition nor the number of seizures before treatment were predictors of outcome. This finding offers evidence against the view that unless treatment is given early, chronic epilepsy will develop.

CLINICAL PATHOLOGICAL STUDIES OF SURGICALLY TREATED TEMPORAL LOBE EPILEPSY PATIENTS

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Resective surgery for intractable temporal lobe epilepsy (TLE) is a successful therapeutic option for the past 50 years, and analysis of pathological substrates in relationship to the clinical presentation provides an opportunity to understand mechanisms of pathogenesis and seizure generation. In this lecture, we will define and illustrate the common clinical-pathological syndromes in surgical TLE patients. Using clinical-pathological techniques, the goal is to determine if the most common TLE substrate, hippocampal sclerosis (HS), is the consequence of an initial precipitating injury (IPI) that evolves to become an epileptogenic focus or is HS the result of repeated seizures over many years. Understanding if HS is the "cause" or "consequence" of seizures has important clinical implications concerning treatment of reactive non-TLE seizures in children and adults, and when patients should undergo surgical therapy for intractable TLE.

These questions were addressed in a retrospective cross-sectional analysis of the UCLA surgical database (1961 to 2000; n=525). Patients were classified based on the pathological substrate into those with HS (50.4%), mass lesion without HS (23.5%), dual pathology (lesion & HS; 17.1%), or no identified pathology (cryptogenic TLE; 9.0%). An IPI history and other clinical data were abstracted from the clinical records. Results showed that IPIs were strongly linked with HS cases compared with the other pathological categories, and that IPIs in HS patients were usually linked to a seizure at young age ($P<0.0001$). In addition, all HS patients had signs of aberrant axon connections of excitatory and inhibitory axon systems. These pathological findings support the concept that HS is likely the result of an acquired injury prior to the onset of TLE, and seizure pathogenesis probably involves synaptic reorganization as a consequence of cell loss. Additional analysis of the dataset also disclosed that long seizure histories were associated with progressive hippocampal neuronal loss in all subfields, and increased mossy fiber and GABAergic axon sprouting. These pathological changes were observed over 30 to 40 years of seizures, and occurred in all pathological sub-categories and was not restricted to HS patients. These finding support the notion that uncontrolled TLE induce long-term progressive pathology in epilepsy patients that adds to the existing pathology, but seizures are unlikely to generate HS. Hence, analysis of a surgical TLE database reveals that HS is most likely the consequence of an IPI (i.e. an acquired injury) that evolves secondary to synaptic reorganization to become a limbic seizure focus. In addition, uncontrolled seizures are also linked with progressive limbic system injury, but only after many years of epilepsy.

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MOLECULAR BASIS OF DRUG-REFRACTORINESS

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Although a series of new anticonvulsant drugs have been launched in the last two decades, drug-refractoriness remains a major problem in epilepsy treatment, concerning 20-30% of the patients. Thereby it figured out to be a complex task to define the biological basis of intractability. Investigations make use of tissue obtained from pharmacoresistant patients undergoing epilepsy surgery and of animal models with subgroups not responding to standard anticonvulsant drugs, thus mimicing the clinical situation.

Recent studies give evidence that changes in drug targets are likely to be involved in intractability in individual cases. Epileptic activity proved to render sodium channels in the hippocampus less sensitive to the effect of carbamazepine. Alterations in channel subunit composition or alterations in the channel phosphorylation state are most probably associated in this variation of drug modulation of sodium channels.

The fact that most patients with refractory epilepsy are resistant to several anticonvulsant drugs acting by different mechanisms, argues that specific target alterations can not be the only cause of pharmacoresistance in the majority of patients. This points to a role of more unspecific mechanisms, like changes in local brain uptake of anticonvulsant drugs. Overexpression of multidrug transporter proteins has been demonstrated in endothelial cells of the blood-brain barrier as well as parenchymal cells in the epileptic focus region of pharmacoresistant patients. Because investigations have given evidence that several anticonvulsant drugs are substrates of multidrug transporters, the enhanced expression of transporter proteins is likely to limit the access of anticonvulsant drugs to the epileptic neurons. In summary overexpression of multidrug transporters is a favorable hypothesis to explain an aspect of multidrug resistance in epilepsy. On the other hand, the basis of pharmacoresistance is likely to be multifactorial and not identical in different patients. Thus, effort is necessary to define additional mechanisms of pharmacoresistance.

ASSOCATION OF IMAGING FINDINGS WITH CLINICAL OUTCOME

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OBJECTIVE: Intractable temporal lobe epilepsy with hippocampal damage is often linked to a precipitating insult during childhood. The data available suggests that once epilepsy has emerged recurrent seizures may cause further structural and functional changes. However, longitudinal follow-up studies are needed to determine the course of epileptic process and to identify surrogate markers for disease modification.

METHODS: We designed a prospective follow-up study of 112 patients with newly diagnosed partial epilepsy who were allocated to treatment with either carbamazepine (CBZ; n=54) or with tiagabine/vigabatrin (TGB/VGB; n=40/18). The aim of the study was to investigate the occurrence of hippocampal damage and to assess whether the changes progress in the long-term follow-up. Specifically, we wanted to compare the hippocampal volumes in patients treated with either standard sodium-blocking agent or with newer gabaergic agents, and to examine whether volumetric measures correlate with clinical outcome. The initial magnetic resonance imaging (MRI) was performed before the antiepileptic medication was started, and later, after 1 year, 2-3 years and 5 years of follow-up. We used Cavalieri method of modern design stereology for volume estimations of the hippocampus. A group of 20 healthy subjects served as control population for MRI. The clinical outcome of the patiens was determined by assessing the efficacy and retention rate of the initial treatment.

RESULTS: The mean left and right hippocampal volumes did not differ between controls and patients studied at baseline, 1 year, 2-3 years and 5 years of follow-up. At least a 2 SD reduction in the volume of the hippocampus was observed in altogether 6 patients. In the general linear model of repeated measures there was a trend of volume decrease when left and right hippocampal volumes of each patient were compared during 2-3 years of follow-up but the change was not significant. When patients were divided into two groups according to the treatment (CBZ vs TGB/VGB) or seizure control (seizure-free vs seizures) no difference was observed in the serial hippocampal volumes. Accordingly, the efficacy of treatment in intial treatment groups was similar. Comparing the overall effectiveness of the treatments, CBZ proved to be more effective than TGB/VGB.

CONCLUSIONS: This is first prospective quantitative MRI study that systematically follows large number of newly diagnosed partial epilepsy patients. The study shows that hippocampal damage at the time of diagnosis is rare. No significant progressive change in the hippocampal volume was observed during follow-up. In the future most useful way for evaluating the course of epileptic process and effects of therapy might be combining several measures of outcome such as seizure-control, imaging data and cognitive data.

TREATMENT OF DRUG-REFRACTORY PARTIAL EPILEPSY

Jacqueline French

Epilepsy can be seen as a continuum, from the newly diagnosed patient, who has a high likelihood of responding to antiepileptic drugs, to the drug resistant patient, who is unlikely to remit. Different drug choices are needed, at different points on the continuum. Also, within the epilepsy population there are other characteristics that divide patients into sub-populations, including age (both old and young), sex, and epilepsy type. This abstract will briefly touch on the principles of AED therapy that should be considered when selecting AEDs for refractory epilepsy patients.

Of patients diagnosed with epilepsy, somewhere between 50-70% will respond rapidly to antiepileptic drug therapy. For them, the burden of epilepsy will consist of dealing with antiepileptic drug adverse events, and taking medication on a daily basis. The remainder of the epilepsy population will fail to achieve seizure control. These patients are called medically refractory. In this group, the psycho-social burdens will be much greater, and the physical risks will be higher. These patients will utilize more resources, and potentially require innovative treatments. Often, they will cycle through an endless stream of antiepileptic drug therapies.

What is different about these patients? Does their epileptic diathesis, or their intrinsic ability to respond to antiepileptic drugs define the difference between them and those with “benign” epilepsy? Most likely, both are important. Perhaps it will be necessary to study these patients in novel ways, to search for “hidden” causes of the refractory state. These might include a genetic predisposition, or a biochemical marker.

The impact of new antiepileptic drugs on such patients has been well studied in placebo-controlled add-on trials. Once many drugs have failed, the primary concern will be to find a highly efficacious drug. At this point, although side effects, drug interaction profiles and frequency of dosing are important, they may take a back seat to the goal of seizure freedom. Unfortunately, none of the new AEDs have produced a high percentage of seizure-free patients in controlled trials of this population. Often, seizure free rates are not even provided in reports of controlled clinical trials. 50% seizure free rates, also called responder rates, are routinely provided. While this provides some information about the potential efficacy of new AEDs in an add-on situation, the data must be interpreted with caution. Some of the new drugs, such as gabapentin and lamotrigine were used at doses lower than may be employed in clinical practice, leading to lower than expected responder rates, while others, such as topiramate and oxcarbazepine were used at supra-maximal doses which in the add-on situation may lead to pharmacodynamic interactions, tolerability problems and high discontinuation rates.

Certainly, some characteristics such as lack of pharmacokinetic and pharmacodynamic interactions will enhabce a drug’s ability to be used in the refractory patient. Availability of such drugs, coupled with novel mechanisms of action, make “rational polypharmacy” more attractive than it was a decade ago. At present, there is some evidence for the benefit of combining lamotrigine and valproic acid. Further research is needed into the best combination therapy.

Unfortunately, we still are lacking the magic bullet for treatment-refractory patients. Therefore, it is essential to continue research into new drugs with new mechanisms of action.

HISTORY AND SURGICAL OUTCOME OF DRUG-REFRACTORY PATIENTS WITH TLE

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Altogether 25% of all patients with epilepsy do not achieve good seizure control with the current antiepileptic treatment. It has also been been estimated that 3-4.5% of newly diagnosed patients with epilepsy would be optimal candidates for epilepsy surgery. Especially many patients with temporal lobe epilepsy (TLE) do not achieve good seizure control with the available medication and surgery has gradually become a basic modern treatment for drug-refractory TLE worldwide.

The most common way of estimating the outcome of epilepsy surgery is evaluation of outcome with respect to seizures. In a large series of studies published between 1963-2001 33-93% of patients operated on because of drug-resistant TLE have become seizure-free. In general, it is also estimated that up to 90% of patients benefit from surgery. Most of the operated patients are young adults, but comparable outcomes can also be expected in elderly patients. When analysing the prognostic factors for the outcome, some selected patient populations seem to have significantly higher success rates. These include patients with hippocampal atrophy, patients with complex febrile seizures and patients with foreign tissue lesions. On the other hand the postoperative outcome of patients with normal MR imaging has been significanly worse.

Previously all data concerning the outcome of TLE surgery derived from the series of individual centers. The data was therefore affected by several methodological problems. Today the first randomized controlled trial of surgery for temporal lobe epilepsy has suggested that surgery is superior to prolonged medical treatment in drug-resistant epilepsy (Wiebe et. al., 2001). The focus is now on the optimal timing of the surgical treatment.

Kuopio University Hospital has provided Comprehensive Epilepsy Surgery Program for patients with drug-resistant epilepsy since 1988. We have now analysed all adult patients operated on because of drug-resistant TLE at our hospital between 1988 and 1999. Altogether 140 patients (67 females, 73 males) were included in the study. Patients with temporal lesionectomies (without amygdalohippocampectomy), and those patients in whom any extra-temporal cortical excision had been carried out in addition to the temporal resection, were excluded from the study. In this presentation we review the outcome data with special emphasis on outcome with respect to seizures, prognostic factors for the outcome, complications, and mortality.

Supported by: The Kuopio University Hospital Research Fund, the North-Savo Regional Fund of the Finnish Cultural Foundation, the University of Kuopio, and the Vaajasalo Foundation

MATCHING THE TREATMENT WITH EPILEPSY SYNDROME AND SEIZURE TYPE

Reetta Kälviäinen. Department of neurology, Kuopio University Hospital, Kuopio, Finland

There are several different reasons for uncontrolled seizures. The antiepileptic drug (AED) used can be inappropriate for the specific seizure type or syndrome or may even aggravate the seizures. Re-analysis of the seizure type and syndromic diagnosis should be made always when seizures are uncontrolled. If the diagnosis turns out right and the AED used is selected appropriately according to the syndrome, it may still be used with too low doses or there might still be need for combination therapy in order to achieve enough efficacy. Combinations should be chosen rationally according to what is known of the mechanism of action of AEDs.

Sometimes the AEDs are appropriate for the epilepsy but the individual patient does not tolerate the side-effects and use the drugs according to the treatment plan. Adverse effects should be taken seriously and effort should be put to find a combination that improves the compliance. There might be also other AEDs available that would better suite for the patients needs for other drugs (mood stabilizing, antidepressant, anti-migraine or anti-pain drugs). If AED-treatment does not help, other options like surgical treatment and vagal nerve stimulator should be sought actively.

The treatment needs to be matched to the individual patient and the type of epilepsy. There are now wide range of treatment options available and these offer most patients good seizure control without unacceptable side effects and also patients with difficult epilepsy possibility to lead full and safe life. However, many patients with epilepsy still do not seem to be getting the treatments that are most appropriate for them, and more effort should be paid to achieve the goal of equally good treatment for all patients with epilepsy.

DO FEBRILE SEIZURES CAUSE TEMPORAL LOBE EPILEPSY?

Tallie Z Baram. UCI Comprehensive Epilepsy Program, Irvine, CA, USA

Of all seizures of early childhood, febrile seizures are the most prevalent type. An ongoing controversy about the outcome of these seizures involves the question of whether complex febrile seizures (those that are longer than 15 minutes, recur within a single febrile episode, or have focal features) alter limbic excitability leading to spontaneous seizures (temporal lobe epilepsy) later in life. Indeed, the relationship of childhood febrile seizures to adult temporal lobe epilepsy (TLE) has remained a focus of intense debate: Whereas prospective epidemiological studies have not shown a progression of febrile seizures to TLE, retrospective analyses of adults with TLE have demonstrated a high prevalence (30- >60%) of a history of prolonged febrile seizures during early childhood, suggesting an etiological role for these seizures in the development of TLE. Specifically, neuronal damage induced by febrile seizures has been suggested as a mechanism for the development of mesial temporal sclerosis, the pathological hallmark of TLE. However, the statistical correlation between febrile seizures and TLE does not necessarily indicate a causal relationship. For example, pre-existing (genetic or acquired) 'causes' that result independently in febrile seizures and in TLE would also result in tight statistical correlation.

For obvious reasons, Complex Febrile Seizures cannot be induced in the human, and studies of their mechanisms and of their consequences on brain molecules and circuits are severely limited. Therefore, an animal model was designed to study them. The model reproduces the fundamental, key elements of the human condition: the age specificity, the physiological temperatures seen in fevers of children, the length of the seizures and their lack of immediate morbidity. Data from the model, which help us to understand the consequences of prolonged febrile seizures on the survival and integrity of neurons will be presented. Particularly, mechanisms of the pro-epileptogenic effects of the seizures--effects which do not require cell death--will be highlighted. What these findings mean in terms of the approach to prolonged or complex febrile seizures in children will require further discussion.

EVIDENCE-BASED TREATMENT OF NEWLY DIAGNOSED INFANTILE EPILEPSY

Eija Gaily. HUS, Hospital for Children and Adolescents, Pediatric Neurology, Helsinki, Finland

Of infantile epilepsies and epilepsy syndromes, moderate research-based evidence on treatment efficacy are available only for infantile spasms (West syndrome) and severe myoclonic epilepsy (SMEI). Before ACTH, spontaneous remission rates of infantile spasms were only a few percent per month, with normal development in 0-9 %. In two large cohort studies, spasms stopped in 48-60% and normal development occurred in 24% of all ACTH treated infants. Four under-powered randomized controlled studies (RCTs) found no significant difference between the efficacy of different protocols of ACTH and various other treatments or between low and high doses of ACTH. Response rates in the ACTH-treated groups ranged from 42% to 87%. A population-based open study and a large retrospective study found 26-68% response rates of infantile spasms to vigabatrin (VGB). Four under-powered RCTs compared 100-150 mg/kg/day VGB to placebo, ACTH, low dose VGB or hydrocortisone, with 35-48% response rates in the VGB treated infants (100% in infants with tuberous sclerosis). Both ACTH and vigabatrin are effective, but response rates in different studies cannot be compared because of selection bias. ACTH is associated with potentially life threatening adverse effects and VGB with risk of permanent visual field defects. Fewer spasm relapses and other seizures may occur in VGB than ACTH treated infants. The proposed first treatment in idiopathic and cryptogenic infantile spasms is either ACTH in low to moderate doses or a short (3 months?) course of VGB, switching to the other treatment if the first choice fails. In symptomatic infantile spasms, the first treatment is proposed to be VGB, followed by add-on ACTH in VGB resistant patients. VGB should probably be continued for at least a year in all responders to prevent recurrences and other seizures. In a population-based study using this protocol, 50% of infants with symptomatic etiology had permanent cessation of spasms and 45% were seizure free at age 1-2 years. In SMEI, a randomised controlled study showed stiripentol in combination with valproate and clobazam to be significantly more effective than placebo in reducing seizures.

EVIDENCE BASED TREATMENT (EBT) OF NEWLY DIAGNOSED EPILEPSY IN CHILDHOOD

Kai Eriksson. Senior Lecturer in Pediatric Neurology, Medical School, University of Tampere and Pediatric Neurology Unit, Tampere University Hospital, Finland

What is evidence based? This is a crucial question for the paediatric epilepsy patients e.g. due to the lack of randomised controlled trials (RCT). 'Syndromic' approach, however, does facilitate rational – but not always evidence based – treatment choices.

Benign Childhood Epilepsy with Centrotemporal Spikes (BECT) is characterized by focal oropharyngeal or facial seizures and nocturnal secondary generalization as well as spontaneous remission by the age of 16 years. Many conventional AEDs (CBZ, VPA, PHT, PB, STM)[B,C] and some of the new ones (LTG, GBP)[C] have been shown to be efficient in controlling seizures, however, treatment maybe necessary only in 1/3 of patients [D].

Idiopathic Childhood Occipital Epilepsies consist of two syndromes (Panayiotopoulos and Landau type), with differences in the age at onset, seizure type and prognosis. Treatment (CBZ, VPA)[C] - in those cases it is necessary - and its duration should be adjusted according to syndrome diagnosis.

Studies on conventional AEDs (CBZ, OXC, VPA, PHT, PB)[A,B] in cryptogenic or symptomatic focal epilepsies show efficacy but no difference in the efficacy between AEDs; studies on new AEDs favour TPM[B], LTG[C], VGB[C]. Treatment should be based on individual level more on safety, tolerability, long-term side effects and expense than efficacy.

Lennox-Gastaut Syndrome is a difficult to treat epilepsy with often pre-existing brain damage and mental retardation. Trials favour new AEDs (TPM, LTG, FBM, VGB)[A,B,C] although conventional AEDs (VPA, BZD)[C] are usually recommended as the first line treatment. Epilepsy surgery (callosotomy)[D] may help in the most catastrophic situations.

Landau-Kleffner Syndrome consists of a triad of verbal auditory agnosia, acquired aphasia and behavioural and psychiatric problems and multiple seizure types. First line treatment is usually VPA and/or ETM and/or BZD[B,C], some evidence of the efficacy of FBM[D] also exists. Second line treatment is usually corticosteroids[C]. MST(multiple subpial transections)[C] have also been shown to have some efficacy.

EBT of epilepsy in this age range lacks RCTs. However, the focus of EBT should maybe shift from treating the seizures into treatment of the patient. This would mean setting new goals for EBT of epilepsy in childhood; such as long-term outcome, neurological development and quality of life.

EVIDENCE BASED TREATMENT OF NEWLY DIAGNOSED EPILEPSY IN PUBERTY

Leena Vainionpää. Department of Pediatrics and Adolescence, Oulu University Hospital, Oulu, Finland

The heterogeneous group of idiopathic generalized epilepsies represents the most frequent forms with adolescent seizure onset. Valproate has been the treatment of choice for these generalized seizures (generalized tonic-clonic, absence and myoclonic seizures) and epilepsy syndromes.

There are many clinical reports of the efficacy of valproate for absence seizures. It has been established in double-blind prospective comparative studies that valproate and ethosuximide are equally effective in controlling absence epilepsy, and valproate is also effective against generalized tonic-clonic seizures. On the other hand, several open-label add-on studies in children have indicated that lamotrigine may be an effective monotherapy for generalized epilepsy syndromes in childhood. One placebo-controlled study of lamotrigine administered for childhood absence epilepsy in newly diagnosed patients showed it to be effective for typical absence seizures and to be generally well tolerated.

There are reports of a dramatic response of juvenile myoclonic epilepsy to valproate, based on one prospective study and various retrospective reports on clinical trials, with 80-90% of such patients becoming seizure-free. There is a wide consensus that valproate is best for juvenile myoclonic epilepsy and that carbamazepine may exacerbate this type of epilepsy, although there are no comparative randomized trials. There are favourable reports on the efficacy of lamotrigine involving about 12 patients with juvenile myoclonic epilepsy, but there are no randomized trials comparing its efficacy with valproate.

Valproate monotherapy was associated with significantly greater weight gain than lamotrigine monotherapy in a randomized, double-blind study in patients with newly onset or previously diagnosed partial or generalized seizures, and valproate may induce hyperandrogenism in girls with epilepsy during pubertal maturation. These points emphasize the importance of careful endocrine observation of children and adolescents with epilepsy who are taking valproate.

It would be good in future to conduct randomized trials in which only patients with specific epilepsy syndromes are recruited, especially those with adolescent onset, if we want to detect whether particular antiepileptic drugs are to be preferred for these syndromes. Newer drugs such as lamotrigine and topiramate could be compared with valproate, which is the drug of choice at the present moment.

EVIDENCE BASED TREATMENT OF NEWLY DIAGNOSED EPILEPSY IN ELDERLY

Tapani Keränen. Department of Neurology, University of Turku and Turku University Hospital, Turku, Finland

Epidemiological studies have shown that incidence and prevalence rates of epilepsy increase sharply after the age of 60 years. Annual incidence rates reach 100 - 150/100 000, a figure much higher than in adolescence and young adulthood, and patients aged 60 years or over account for about one quarter of all incidence cases.

Epilepsy in elderly patients differs in many respects from that in children and in young adults. Epilepsy starting in old age is almost exclusively of localisation related type and complex partial seizures are the most common seizure type. In most of the newly diagnosed cases, epilepsy is due to a remote symptomatic cause cerebrovascular disorders being the most common single etiology. Other common symptomatic cases are traumas, tumours and degenerative diseases. Elderly patients also have a high incidence of acute symptomatic seizures due to either cerebral disorders (such as cerebrovascular accidents) and other illnesses.

Correct diagnosis of a seizure disorder represents a more demanding challenge in the elderly than in younger adults. Elderly patients may have other diseases which may cause symptoms resembling of epilepsy. Syncopal attacks are common in old age, and these attacks may also be associated with a short stiffening of the body or a few jerks. Complex partial seizures may be confused with confusional states.

A major problem in assessing the usefulness of different antiepileptic drugs (AED) in elderly patients is almost a total lack of clinical trials in this patient population. There are data suggesting that pharmacokinetics and also –dynamics of various AED are altered in the elderly. The distribution and elimination of AED in elderly patients is changed due to alterations in plasma protein binding and in both hepatic and renal clearance. There is also evidence that the tolerability of AED may be poorer in elderly patients compared with young adults.

To date, there is only one published study addressing the efficacy, tolerability and safety of specific AED in elderly patients with newly diagnosed epilepsy. In this study (Brodie et al. Epilepsy Res 37:81-7, 1999), lamotrigine (LTG) and carbamazepine (CBZ) were compared in a randomised, double-blind trial. The authors concluded that the drop-out rate was significantly higher with CBZ than with LTG. More patients continued LTG than CBZ, and a greater proportion of LTG-treated patients remained seizure-free during the last 16 weeks of treatment.

Another study in elderly patients, comparing carbamazepine, gabapentin and lamotrigine is uderway.

There is urgent need for further studies with different AED in elderly patients with epilepsy.

MEG SIGNS OF NORMAL AND ABNORMAL BRAIN FUNCTION IN NEUROLOGICAL PATIENTS

J.P.Mäkelä. Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, and Central Military Hospital, Helsinki, Finland

Magnetoencephalography (MEG) allows evaluation of the brain areas activated by sensory stimuli or producing spontaneous brain activity. The source areas can, in favourable conditions, be located accurately, and their activation sequence unraveled in milliseconds. Recent MEG studies have provided data about cortical reorganization after lesions, of speech- and reading-related cortical activities, and relations of cortical sensorimotor spontaneous activity to muscle activity.

Due to its non-invasiveness, MEG is ideally suited for studies of neurological patients. Epileptic activity produces robust magnetic signals; activity from epileptic cortex deep in the sulci is easily visible in MEG recordings. Detection of interictal activity, its source location and spread can in favourable conditions be depicted accurately by MEG. Ictal recordings are more demanding since MEG is sensitive to movement artefacts. Mesial temporal cortex activity is poorly visualized in traditional gradiometers, but new devices, including magnetometer detectors, may be more sensitive to it. MEG may be practical in detection of epileptic activity after lesionectomy or epileptic surgery, when subdural electrodes are difficult to apply due to dural adherences. In addition to direct clinical applications, MEG studies reveal cortical functions in genetically delineated epilepsies, providing clues about generation of epileptic activity.

The estimated sources of MEG activity can be superimposed on MR images of individual subjects. In presurgical evaluation of tumor patients, we have generated functional landmarks for somatosensory, motor and speech-related cortical areas by MEG, and compared them with active sites detected by electric simulation and evoked potential recordings during awake craniotomy. The sources of somatosensory evoked fields and of spontaneous activity correlating maximally with EMG signals match the intraoperative localization of somatosensory and motor cortex. These landmarks are equally practical in designing epilepsy surgery.

VAGAL NERVE STIMULATION IN THE TREATMENT OF EPILEPSY. CRITICAL OVERVIEW

Elinor Ben-Menachem, M.D., Ph.D. Department of Clinial Neuroscience, Sahlgrenska University Hospital, Göteborg, Sweden

Vagal nerve stimulation (VNS) is a treatment for patients with refractory epilepsy. The first implant was performed in l988, and since then more than 12000 patients have received this therapy. VNS has been compared to epilepsy resective surgery but it is best compared to the efficacy and side effects of the newer antiepileptic drugs. All patients given VNS are usually evaluated first for epilepsy surgery. Unfortunately the majority of refractory patients are not epilepsy surgery candidates so the development of other techniques as new drugs and VNS are imperative.

The VNS generator is implanted in the upper left chest with the stimulating lead attached to the left vagus nerve in the neck. The most common studied stimulation paradigm has been 20-30 Hertz, 1.0-2.0 mAmps, 500 microsecond pulsewidth, 30 seconds ON time/3-5 minutes OFF, 24 hours a day. There is a magnet provided which can restart the VNS at its own parameters for a brief time to try to abort an emerging seizure.

VNS is approved around the world including the EU and USA since 1997 so this procedure is now used in normal clinical practice. Efficacy results of the VNS studies were remarkably similar with a median of between 24% and 27% reduction of seizure frequency and 30% respective 23% with >50% seizure reduction for the patients receiving HIGH stimulation. After 3 years of VNS, 43 % had experienced a >50% seizure reduction. A postmarketing registry is in effect and collects efficacy and safety data from patients not participating on clinical trials.

The safety profile is favorable and side effects different from those seen with AEDs. CNS side effects are not generally reported. In fact, many actually report an increase awareness and memory. Side effects are restricted to local irritation, hoarseness, coughing and in a few cases swallowing difficulties when the stimulator is ON. All are reversible with reduction of the stimulation parameters or when the generator was turned off. VNS does not interfere with concomitant AEDs or any other drug.

The mechanism of action of VNS is unknown but afferent projections of the vagal nerve are synaptically connected to many areas of the brain involved in the initiation and propagation of seizures. Studies in humans demonstrates metabolic and blood flow changes in the brain during stimulation as seen in PET and fMRI.

Compared to the new AEDs, VNS has similar efficacy results in clinical trials, but the long-term efficacy results are more positive. Efficacy continues to improve over a period of 3 to 18 months and there have been no new side effects or tolerance development over observation times of up to 12 years. VNS battery life is 8-10 years. From the clinical trials 78% have elected to replace the NCP. The cost of the implantation of the NCP, when spread out over 8-10 years (battery length), is actually less than the cost of using one new AEDs over an eight to ten year period.

VAGUS NERVE STIMULATION IN THE TREATMENT OF EPILEPSY - FINNISH EXPERIENCES

Jouko Isojärvi. Department of Neurology, University of Oulu, Oulu, Finland

According to the Finnish treatment guidelines of epilepsy vagus nerve stimulation is an option in the treatment in those drug refractory cases, where resective epilepsy surgery is not possible. The price of the device is high, and the implantation should be done only after thorough investigations and careful consideration. Vagus nerve stimulation has so far not been widely used for treatment of refractory epilepsy in Finland. Most of the current experience in Finland is from Oulu University Hospital. Fourteen vagus nerve stimulators have been implanted for epilepsy patients in Oulu University Hospital since February 1999. All patients were drug-refractory and resective surgery was not considered possible. The last two implantations were done at the end of 2001, and, thus, follow-up data is available for 12 patients.
67 % of the patients have responded favorably to the treatment (> 50 % decrease in seizure frequency). One of these patients has been seizure-free for 12 months. The stimulator has generally been well tolerated. Hoarseness and cough during stimulation have been the most common adverse events. They have been experienced by 67 % of the patients, whereas 42 % has had painful sensations in the neck or head. Shortness of breath and esophagitis were both seen in one patient (8 %). However, the adverse events have been mild, and they have not lead to withdrawal of the treatment in any of the cases. The experiences of vagus nerve stimulation - treatment in Oulu University Hospital have so far been promising and the results are in accordance with published reports from other centers. It has been planned that in the future the treatment will be continued with a rate of five to six new implantations per year.

KUOPIO EPILEPSY SYMPOSIUM
March 15-16, 2002
Kuopio Music Center
Kuopio, Finland

PROCEEDINGS

Friday, March 15th 2002

Abstracts (pdf file)
Poster abstacts (pdf file)

On behalf of the Finnish Epilepsy Society and the Finnish Epilepsy Association, we cordially welcome you to participate in "Kuopio Epilepsy Symposium 2002" in Kuopio, March 15-16 2002.

The meeting will be third in a series of epilepsy meetings that are organized jointly by the A.I.Virtanen Institute for Molecular Sciences and the Department

Saturday, March 16th 2002

Key note address: Do febrile seizures cause temporal lobe epilepsy ?

Prof. *Tallie Z. Baram* (USA) Key slides (pdf file)

Evidence based treatment of newly diagnosed epilepsy at special ages
Chair: *Dr. Aarne Ylinen* (Finland)

In infancy Dr. Eija Gaily (Finland) Key slides (pdf file)
In childhood Dr. *Kai Eriksson* (Finland) Key slides (pdf file)
In puberty Dr. *Leena Vainionpää* (Finland) Key slides (pdf file)
In elderly Dr. *Tapani Keränen* (Finland) Key slides (pdf file)

Update of epilepsy research in Finland: selected abstracts
Chair: Prof. Hilkka Soininen

Click here for abstracts of oral presentations (pdf file)

Oral presentation I
THE LEVELS OF IL-6 AND ITS SOLUBLE RECEPTORS IN CEREBROSPINAL FLUID AND SERUM AFTER SEIZURES
KA Lehtimäki, J Palmio, J Ollikainen, J Honkaniemi, H Huhtala, T Keränen, J Peltola.

Oral presentation II

UPREGULATION OF CYSTATIN C IN THE RAT HIPPOCAMPUS DURING EPILEPTOGENESIS
TJ Pirttilä, K Lukasiuk, A Pitkänen. A.I.Virtanen Institute for Molecular Sciences, University of Kuopio, P.O.B. 1627, 70211 Kuopio, Finland.

Oral presentation III

SEVEN FINNISH FAMILIES WITH GENETIC EPILEPSY
A Sirén, H Rantala, A Nuutila, O Saarenpää-Heikkilä, K Eriksson, M Koivikko, M Pandolfo. Department of Neurology, Erasmus Hospital, Brussels, Belgium; Department of Pediatrics, University Hospital of Tampere, Finland; Department of Pediatrics, University Hospital of Oulu, Finland; Department of Pediatrics, Central Hospital of Etelä-Pohjanmaa, Finland.

of Neuroscience and Neurology, University of Kuopio.

The objective of the meeting is to present up-to-date knowledge of selected topics related to epilepsy. Both experimental and clinical data will be presented.

We hope to bring together people working on 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.

Asla Pitkänen
Professor
Chairperson of
the Organizing Committee

Reetta Kälviäinen
Docent
Co-chairperson of
the Organizing Committee

Oral presentation IV

REPRODUCTIVE ENDOCRINE DISORDERS IN YOUNG WOMEN WITH EPILEPSY
KH Ruotsalainen, LK Vainionpää, JS Tapanainen, I Järvelä, JI Isojärvi. Departments of Pediatrics, Neurology and Gynecology, University of Oulu, Oulu, Finland.

Oral presentation V

MULTIPARAMETRIC MRI ANALYSIS OF DRUG-RESISTANT TLE
PM Goncalves Pereira, M Forjaz Secca, A Leal, C Ribeiro, P Evangelista, P Rosado. Neuroradiology Dept, H. Egas Moniz, Lisbon, Portugal; Physics Dept. New University of Lisbon, Portugal; Neurology Dept, H.Fernado Fonseca, Lisbon, Portugal; Caselas Magnetic Resonance Center, Lisbon, Portugal; Neurology Dept, H.Egas Moniz, Lisbon, Portugal.

Plenary lecture

MEG signs of normal and abnormal brain function in neurological patients
Dr. *Jyrki Mäkelä* (Finland) Key slides (pdf file)

Vaajasalo Foundation Young Investigator Award

Vagus nerve stimulation in the treatment of epilepsy

Chair: Dr. Jouko Isojärvi (Finland)

Critical overview
Prof. *Elinor Ben-Menachem* (Sweden) Key slides (pdf file)

Finnish experience
Dr. *Jouko Isojärvi* (Finland) Key slides (pdf file)

Panel discussion:

Place of vagus nerve stimulation in the treatment of epilepsy
(Invited Panel: Dr. *Mervi Kotila*, Dr. *Elina Liukkonen*, Prof. *Matti Vapalahti* and the audience)

Closing of the Kuopio Epilepsy 2000 Symposium
Prof. A*sla Pitkänen*

of Neuroscience and Neurology, University of Kuopio.

The objective of the meeting is to present up-to-date knowledge of selected topics related to epilepsy. Both experimental and clinical data will be presented.

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Asla Pitkänen
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Reetta Kälviäinen
Docent
Co-chairperson of
the Organizing Committee

Spectrum of brain pathologic lesions associated with drug-refractory temporal lobe epilepsy
Prof. *Gary Mathern* (USA) Key slides (pdf file)

Molecular basis of drug-refractoriness
Prof. *H. Potschka* (Germany) Key slides pdf file)

Association of imaging findings with clinical outcome
Dr. *Tuuli Salmenperä* (Finland) Key slides (pdf file)

Treatment of drug-refractory partial epilepsy
Prof. *Jacqueline French* (USA) Key slides (pdf file)

History and surgical outcome of drug-refractory patients with TLE
Dr. *Leena Jutila* (Finland) Key slides (pdf file)

Interactive epileptology through challencing case studies

Chair: Dr. Reetta Kälviäinen

Matching the treatment with epilepsy syndrome and seizure type
Dr. *Reetta Kälviäinen* (Finland) Key slides (pdf file)

Case studies
Dr. Leena Jutila, Dr. Aarne Ylinen, Professor Juhani Partanen
- Commented by special guests (Dr. Marja-Liisa Granström, Professor Tapani Keränen, Professor Martin Brodie, Professor J.W.A.S. Sander and the audience)

Do Prolonged Febrile Seizures Cause Temporal Lobe EPILEPSY?

From the clinic to the bench- and back

Tallie Z. Baram, MD, PhD
Professor, Pediatrics, Anatomy / Neurobiology and Neurology
Scientific Director,
UCI Comprehensive Epilepsy Program

- **Epilepsy: 2.5 million persons in U.S**
- **70,000 - 128,000 new cases a year**
- **Febrile seizures: ~600,000 /year**

Prospectively: FS do not lead to TLE

Retrospective Studies: 30-70% of patients with TLE have history of FS

Correlation versus causality

Alternative I:
Normal hippocampus ➔ FS ➔ neuronal injury ➔ TLE

Alternative II:
Pre-existing injury/ lesion ➔ fever-triggered seizure
= first sign of TLE

Issues in Human Research

Induction of febrile seizures

- Genetic predisposition to seizures or outcome
- Presence of acquired lesions predisposing to seizures or adverse outcome

Animal Models:

- **Standardized and controlled**
- **Rapid prospective studies**
- **Mechanisms and intervention**
- **Genetic and acquired homogeneity (justified by studies of discordant monozygotic twins)**

Immature rat model of prolonged (complex) FS

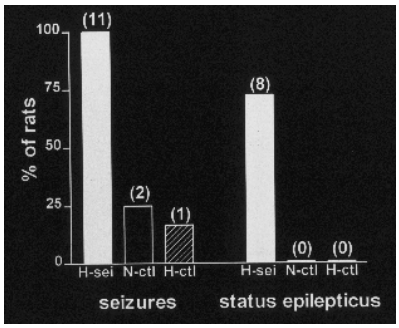
- **Age appropriate**
- **Physiological temperature**
- **>98% seizure induction**
- **EEG validated**
- **Benign (in >400 animals)**
- **'Normal' brain**

- Do febrile seizures cause brain damage?
- Do febrile seizures cause temporal lobe epilepsy?

Study Design: Early in life

1. Hyperthermic Seizures (22 min)
2. Hyperthermia alone Pentobarbital)
3. Normothermia

Animals permitted to grow for 2 months.



Conclusions:

- Prolonged FS do not cause spontaneous limbic seizures during adulthood.
- However, they reduce threshold to convulsants.
- Prolonged FS cause persistent enhancement

of limbic excitability that may facilitate epilepsy.

Normal ➡ Prone ➡ Epileptic

DOGMA: seizure-induced epilepsy requires neuronal death

FACT: In the febrile seizures model: No cell death; profound transient structural changes and persistent plasticity of gene expression.

Implication for treatment:

Do we aim for:

- Prevention of changes induced by complex FS in normal CNS?
- Prevention of epileptogenesis after the second 'hit'?

Using what?

VNS in Amygdala Kindling (AK) in Cats

- N=5 (AK only), N=10 (VNS + AK)
- **Controls:** AK to Stage VI in 23.4 + 3.7 trials
- **VNS:** AK to Stage VI Never Reached
- **VNS:** Stages I-III Significantly Delayed

Epilepsia, 40(7): 822-829, 1999, Fernandez-Guardiola et al.

Possible Mechanism of Action

- Arousal of Reticular Formation
- Stimulation of Locus Coeruleus and Noradrenaline Pathways *(S. Krahl, et al.)*
- Peripheral Sensory Stimulation
- Changes in Some Neurotransmitter, Amino Acid or Neuropeptide *(E. Ben-Menachem, et al; D.Naritoku, et al.)*
- Long-Term Learning through Synaptic Structural Changes

VNS and fMRI

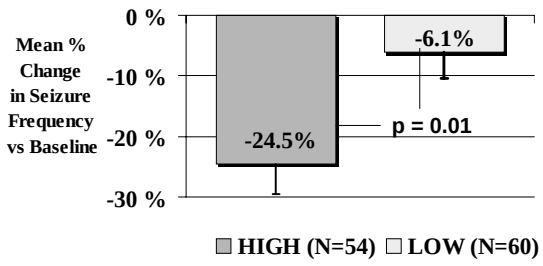
- fMRI during VNS showed changes in blood oxygenation levels reflecting changes in neuronal activity

Epilepsia, 40(7): 181-182, 1999, Morris et al.;
M. George (In Press)

Summary of VNS Clinical Studies

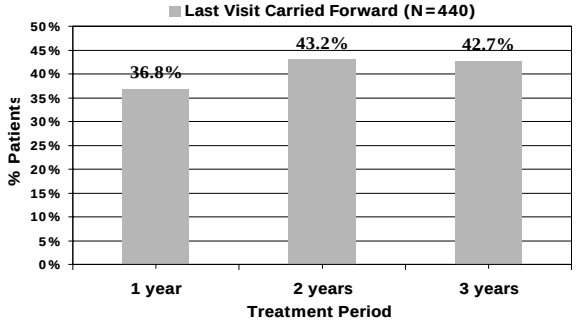
- 1988 Pilot Study (Penry, Wilder, Ramsay, Uthman, Slater)
- 1990-6 2 RCT and 3 open label studies (N=454)
- 1994 EC Approval
- 1997 FDA Approval
- 2100 12,000+ Patients

VNS Study E03: Efficacy Results



Neurology, 45: 224-230, 1995, Salinsky et al.

VNS Long-Term: % of Patients with ≥50% Seizure Reduction (EO1-E05)



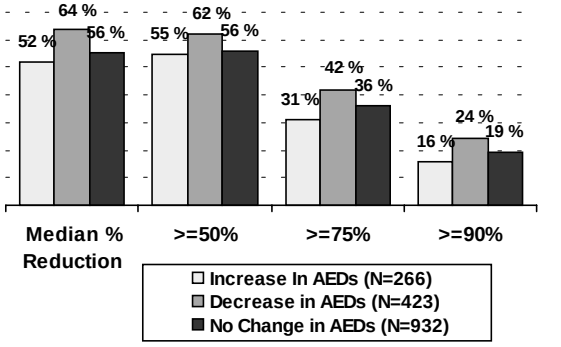
Neurology, 53(7): p. 1731-1735, 1999, Morris et al.

Long-Term Responder Rates for New AEDs and VNS

	N	% Responders	Years Follow-up
Gabapentin	309	38	2
Lamotrigine	178	30	2
Topiramate	292	39	0.5
Zonisamide	120	42	0.5
VNS	188	43	2

Epilepsia, 41(10): 1439-1445; 1999, Wong et al.

VNS Seizure Reduction at 12 Months
Grouping Patients by AED Status



VNS (PADS Group)

- Prospective, N = 151
- Avg. Age 31.4, Duration 23 yrs, 78 M / 73 F
- > 50% Reduction in 50% with Partial Sz.
- Global Evaluations Better / Much Better in 64%
- "VNS is effective in partial and generalized seizure types. Results are similar or slightly better than clinical trials."

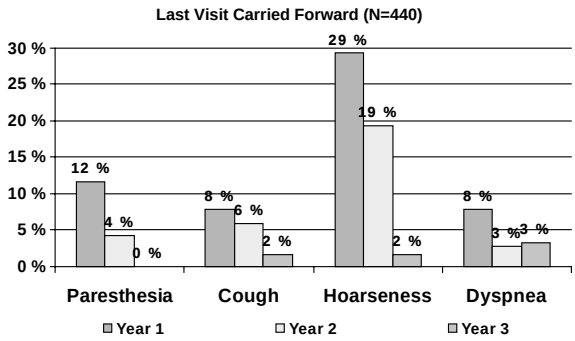
Epilepsia, 40(7): 142, AES 1999, Morris et al.

VNS in Younger Patients

- 38 children (ages 11 months-16 years)
  - 29 <12 years old, followed average of 9 months
- 63% had >50% seizure reduction
  - 26% had >90% seizure reduction
- Atonic seizures reduced by 76%
- Absence seizures reduced by 63%
- Complex partial seizures reduced by 44%
- GTC seizures reduced by 42%
- QOL improved in 86% of patients

Accepted for publication, Neurosurgery, December 2000, Patwardhan, Bebin et al.

VNS Long-Term: Adverse Events (EO1-E05)



Neurology, 53(7): p. 1731-1735, 1999, Morris et al.

Place of VNS in Epilepsy Treatment

- Broad spectrum antiepileptic therapy which appears effective in all age groups
- In refractory patients after use of 2-3 AEDs
- If epilepsy surgery is not possible
- Before callosotomy?

EARLY IDENTIFICATION OF REFRACTORY EPILEPSY

Patrick Kwan and Martin J Brodie

Epilepsy Unit, University Department of Medicine & Therapeutics

Western Infirmary, Glasgow, Scotland

New England Journal of Medicine 2000; 342: 314-319

NEWLY DIAGNOSED EPILEPSY

Results

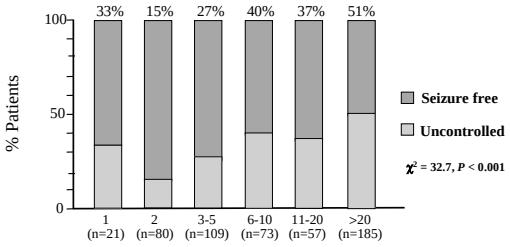
525 patients

333 (63%) seizure free

192 (37%) uncontrolled

No difference with age, sex, FH, febrile convulsions, EEG

OUTCOME IN PATIENTS WITH DIFFERENT PRE-TREATMENT SEIZURE NUMBERS



Number of pretreatment seizures

Figure on top of bar represents percentage uncontrolled

NEWLY DIAGNOSED EPILEPSY

Syndrome classification

	n	Seizure free
Idiopathic	140	74% *
Symptomatic	150	57%
Cryptogenic	235	62%

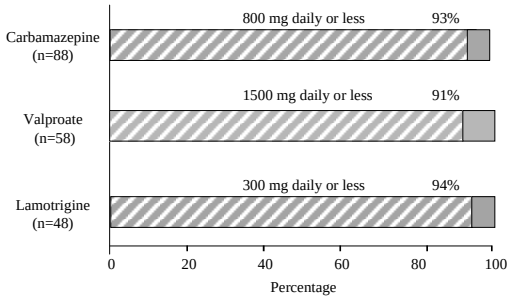
*p=0.004; idiopathic versus symptomatic + cryptogenic

NEWLY DIAGNOSED EPILEPSY

Seizure freedom for at least one year

First drug monotherapy	47%
Second drug monotherapy	13%
Third drug monotherapy	1%
Duotherapy	3%
Total seizure free	64%

DOSE OF FIRST ANTIEPILEPTIC DRUG RESULTING IN SEIZURE FREEDOM



OUTCOME AFTER FAILURE ON FIRST ANTIEPILEPTIC DRUG

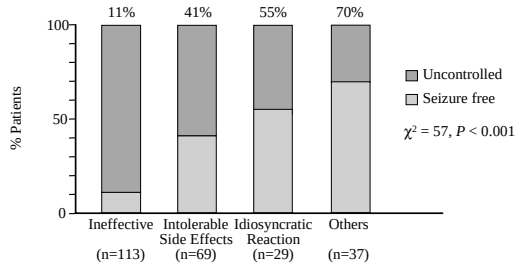


Figure on top of bar represents percentage seizure free

NEWLY DIAGNOSED EPILEPSY

Two populations

Responsive to monotherapy ~ 60%

Difficult-to-treat de novo ~ 40%

Kwan P and Brodie MJ, N Engl J Med 2000; 342: 314-9

RATIONAL MANAGEMENT

A staged approach

If the patient's seizures are not controlled on the first two drugs as monotherapy or on the initial choice and first combination, consider work up for epilepsy surgery if there is an operable structural abnormality

RATIONAL MANAGEMENT

Conclusion

A staged approach to the pharmacological management, and, when appropriate, surgical workup of each epilepsy syndrome will optimise the chance of perfect seizure control and help more patients achieve a fulfilling life

University of Tampere
Medical School

Tampere University Hospital
Pediatric Neurology Unit

Evidence Based Treatment of Newly Diagnosed Epilepsy in Childhood

= after infancy and before puberty …

Kai Eriksson, MD PhD

Evidence Based Treatment of Newly Diagnosed Epilepsy in Childhood

"Syndromic" approach…

1. Idiopathic Focal Epilepsies
2. Non-idiopathic Focal Epilepsies
3. ~~Idiopathic Generalized Epilepsies~~
4. Symptomatic Epilepsies with Multiple Seizure Types

Kai Eriksson, MD PhD

1. Idiopathic Focal Epilepsies

- Benign Childhood Epilepsy with Centrotemporal Spikes (BECT, 'Rolandic')
- Early Onset Benign Childhood Occipital Epilepsy (Panayiotopoulos type)
- Late Onset Childhood Occipital Epilepsy (Gastaut type)

Kai Eriksson, MD PhD

BECT, 'Rolandic Epilepsy'

- age at onset 9.9 years (3-13 y.); AD inheritance?
- 8-24% of childhood epilepsies
- spikes over centro/midtemporal region(s), normal backgr.
- oropharyngeal/facial sz's: drooling, tonic contraction of jaw, unilateral paresthesia of tongue, lips and cheek, speech arrest, nocturnal 2° generalization into T-C sz's
- spontaneous remission by the age of 15-16 years

Evidence Based Treatment (EBT):
1) efficient as monotherapy: CBZ, PB, PHT, STM, VPA [**B,C**] (Verrotti et al 2002, Rating et al 2000, Lerman 1998), GBP [**C**](Bourgeois et al 1999) LTG [**C**] (Barron et al 2000)
2) duration of treatment: only one year [**C**] (Braathen et al 1996)
3) necessary only in 1/3 of patients [**C**,**D**] (Peters et al 2001,Loiseau et al 1989)

Kai Eriksson, MD PhD

Early Onset Benign Childhood Occipital Epilepsy
(Panayiotopoulos type)

- age 1-12 years, mean 5 y., 'common', underdiagnosed ?
- high occipital spikes/sharp SW continuously when eyes closed
- autonomic/behavioural signs, vomiting, deviation of eyes, *no visual sympt*., 2° gener T-C sz's
- *sz frequency very low* (1-3 sz's), progn. good: remission in 1-2 y.

EBT:
1) no difference in effic. as monoth.: CBZ,VPA,PB vs. no treatment [**C**](Ferrie et al 1997)
2) duration: 1-2 years [**D**] (Caraballo et al 2000)

Late Onset Idiopathic Childhood Occipital Epilepsy
(Gastaut type)

- age 3-16 years, mean 8 y., rare, <1% of childhood epilepsies
- interictal EEG as in 'Early Onset' type, ictal different
- elementary *visual hallucinations, and/or blindness*, ocular pain, eye deviation, eyelid fluttering, 2° gen
- *sz's frequent*, diurnal, generaliz. rare, prognosis variable

EBT:
1) CBZ monotherapy [**C**] (Tsai et al 2001, Panayiotopoulos 1999)
2) duration: 2-3 years [**D**] (Panayiotopoulos 1999)

Kai Eriksson, MD PhD

2. Non-idiopathic Focal Epilepsies

- variable etiologies
  - 'cryptogenic' = probably symptomatic
  - 'truly symptomatic', e.g. cortical dysplasia, perinatal asphyxia, CNS infection, tumour, trauma, leukodystrofies, vascular insults
- variable localization
  - temporal, frontal, occipital, parietal

EBT:
1) 'old' AEDs – no difference in efficacy: CBZ, OXC, VPA, PHT, PB [**A,B**] (Marson et al 2001, Guerreiro et al 1997, de Silva et al 1996)
2) 'new' AEDs: TPM [**B**] (Gilliam et al 1999), LTG [**C**] (Barron et al 2000), VGB [**C**] (Zamponi et al 1999)

Kai Eriksson, MD PhD

3. (Often) Symptomatic Epilepsies with Multiple Seizure Types

- Lennox-Gastaut Syndrome
- Landau-Kleffner Syndrome
- Epilepsy with Continuous Spike-Waves during Slow Wave Sleep (CSWS)

Kai Eriksson, MD PhD

Lennox-Gastaut Syndrome

- age 1-8 years (peak 3–5 y.), pre-existing brain damage/ cortical dysplasia/tuberous sclerosis:70%, 'cryptogenic':30%
- <10% of childhood epilepsies
- slow spike-waves (~2 Hz), multifocal abnormalities and abnormal background act., bursts of fast rhythms (~10 Hz)
- myoclonic, atonic/astatic, tonic (nocturnal), and atypical absence seizures
- treatment often difficult and discouraging, MR as a rule

EBT:
1) TPM, LTG, FBM [**A,B**] (Glauser et al 2000, Motte et al 1997, Jensen 1994)
2) VPA, BZD, VGB [**C,D**] (Friis 1998, Feucht et al 1994)
3) epilepsy surgery: callosotomy('drop attacs') [**D**] (Gates 1993)

Kai Eriksson, MD PhD

Landau-Kleffner Sndr / CSWS

- age 4-14 years, age at onset 3-8 years
- <2% (~0,5%?) of childhood epilepsies
- bilateral symmetrical/asymmetrical multifocal spikes and SW in temporal and parieto-occipital regions, sleep enhances spiking up to CSWS (85% of slow wave sleep)
- verbal auditory agnosia→acquired aphasia→behavioural and psychiatric problems
- sz's present in 70-80%: atypical absences, myoclonic sz, focal sz's w/ 2° generalization, variable prognosis

1) VPA, ETM, BZD [**B,C**], STM [**C**], FBM [**D**] (Marescaux et al 1990, Glauser et al 1995, Doose et a. 1998)
2) corticosteroids [**C**] (Lerman et al 1991, Tsuru et al 2000),
3) iv. immunoglobulins [**C,D**] (Lagae 1998, Mikati et al 2000)
4) epilepsy surgery: MST(multiple subpial transections) [**C,D**] (Morrell et al 1995, Irwin et al 2001)

Kai Eriksson, MD PhD

Conclusions 1

- BECT, 'Rolandic'
  - treatment not necessary in all patients
  - many AEDs equally efficient
  - duration of treatment only 1 year ?
- Benign/Idiopathic Occipital Epilepsies
  - treatment according to syndrome diagnosis
- Non-idiopathic Focal Epilepsies
  - no difference in efficacy of old AEDs, trials on new AEDs lacking – treatment choice should be based individual level on safety, tolerability, expense and long term side-effects

Kai Eriksson, MD PhD

Conclusions 2

- Lennox-Gastaut Syndrome
  - RCTs favour novel AEDs: FBM, LTG, TPM – but fear of serious side-effects and tolerability limit their use
  - ➡conventional AEDs (VPA, BZD) usually the first line treatment
  - palliative surgery (callosotomy) sometimes efficient
- Landau-Kleffner Syndrome / CSWS
  - VPA and/or ETM and/or BZD first line treatment
  - corticosteroids second line
  - surgery (MST) efficient in some cases

Kai Eriksson, MD PhD

Conclusions 3

- lack of randomized controlled trials in pediatric patient populations
- evidence based treatment of … *what ?*
  ? seizures or *epilepsy…* or *the patient ?*
- ➡new goals ? for EBT
  long term outcome, neurological development, quality of life
- syndromic approach facilitates rational treatment choices – evidence based or not

Kai Eriksson, MD PhD

REFRACTORY EPILEPSY: IDEAL CHARACTERISTICS

- High responder rate
- High seizure free rate
- Well tolerated as adjunctive Rx
- Ability to convert to monoRx
- No development of tolerance

OUTCOME AFTER FAILURE ON FIRST AED

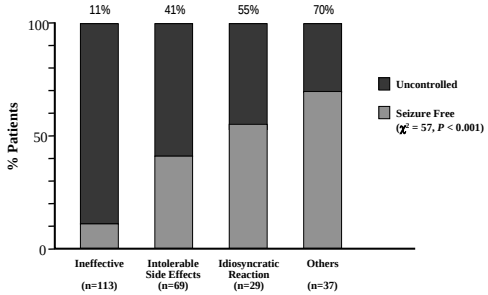
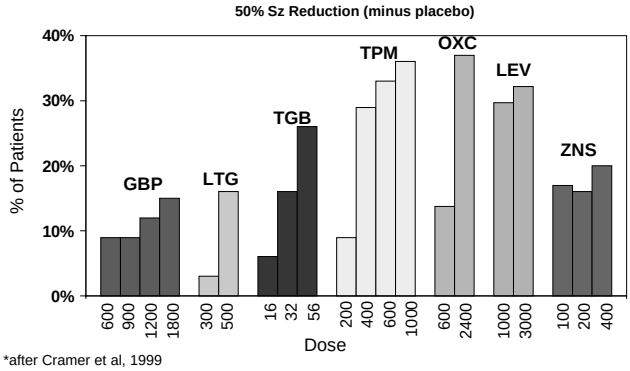


Figure on top of bar represents percentage seizure free.

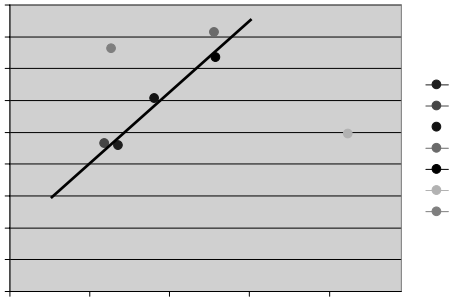
Kwan and Brodie, NEJM 2000

EFFICACY OF NEW AEDS IN REFRACTORY PATIENTS



*after Cramer et al, 1999

ODDS RATIO OF RESPONSE VS. WITHDRAWAL



Marson et al., 1997
Data on file, UCB

DOSE-RELATED CNS SIDE EFFECTS: NEW AEDS (RATE MINUS PLACEBO)

# AED/ PCB	GPN 543/378	LTG 711/419	TGB 404/275	OXC 171/139	TPM 200400 113/174	LEV 769/439	ZNS 269/230
DIZZINESS	**10**	**25**	**12**	**20**	**14**	**5**	**6**
ATAXIA	**7**	**16**	**2**	**9**	**14**	**2**	**5**
SPEECH/ LANGUAGE				**2**	**19**		**3**
DIPLOPIA	**4**	**21**		**16**	**8**	**1**	
HEADACHE		**10**		**12**		**1**	**2**
PARESTHESIA					**12**	**1**	**3**
TREMOR	**4**		**6**	**2**	**5**		
INCOORDI NATION		**4**		**9**		**2**	**5**
BLURRED VISION	**11**						

After Cramer et al,1999

PSYCHOLOGICAL SIDE EFFECTS: NEW AEDS (RATE MINUS PLACEBO)

# AED/ PCB	GPN 543/378	LTG 711/419	TGB 404/275	OXC 171/139	TPM 200400 113/174	LEV 769/439	ZNS 269/230
ASTHENIA			**6**		**7**	**6**	**6**
SOMNOLENCE	**10**	**7**	**3**	**12**	**20**	**7**	**10**
FATIGUE	**6**			**4**			**2**
PSYCHOMOTOR SLOWING					**15**		
NERVOUS			**7**	**1**	**8**	**2**	**2**
CONC DIFF			**4**	**1**	**7**		**3**
MEMORY DIFF					**9**		**4**
CONFUSION			**2**		**5**	**2**	**3**

After Cramer et al, 1999

GENERAL SIDE EFFECTS: NEW AEDS (RATE MINUS PLACEBO)

# AED/ PCB	GPN 543/378	LTG 711/419	TGB 404/275	OXC 171/139	TPM 200400 113/174	LEV 769/439	ZNS 269/230
VISION ABNORMAL				**12**	**11**		
RASH		**5**	**1**				**1**
NAUSEA		**9**	**2**	**14**			**3**
VOMITING		**5**	**3**	**19**	**6**		
DYSPEPSIA		**3**		**2**	**3**		**2**
DIARRHEA		**2**	**4**				**3**
CONSTIPATION				**3**	**4**		**1**
INSOMNIA		**4**					**3**
ANOREXIA/ WEIGHT LOSS					**5**	**1**	**7**

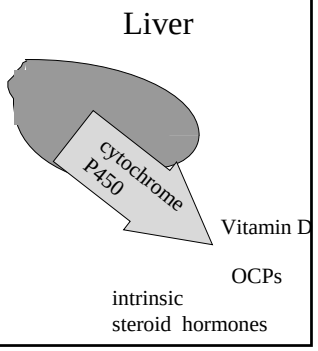
After Cramer et al, 1999

NEW AEDS:SPECTRUM OF ACTIVITY

	PARTIAL	LENNOX-GASTAUT	JME	ABSENCE
ZNS	+	?	?+	?
GBP	+			
LTG	+	+	?	?+
OXC	+			
TPM	+	+	?+	?
LEV	+	?	?+	?+
TGB	+			

WOMEN OF CHILDBEARING AGE

- New AEDs do not induce/inhibit hepatic metabolism
  - No interaction with OCP's
  - No polycystic ovary concern
  - No alteration in vitamin D/K metabolism
  - No alteration in testosterone/estrogen metabolism



Evidence-based treatment of newly diagnosed infantile epilepsy

Eija Gaily, MD
Hospital for Children and Adolescents, Helsinki

Level of evidence: C**ode**. Level

A. Strong research-based evidence
B. Moderate research-based evidence
C. Limited research-based evidence
D. No scientific evidence

www.ebm-guidelines.com

Natural history of infantile spasms not treated with ACTH

- Spontaneous remission rates: 2% at 1-2 mo, 5% at 3 mo, 11% at 6-7 mo, 14-18% at 8-10 mo (Hrachovy et al. 1991)
- Spasm-free at 12 mo: 10-25% (Jeavons and Bower 1961, Hrachovy et al. 1991)
- Normal or nearly normal development after age 12 months: 0-9% (Jeavons and Bower 1961&1964, Hrachovy et al. 1991)
- Cryptogenic and symptomatic cases included

ACTH is effective against infantile spasms (B)

- Large (>100 infants) clinic-based cohort studies (Riikonen 1982, Lombroso 1983)
- Randomized controlled study (RCT) comparing ACTH and vigabatrin (Vigevano et al. 1997)
- RCTs comparing ACTH and prednisone (Baram et al. 1996, Hrachovy et al. 1983)
- RCTs comparing low and high dose ACTH (Hrachovy et al. 1994, Yanagaki et al. 1999)
- RCT comparing ACTH and nitrazepam (Dreifuss et al. 1986)

ACTH & IS: Large cohort studies

- Riikonen 1982
  - 151 pts (majority newly-diagnosed) on 20-40 or 120-160 IU/d long-acting ACTH for 3 wks → spasms stopped in 60% → 32% relapsed
  - Normal or nearly nl development in 24% of all pts, 72% of 25 pts with idiopathic etiology (age> 3yrs)
- Lombroso 1983
  - 128 pts (minority newly-diagnosed) on natural ACTH 110 U/m^2/d 3 wks → spasms stopped in 48% → ?relapsed
  - Normal development at 6 yrs in 55% of 73 ACTH-treated pts with cryptogenic etiology

RCTs looking at ACTH in IS

- RCT comparing ACTH and vigabatrin (Vigevano et al. 1997): 42 pts, long-acting ("Depot") ACTH 10 U/d vs. VGB 100-150 mg/kg/d. **Response ACTH 78%, VGB 48%**
- RCTs comparing ACTH and prednisone (Baram et al. 1996, Hrachovy et al. 1983): 29+24 pts, natural ACTH 150 U/m^2/d - (20-30) U/d vs. prednison 2 mg/kg/d. **Response ACTH 87-42%, prednison 29-33%**
- RCTs comparing low and high dose ACTH (Hrachovy et al. 1994, Yanagaki et al. 1999): 50+26 pts, high= 150 U/m^2/d natural or 1Ukg/d synthetic, low=20-30 U/d or 0.2 U/kg/d. **Response high dose 50-87%, low dose 58-75%**
- RCT comparing ACTH and nitrazepam (Dreifuss et al. 1986): 52 pts, natural (?) ACTH 40 U/d vs. NZP 0.2-0.4 mg/kg/d. 75-100%. **Response (**75-100% spasm reduction) **ACTH 50%, NZP 52%**

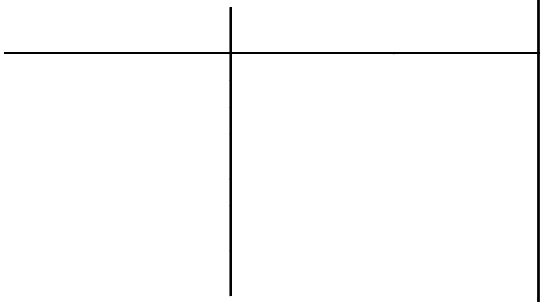
Vigabatrin is effective against infantile spasms (B)

- **Population-based** study of VGB as first drug (Granström et al. 1999)
  - 10 C, 32 S etiology, VGB 40-150 mg/kg/day for 9-15 days
  - 11/42 (26%) total cessation of spasms (video-EEG confirmed) (5 C, 6 S), one relapse (9%)
- **Large retrospective** study on VGB as first drug (Aicardi et al. 1996)
  - 62 C, 130 S, mean dose 99 mg/kg/d
  - 68% sz-free within 7 d, 21% of responders relapsed within 4 mo (no video-EEG).
- RCT comparing vigabatrin and placebo (Appleton et al. 1999)
- RCT comparing low and high dose of VGB (Elterman et al. 2001)
- RCT comparing VGB and ACTH (Vigevano and Cilio 1997)
- RCT comparing VGB and hydrocortisone (Chiron et al. 1997)

RCTs looking at vigabatrin in IS

- Appleton et al. 1999
  - 40 patients, VGB 50-150 mg/kg/day vs placebo for 5 d
  - spasm-free 7 pts **(35%)** (5 C) VGB vs. 2 pts placebo, p=0.06
- Elterman et al. 2001
  - 142 patients, VGB 18-36 vs 100-148 mg/kg/day for 14 days
  - Spasm-free 8/75 (11%) on low dose, 24/67 **(36%)** on high dose, p < .001 (video-EEG-confirmed)
- Vigevano & Cilio 1997
  - 42 pts, long-acting ("Depot") ACTH 10 U/d vs. VGB 100-150 mg/kg/d, spasm free VGB **48%**, ACTH 78%
- Chiron et al. 1997
  - 22 pts with tuberous sclerosis, VGB 150 mg/kg/d vs. hydrocortisone 15 mg/kg/d. Spasm free VGB **100%**, hc 45%

ACTH or vigabatrin for IS?



First treatment of idiopathic and cryptogenic infantile spasms

If vigabatrin:

- dose 100-150 mg/kg/day, short course (3 mo??)
- evaluation of visual fields at each neuro-exam

If ACTH:

- natural ACTH 3-6 U/kg for 2-4 wks, slow tapering and cortisol substitution until ACTH test returns to normal
- careful monitoring and early treatment of cardiovascular SE and infections

Switch if first choice fails

Proposed treatment of symptomatic IS

- Start with vigabatrin (VGB) up to 150 mg/kg/day
- If spasms continue after 2-3 wks of VGB, give ACTH 6-12 U/kg/d for 4 wks (→taper and cortisol substitution), continue VGB through ACTH
- Always document clinical response with video-EEG Gaily et al. Dev Med Child Neurol 2001; 43: 658-667
- Continue VGB after VGB or ACTH response for at least one year to prevent recurrences and other seizures
- Evaluate visual fields as well as possible at each neurological examination

50% of infants with symptomatic IS were spasm-free and 45% seizure-free at age 1-2 yrs with this protocol in a *population-based* study Granström et al. Epilepsia 1999;40; 950-957

Treatment of severe myoclonic epilepsy of infancy

- **Stiripentol** combined with valproate & clobazam is effective (B), Chiron et al. 2000
  - RCT 41 pts, stiripentol vs. placebo added to a combination of valproate and clobazam for 2 mo
  - >50% sz reduction in 15/21 on stiripentol, 1/20 on placebo
  - efficacy based on increased levels of norclobazam?
- Lamotrigine makes seizures worse (C-D), Guerrini et al. 1998
  - 21 pts 2-18 yrs, open add-on, >50% sz increase in 17/21 (80%)
- Topiramate has some efficacy (C-D), Nieto-Barrera et al. 2000
  - 18 pts 2-22 yrs, open add-on, >50% reduction in 10/18, 3/18 sz-free
- Valproate has some efficacy (D), Hurst 1987

Vagus nerve stimulation in the treatment of epilepsy - Finnish experiences

Jouko Isojärvi
Department of Neurology
University of Oulu
Finland

Vagus nerve stimulation in the treatment of epilepsy - Finnish experiences

- First eight implantations in Helsinki University Hospital in the 1990's
- 14 implantations in Oulu University Hospital 1999-2001
- Three implantations in the Hospital for Children and Adolescents in Helsinki 1999-2001

Vagus nerve stimulation - experiences from Oulu

- Implantation at the Department of Neurosurgery
- Hospitalization usually 2 nights
- General anaesthesia
- The generator's output current is set to 0,25 mA next day following the implantation
- Ramping up of the output current tailored to individual patient response and tolerance
- Visits usually every other week at the Outpatient Department of Neurology

Vagus nerve stimulation - experiences from Oulu

Stimulation parameters

Current (mA)	Up to 3.5
Frequency (Hz)	30
Pulse width (μsec)	500
On time (sec)	30
Off time (min)	5
Manual activation mode	enabled/disabled

VNS- patients from Oulu

No	Sex	Age (y) at implantation (at onset)	Epilepsy type	Etiology	AEDs	Seizures/ month
1	F	30 (5)	Absence TLE	Heterotopia	CBZ ETO GBP VPA	>30
2	M	39 (5)	TLE	HS	LTG TPM	1-2 SGTC ~30 partial
3	M	52 (<7)	TLE	HS	CBZ CLP	~15
4	M	26 (10)	FLE	Bilateral meningioma of the ON	VPA LTG GBP	~40
5	M	32 (<1)	Multifocal	Schizencephaly	VPA LTG GBP	~100
6	M	34 (11)	FLE	CR	VPA LTG GBP	25-30

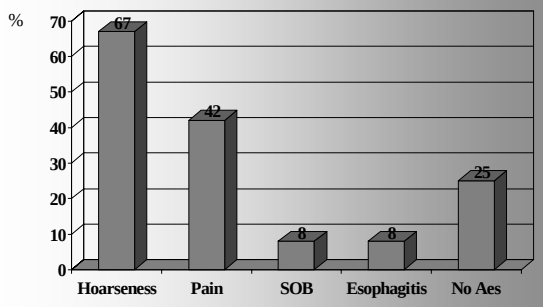
VNS- patients from Oulu

No	Sex	Age (y) at implantation (at onset)	Epilepsy type	Etiology	AEDs	Seizures/ month
7	M	44 (21)	PLE	Hemangioma	OXC LTG GBP	~17
8	M	27 (7)	FLE	CR	CBZ LTG	~100
9	F	38 (<1)	TLE	HS	CBZ TPM	~10
10	F	27 (<1)	FLE	CR	OXC LTG GVG	~100
11	F	44 (11)	FLE	CR	OXC PHT GBP	~100
12	M	21 (3)	Multifocal	CR	OXC PHT GBP	~30

VNS- patients from Oulu
Efficacy

- 12 patients
- 6 patients with seizure calendar
  - 5 responders (seizure decrease > 50 %); decrease in total seizure frequency from 204/month to 39/month (81 %)
  - seizure decrease 30 % in 1 patient
- 6 patients without seizure calendar
  - 3 responders
  - seizure decrease 30 % in 1 patient
  - no change in 2 patients
- Altogether 8/12 (67 %) responders

VNS- patients from Oulu
Adverse events



Vagus nerve stimulation in the treatment of epilepsy
- Finnish treatment guidelines

- Vagus nerve stimulation is an option in the treatment of epilepsy in those drug refractory cases, where resective surgery is not possible.
- The price of the device is high* and its use should be restricted to special cases, and the implantion should be done only after thorough investigations and careful consideration.

*The implantion of a vagus nerve stimulator in the Department of Neurosurgery in Oulu University Hospital costs 16 600 €.

Title: Pharmacogenetics: can we predict and prevent the side effects of AEDs with profiling?

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Characteristics of Type A and Type B ADRs

Characteristic	Type A	Type B
Dose dependency	Yes	No
Predictable	Yes	No
Frequency	Common	Uncommon
Severity	Usually mild	Often severe
Mortality	Rare	Common

Remit of talk

- Detection and prediction of serious, life-threatening, idiosyncratic, adverse drug reactions (Type B) – rather than predictable, usually mild dose dependent adverse effects (Type A)
- Taken as starting point, a prior population risk of a life threatening Type B ADR as 1 in 200 (0.05)
- The question is, will the new genetics allow us to accurately predict a patients risk for developing a serious Type B ADR of this frequency?

Q. What constitutes a good diagnostic test?

A. One that provides certainty as to the presence or absence of disease

Q. Is routine inter-ictal EEG a good diagnostic test for epilepsy?

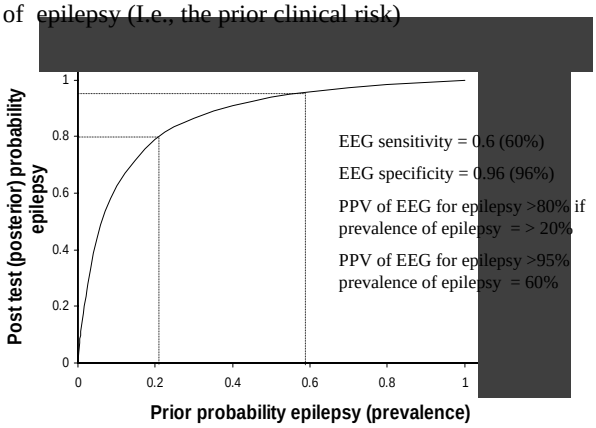
- Epilepsy prevalence is 1 in 200 (0.005)
- Data from Goodin & Aminoff (Lancet 1984)

Significance of epileptiform EEG activity in unselected sample (1000) of the population

	Epileptic	Non-epileptic	
EEG +ve	3	40	43
EEG –ve	2	955	957
	5	995	1000

Sensitivity = prob +ve EEG in people with epilepsy = 3/5 = 0.6
Specificity = prob –ve EEG in people without epilepsy = 955/995 = 0.96
Positive predictive value (PPV) of EEG for epilepsy (I.e., the proportion of patients with a +ve EEG who have epilepsy) = 3/43 = 0.06!!
I.e., in an unselected population (epilepsy prevalence 0.05), of people with a +ve EEG, only 6% will have epilepsy

Significance of +ve EEG depends on population prevalence of epilepsy (I.e., the prior clinical risk)



Positive predictive value of a test depends on:

- Test sensitivity
- Test specificity
- Disease prevalence (prior clinical risk)

- For diseases with low prevalence (e.g., Type B ADRs or epilepsy in unselected population), there is a high risk of false positive test results - even for tests with high specificity
- E.g., In an unselected population with epilepsy prevalence 0.05, 94% of +ve EEG results = false positive

Positive predictive value (PPV) of test for susceptibility allele for disease with prevalence 0.005 (1 in 200)

	relative risk conferred by allele					
	2	5	10	50	100	200
Allele frequency	Positive predictive value (%)					
0.1%	0.99	2.49	4.95	23.83	45.49	83.41
0.5%	0.99	2.45	4.78	20.08	33.44	50.11
1%	0.99	2.41	4.58	16.77	25.12	33.44
10%	0.91	1.78	2.63	4.23	4.58	4.78
30%	0.76	1.13	1.35	1.59	1.62	1.64

Proportion of cases of a disease that can be *attributed* to a susceptibility conferring allele

	relative risk conferred by allele			
	2	5	10	20
Allele frequency	Attributable risk (%)			
0.1%	0.10	0.40	0.90	1.90
0.5%	0.50	2.00	4.30	8.70
1%	1.00	3.90	8.30	16.00
10%	4.80	28.60	47.40	65.50
30%	13.0	54.60	73.00	85.1

- E.g., allele with frequency 10% and relative risk 10, would account for 47% of all cases of disease (e.g., Type B ADR)
- But, PPV for that allele = 2.63% (for ADR prevalence 0.005)

Summary: In what circumstances will genetic tests be useful?

- Depends on the population prevalence of the ADR - most Type B ADRs are uncommon (1 in 200)
- For such uncommon, but serious Type B ADRS, tests will not have clinically useful PPV unless determined by rare alleles (< 0.01) that confer high relative risk (>50)
- Common alleles with low relative risk may account for a sizable proportion of Type B ADRs, but will have little clinical utility (PPV will be low and false positive test results high)

Exception!

- If common alleles, each conferring low relative risk, come together in rare combinations which confer high relative risk

Can we predict and prevent the side effects of AEDs with profiling?

1. Low population prevalence of serious Type B ADRs means the potential for high false positive test results even for tests with high specificity
2. Tests will only have clinical utility for rare genotypes (single alleles or rare combinations of more common alleles) with high relative risk

History and surgical outcome of drug-refractory patients with TLE

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Contents

- Introduction
- Surgical treatment of TLE in adult patients at Kuopio University Hospital, 1988-1999
  - Preoperative evaluation
  - Outcome with respect to seizures
  - Prognostic factors for the outcome
  - Complications and mortality
- Conclusions

Surgical outcome with respect to seizures

- Between 1963-2001 33-93% of operated TLE patients have become seizure-free
  - 1991-2000 median 70%
- 90% of patients benefit from surgery
- Comparable outcomes can also be expected in elderly patients
- Outcome at one or at two years postoperatively is highly prognostic for the long-term outcome

Prognostic factors for the outcome

- Selected patient populations have significantly higher success rates with 80-96% of patients becoming seizure-free
  - patients with hippocampal atrophy
  - patients with complex febrile seizures
  - patients with foreign tissue lesions
- Only 16-56% of patients with normal MR imaging become seizure-free

Surgical treatment or medical therapy?

- Most of the surgical outcome data derive from series of individual centres
- Quality of life and psychosocial outcomes have failed to demonstrate a consistent superiority of surgery
- A randomised, controlled trial of surgery (Wiebe et al., 2001) → Surgery is superior to prolonged medical therapy

Aims of the study

1) To analyse the long-term results of TLE surgery in a national epilepsy surgery centre for adults

2) To evaluate the preoperative factors that best predict good postoperative outcome in long-term follow-up.

Patients

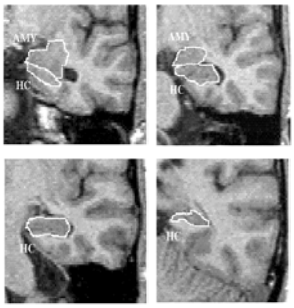
- 140 adult patients with drug-refractory TLE
- 67 females, 73 males
- Operated on between 1988-1999
- Selected to outcome analyses based on the presurgical assessment and type of operation

Preoperative evaluation

- Magnetic resonance imaging (n=140)
- Ictal video-EEG monitoring (n=136)
  - scalp and sphenoidal electrodes (n=136)
  - subdural strip-electrodes (n=50)
- Neuropsychologic evaluation (n=135)
- Psychiatric evaluation (n=118)
- WADA (n=140)

Magnetic resonance imaging (MRI)

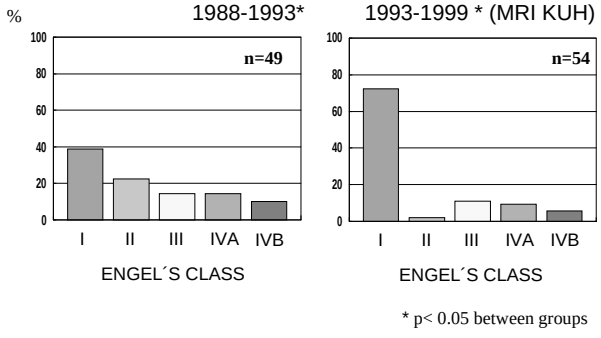
- At Kuopio University Hospital since 1993
- 1.5 T imager
- MP-RAGE: TR 10 ms, TE 4 ms TI 250 ms, flip angle 12°, FOV 250, matrix 256 x 192
- HC and AM volumes available for 67 patients



Engel´s classification (Engel, 1993)

- **Class I: Seizure-free**
  - IA Completely seizure-free (ILAE 1)
  - IB Only postoperative auras (ILAE 2)
- **Class II: Rare seizures**
  - fewer than 3 seizures per year (ILAE 3)
- **Class III: Worthwhile seizure-reduction**
  - at least 80% seizure reduction
- **Class IV: No worthwhile seizure-reduction**
  - IVA at least 50% seizure reduction

Unilateral TLE - 1 year follow-up



* p< 0.05 between groups

Conclusions

- Surgery is superior to prolonged medical treatment of drug-resistant TLE
- Most TLE patients requiring surgery should be identified already in the early course of their disease
- In Kuopio 76% of patients operated on 1993-1999 because of drug-resistent TLE have reached Engel I-II postoperative outcome in the long term follow-up

Matching the treatment with epileptic syndrome and seizure type

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Analysis of causes of uncontrolled seizures

- Inappropriate AEDs
  - seizure aggravation
- Inadequate drug treament
  - doses, amount of drugs
- Unacceptable side-effects of treatment
  - leading to rational non-compliance
- Seizures unresponsive to treatment options
  - AEDs, surgery,VNS

Analysis of Diagnosis

- Obtain the description of the seizure(s)
- Classify the seizure
- Consider some of the following
  - seizures types
  - age of onset (many epilepsies are age-specific)
  - family history
  - precipitating factors, e.g. photic stimulation
  - EEG evidence of generalized or focal abnormality
  - imaging for evidence of structural lesion or idiopathic epilepsy
  - metabolic abnormality
- Classify the syndrome

Diagnostic features of idiopathic generalized epilepsy

- age of onset-late childhood to early adult life
- seizure type - absence, myoclonus, tonic-clonic
- lack of underlying structural etiology although microscopical/QMRI changes may be present
- specific EEG finding (3 Hz spike and wave/photosensitivity)
- genetic basis and positive family history
- diurnal pattern of seizure occurence (awakening)
- excellent response to ”valproate”-like AEDs

Diagnostic features of partial epilepsy

- age of onset-throughout lifetime
- seizure type – simple/complex partial and/or secondarily generalized tonic-clonic
- underlying structural etiology may be found and MRI should be performed
- focal EEG finding may be present, but interictal EEG may be also normal
- response to ”carbamazepine”-like AEDs

Partial epilepsy

- **first-line treatment ”Na-channel-blocker”**
  - **oxcarbazepine/carbazepine**
  - **lamotrigine**
  - **(valproate)**
- **combination therapy ”GABAergic” /multiple/other mechanims**
  - **tiagabine**
  - **gabapentin**
  - **topiramate**
  - **levetirasetame**
- **experimental**

Generalized epileptic seizures and syndromes

- **first-line**
  - **valproate**
  - **lamotrigine**
  - **topiramate**
- **combination treatment**
  - **valproate + lamotrigine**
  - **valproate + topiramate**
  - **lamotrigine + topiramate**
  - **valproate + lamotrigine + topiramate**
- **newer/experimental drugs**
  - **levetirasetame**

Analysis of seizure aggravation

• **barbiturates**	• **absence, tonic seizures**
• **carbamazepine, oxcarbazepine, phenytoin**	• **absence, myoclonic, atonic, tonic seizures**
• **vigabatrin, tiagabine, gabapentin**	• **absence, myoclonic seizures**
• **lamotrigine**	• **(difficult myoclonic syndromes in infancy)**

Surgical treatment

- **Drug-resistant, focal-onset epilepsy cases should be evaluated for surgical treatment**
- **It takes only 2-3 years to know whether a patient has a drug-resistant epilepsy, one needs not to try all AEDs available**
- **Epilepsy is intractable when patients continue to have recurrent seizures or other symptoms of epileptic syndrome restricting their ability to lead a full and safe life**
- **Patient must also be able to cooperate with pre- and postsurgical procedures**

Individualized choice of treatment according to adverse event profile

- **idiosyncratic reactions**
- **CNS-related adverse effects**
- **endrocrine and hormonal effects**
- **weight increase/decrease**
- **cognitive effects**
- **behavioral adverse effects**

Choice of treatmnet according to the mood and affect profiles of AEDs

- potentiation of GABA leads to sedating, anxiolytic and antimanic effects
  - treatment of agitation and aggression
  - side-effects fatigue cognitive slowing and fatigue
- activating and mood-elevating effect associated with the predominance of glutamate excitatory mechanism of action
  - treatment of depression
  - side-effects hyperactivation, hypeirritability, insomnia

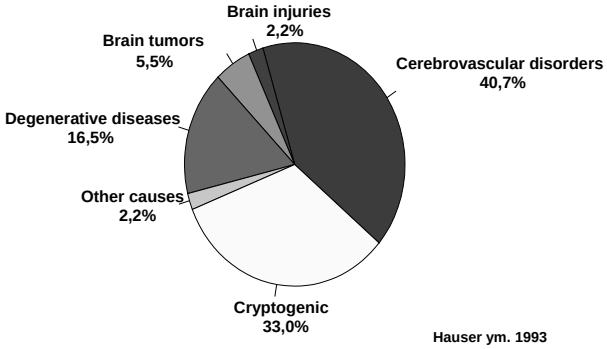
Conclusions

- The treatment needs to be matched to the individual patient and the type of epilepsy
- Treatment options available offer most patients good seizure control without unacceptable side effects and also patients with difficult epilepsy possibility to lead full and safe life
- Many patients still do not seem to be getting the treatments that are most appropriate for them

Epilepsy in the elderly: Special issues

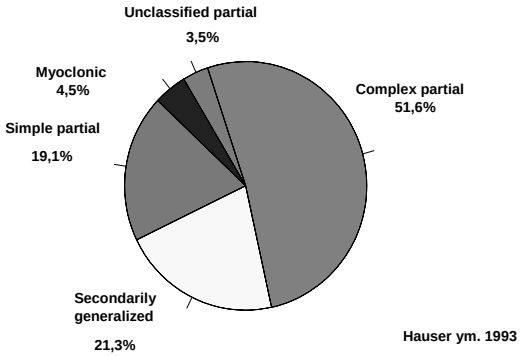
- High incidence and prevalence
- Special problems in differential diagnosis of seizures
- High incidence of seizures associated with acute medical disorders
- Most cases of epilepsy due to a remote symptomatic cause
- Data on the efficacy, tolerability and safety of antiepileptic drugs in elderly is sparse
  - Elderly patients have been generally excluded from clinical trials with AED

Etiology of epilepsy in patients aged over 60 years



Hauser ym. 1993

Seizure types in patients aged over 60 years



Hauser ym. 1993

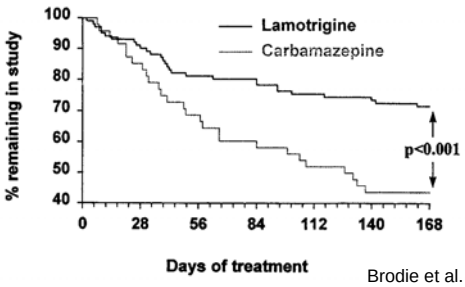
Special issues in the treatment of epilepsy in the elderly

- Age related changes in the pharmacokinetics and -dynamics of antiepileptic drugs (AED)
- Tolerability of AED is poorer than in young adults
- Allergic reactions to AED are more frequent tahn in children and in young adults
- Patients often have other diseases and/or treatments which may interfere with AED
- Special needs for information and motivation of patients and their relatives

Tolerability and safety issues of AED treatment in the elderly

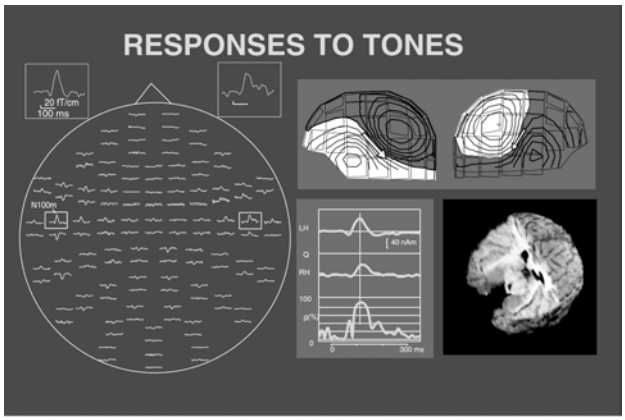
- Adverse effects on the central nervous system, especially on cognitive functions
- Blood disorders
  - leucopenia, aplastic anemia
- Metabolic changes
  - hyponatremia - oxcarbazepine/carbamazepine
  - osteomalacia - phenytoin, carbamazepine
- Cardiac condunction defects
  - carbamazepine, oxcarbazepine, phenytoin

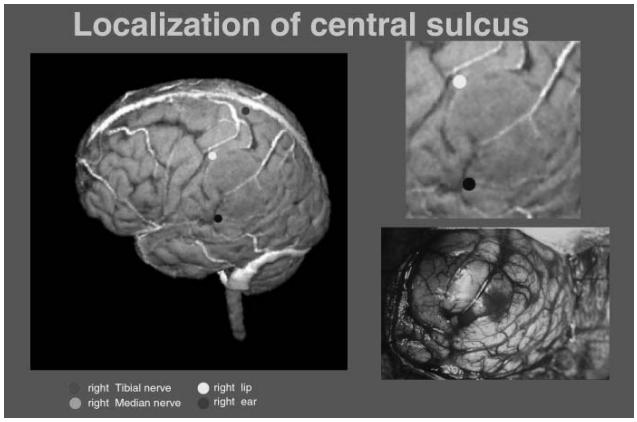
Lamotrigine versus carbamazepine in elderly patients with newly diagnosed epilepsy



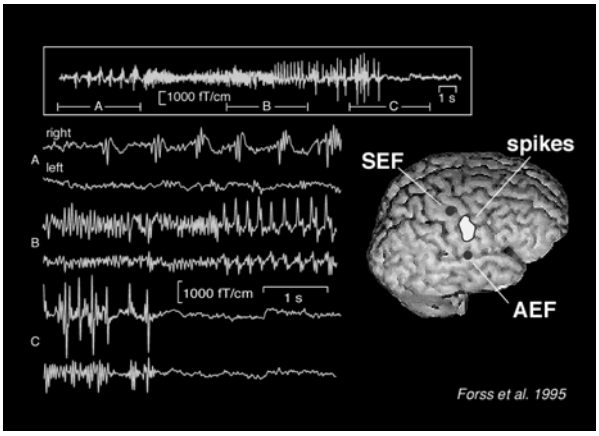
Brodie et al. 1999

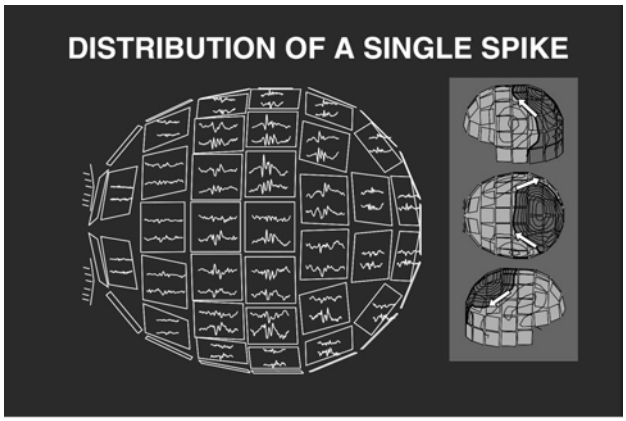
306-channel MEG

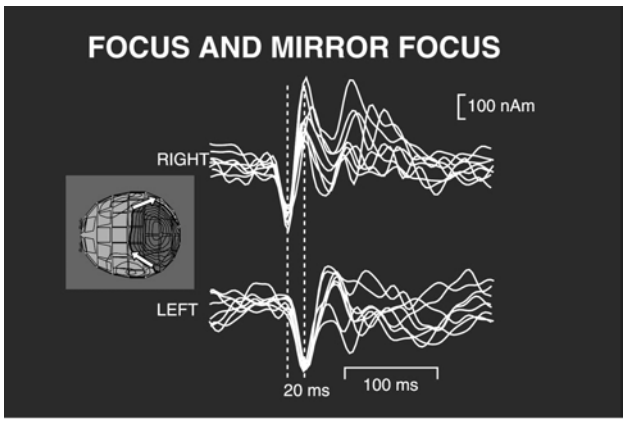


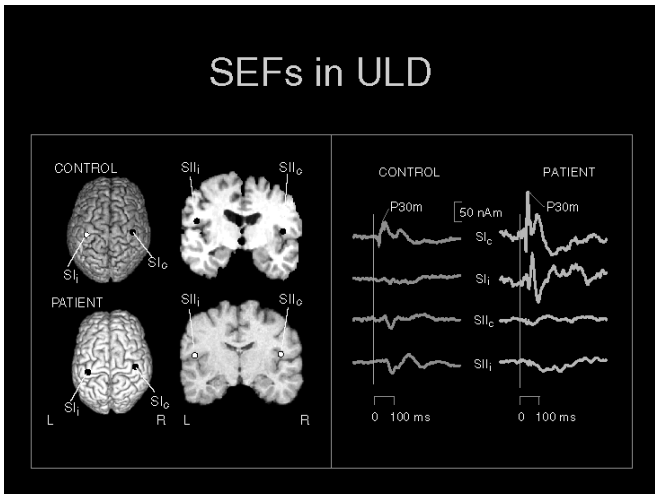


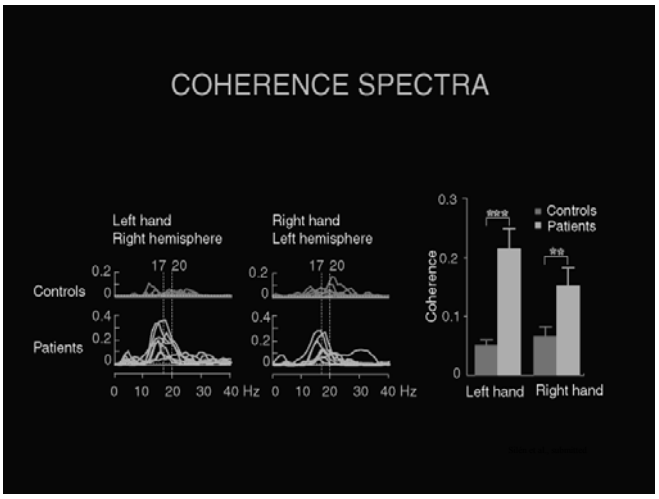
Hemifacial Convulsions

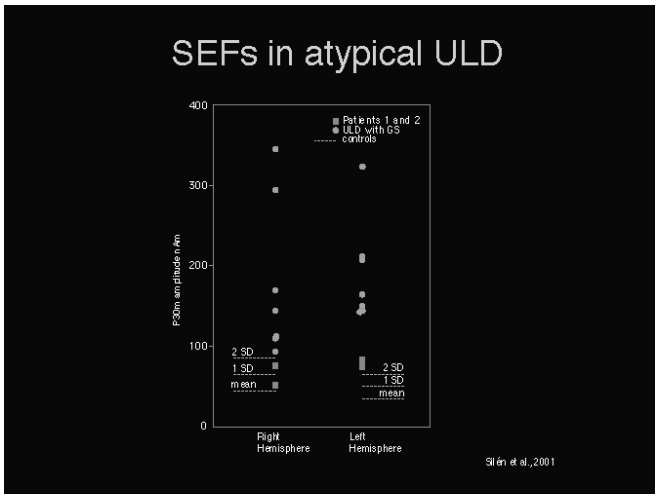












MEG IN EPILEPSY

- Detection of interictal spikes
- Temporal sequence of spike propagation
- Ictal measurements
- Extratemporal epilepsy
- Detection of epileptic activity after lesionectomy or removal of epileptogenic zone
- Epileptic activity deep in the sulci

10

MEG in epilepsy

- Orientation of source currents of interictal spikes tells about origin of spikes in temporal epilepsy?
- Deep activity in temporal lobes detectable by magnetometers?
- Mechanisms of epileptic activity generation: Study of cortical processing in genetically delineated epilepsies?

11

Spectrum of Brain Pathological Lesions Associated With Drug-Refractory Temporal Lobe Epilepsy

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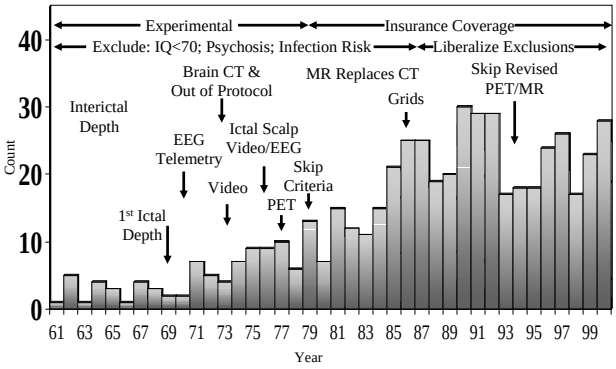
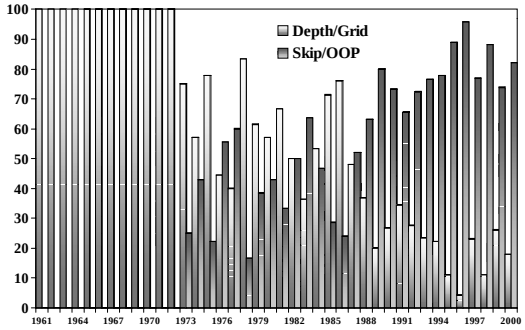
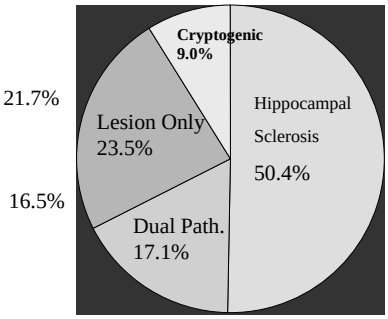
History of Temporal Lobe Surgeries
At UCLA From 1961 to 2000



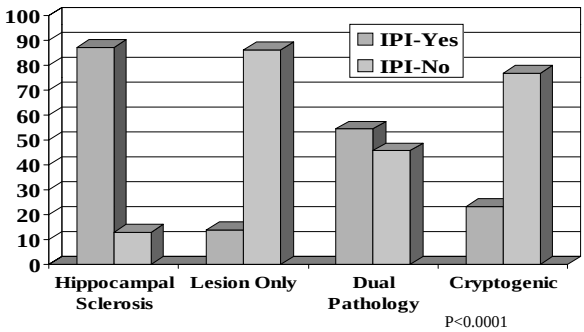
Percentage of UCLA TLE Cases Diagnosed
Using Intracranial Electrodes (Depth/Grid) Compared with
Non-Invasive (Skip/OOP) Criteria From 1961-2000



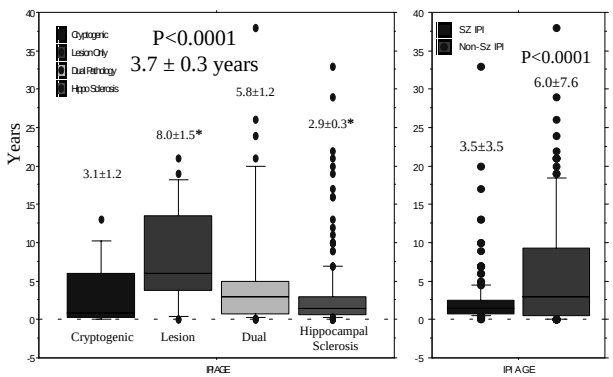
Percent of Temporal Lobe Epilepsy Cases by Pathology at UCLA (n=498)



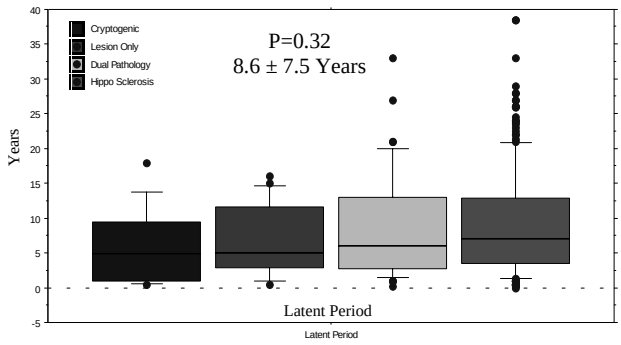
IPI By TLE Clinical-Pathology Syndrome



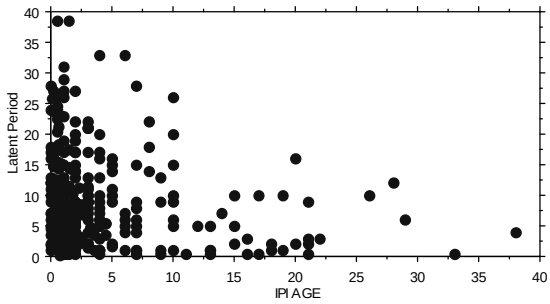
Age at Initial Precipitating Injury Varies
By TLE Clinical-Pathology Category & Etiology



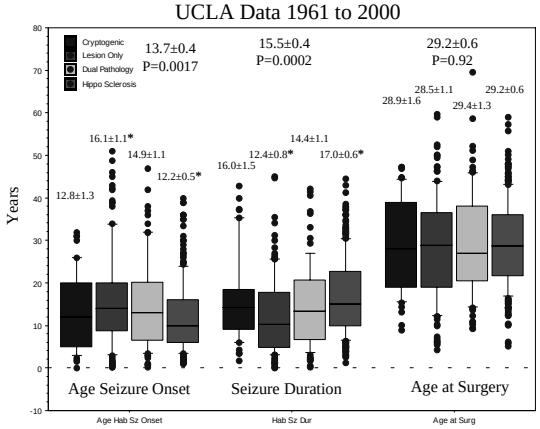
Latent Period In TLE Patients by Clinical-Pathology Category



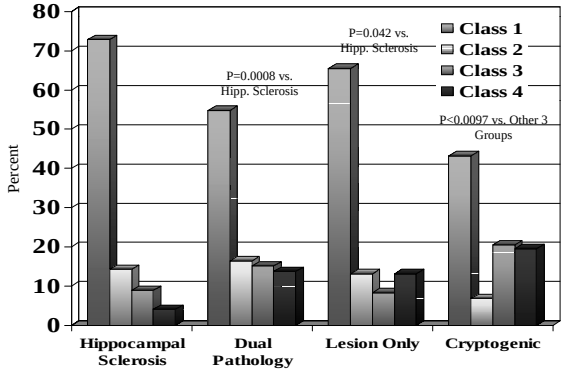
TLE: Relationship Between Latent Period and IPI Age



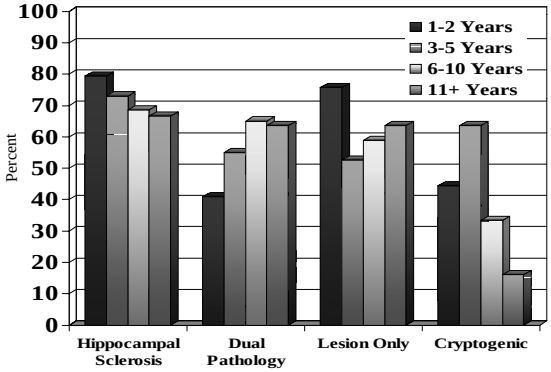
TLE Clinical Variables by Pathological Category UCLA Data 1961 to 2000



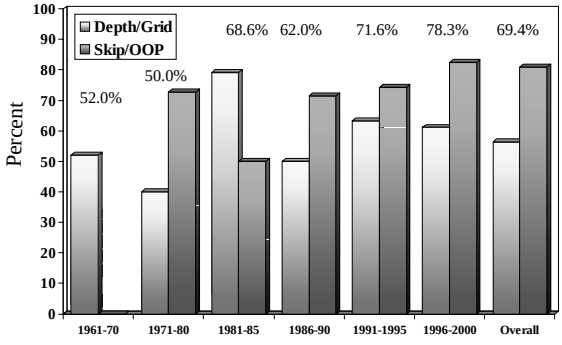
Post-surgery Seizure Control by Pathological Categories in TLE Patients From 1961 to 2000 at UCLA (P<0.0001)



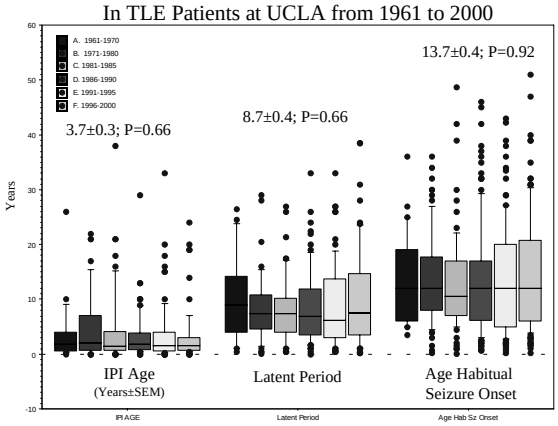
Seizure Free By Pathological Substrate & Duration of Follow-up; TLE Patients From 1961 to 2000 at UCLA



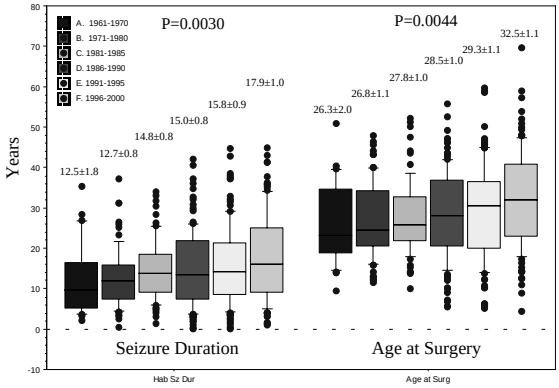
TLE Patients Seizure Free By Diagnostic Procedure From At UCLA 1961 to 2000



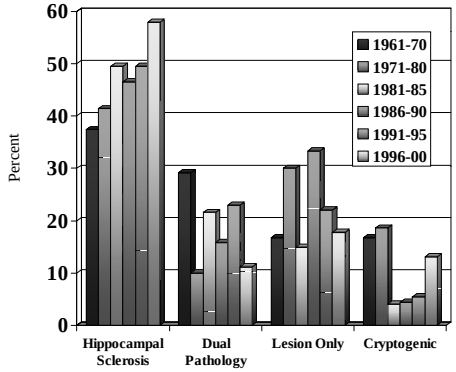
IPI Age, Latent Period, & Age of Seizure Onset Are Unchanged
In TLE Patients at UCLA from 1961 to 2000



Seizure Duration & Age at Surgery Have Increased
In TLE Patients at UCLA from 1961 to 2000



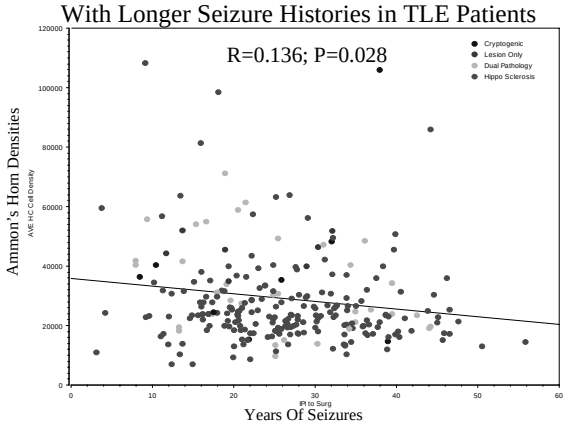
Pathological Substrate in TLE Patients
From 1961 to 2000 at UCLA



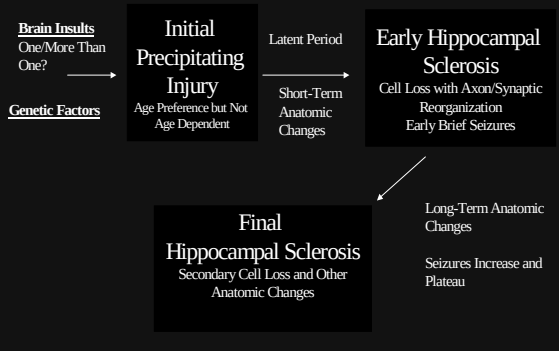
Types of Lesions & Surgical Outcomes in TLE Lesion/Dual Pathology Categories

N=198	Lesion Only	Dual Pathology	% Seizure Free Lesion/Dual	**Overall % Seizure Free**
Mass Lesions (50.0%)	66	33	66.7/60.0	64.5%
Vascular Lesions (12.1%)	16	8	90.9/50.0	76.5%
Atrophic Lesions (18.2%)	12	24	37.5/52.6	48.1%
Cortical Dysplasia (15.6%)	14	17	55.6/50.5	51.8%
Developmental Cysts (4.0%)	6	2	60.0/100	71.4%

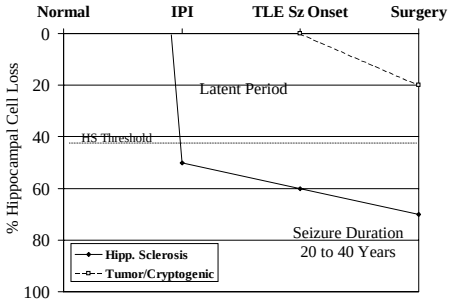
Decreased Hippocampal Neuronal Densities
With Longer Seizure Histories in TLE Patients



Modification of Meyer's Hypothesis: Pathogenesis of Ammon's Horn Sclerosis



Time Line of Hippocampal Damage In TLE



Conclusions

Seizure control depends on identifying a pathological substrate in temporal lobe epilepsy.

The pathological substrate influences the clinical presentation and seizure history.

Hippocampal cell loss and sprouting (i.e. sclerosis) are based on IPI history and duration of seizures.

Despite improvements in identifying pathological substrates and better post-surgery seizure control, patients are seizing longer before surgery.

MOLECULAR BASIS OF EPILEPTOGENESIS IN EXPERIMENTAL MODELS

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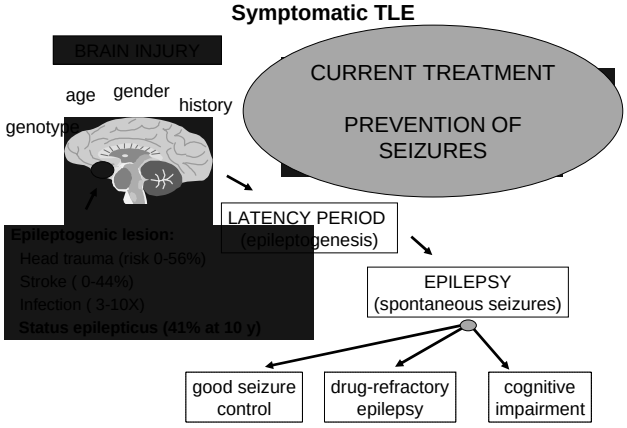
EPILEPTIC PROCESS
Symptomatic TLE



CANDIDATE EPILEPTOGENESIS-RELEATED GENES IN THE HIPPOCAMPUS (Lukasiuk and Pitkänen, 2000)

Gene function
receptors, channels and transporters
signal transduction
transcription factors
energy homeostasis
lipid metabolism
proteinases and their inhibitors
vesicle and synaptic function
antioxidant
cytokines
complement function
polyamine metabolism
Ca^{2+}homeostasis
stabilization of extracellular matrix
unknown function
ESTs (expressed sequence tags)

GENES WITH ALTERED EXPRESSION ON cDNA ARRAY AND PREVIOUSLY LINKED TO SEIZURES OR EPILEPSY

(Lukasiuk and Pitkänen, 2000)

Gene	ratio	species		condition
Ca^{2+}-ATPase	0.51	rat	⇩	after PTZ seizures
Apolipoprotein B	1.72	human	⇩	CSF in epilepsy
Myelencephalon specific protease	1.92	rat	⇧	after KA
Ornithine aminotransferase	1.90	rat		inactivation protects against sz
GADD45	2.02	rat	⇧	after KA
Transthyretin	5.20	human	⇧	CSF in epilepsy

THERAPEUTIC APPROACHES TO PREVENT EPILEPTOGENESIS

1. AEDs
   - no evidence of effect

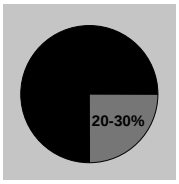
2.Experimental approaches
- NMDA antagonists
- enhancement of noradrenergic neurotransmission
- immunosupressants
- neurotrophins
- enriched environment
- electrical stimulations
- vaccination
- gene therapy

MOLECULAR BASIS OF DRUG-REFRACTORINESS

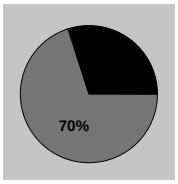
Heidrun Potschka and Wolfgang Löscher

DRUG-REFRACTORY EPILEPSY

EPILEPSY / ALL TYPES



TEMPORAL LOBE EPILEPSY



Regesta et al., Epilepsy Res. 1999

The population of pharmacoresistant epileptic patients is not uniform.

Multiple factors must be involved in drug-refractoriness.

MOLECULAR BASIS OF DRUG-REFRACTORINESS

- **Changes in drug targets?**
- **Changes in local brain uptake of anticonvulsant drugs?**

Impact of

Genetic factors | **Disease associated factors** | **Drug induced factors**

MODULATION OF SODIUM CURRENTS IN THE HIPPOCAMPUS OF EPILEPTIC PATIENTS AND KINDLED RATS BY AEDS

Tissue	AED	Change in modulation	Reference
Human	VPA	-	Vreugdenhill et al., 1998
Kindled rat	VPA	-	Vreugdenhill et al., 1999
Human	CBZ	+ (?)	Reckziegel et al., 1999
Kindled rat	CBZ	+ (transient)	Vreugdenhill et al., 1999

CHANGES IN DRUG TARGETS

...are likely to play a role in individual patients.

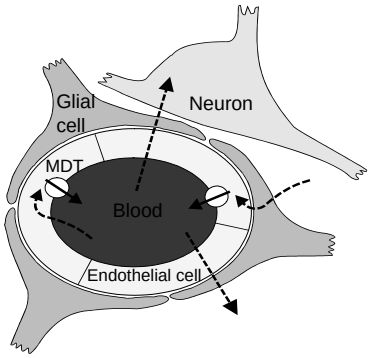
...do not explain drug-refractoriness in the majority of epileptic patients, which are resistant to several AEDs with different mechanisms of action.

ROLE OF MULTIDRUG-TRANSPORTERS ?

- **Mediate transmembrane transport of lipophilic drugs**
- **Expression of different Multidrug-Transporters, at the BBB, BCB, and in brain parenchyma:**
  - **P-glycoprotein (PGP)**
  - **Members of the multidrug-resistance-associated protein (MRP) family**
- **Overexpression in the epileptic focus of pharmaco-resistant epileptic patients**

  (Tishler et al., 1995; Sisodiya et al., 1999 / 2001/2002; Dombrowski et al., 2001)

MULTIDRUG-TRANSPORTERS (MDT) IN THE BBB



Epileptic patient:

Alterations in the epileptic focus rendering the BBB less permeable for AEDS ?

OVEREXPRESSION OF MULTIDRUG-TRANSPORTERS

Human epileptogenic tissue

Transporter	Overexpression in			Reference
	BBB	Glia	Neurons	
P-Glycoprotein (PGP/MDR1)	+	+	?	Tishler et al., 1995 Sisodiya et al., 1999, 2001 and 2002 Dombrowski et al., 2001
MRP1	?	+	+	Sisodiya et al., 2001 and 2002
MRP2	+	?	?	Dombrowski et al., 2001

OVEREXPRESSION OF MULTIDRUG-TRANSPORTERS: SUMMARY

- **Different multidrug transporters are upregulated in human epileptogenic tissue.**
- **Severe, long-lasting seizure activity is sufficient to induce PGP overexpression in mice and rats.** **(Zhang et al., 1999, Rizzi et al., 2001, Seegers et al., unpublished)**
- **Long-term treatment with phenytoin or phenobarbital does not induce PGP expression in rat brain.** **(Seegers et al., unpublished)**

ACTIVE TRANSPORT OF AEDS AT THE BBB OR BCB

Drug	Transporter			Reference
	PGP	MRP	Other	
Valproate	?	+	+	Frey and Löscher,1978 Huai-Yun et al., 1998 Shen et al., 1999
Gabapentin	?	?	+	Luer et al., 1999
Topiramate	+	?	?	Kwan et al., 2000
Phenytoin	+	+	?	Potschka and Löscher, 2001
Carbamazepine	+	+	?	Potschka et al., 2001
Phenobarbital	+	-	?	Potschka et al., unpublished
Felbamate	+	?	?	Potschka et al., unpublished
Lamotrigine	+	?	?	Potschka et al., unpublished

Impact of

Genetic factors

+ Known predispositions (e.g. migration disorder)
+ PGP polymorphisms
+ Data from selective breeding of kindled Wistar rats
+ Kindling data from diverse rat strains

Disease associated factors

+ Change of AED sensitivity during course of disease
+ Change of AED sensitivity during kindling
+ Seizure induced changes in AED targets and MDT expression

Drug induced factors

+ Loss of AED efficiacy during treatment -- tolerance?

CONCLUSIONS AND FUTURE PERSPECTIVES

Current hypotheses

- **are promising, but require further proof,**
- **require further effort to yield a basis for new treatment strategies,**
- **probably do not explain all aspects of drug-refractory epilepsy.**

Effort is necessary to identify additional mechanisms of pharmacoresistance.

Association of imaging findings with clinical outcome

Tuuli Salmenperä

15.3.2002

Department of Neurology,
Kuopio University Hospital

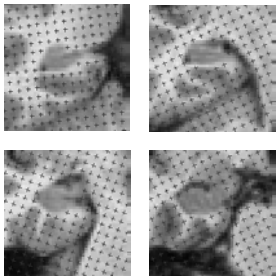
Prospective follow-up study

112 patients with newly diagnosed partial epilepsy
- **(57 females / 55 males)**
- **mean age 35 ± 16 (15 - 65) years**
  - **54 with CBZ treatment**
  - **58 with TGB/VGB treatment**

20 controls
- **(10 females / 10 males)**
- **mean age 31 ± 9 (21 - 50) years**

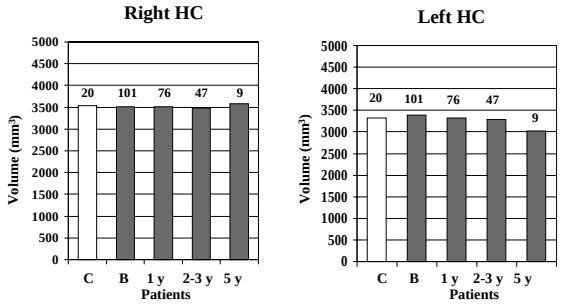
Magnetic resonance imaging

- **MRI scans at baseline, after 1, 2-3 and 5 years**
- **qualitative visual analysis**
- **quantitative analysis: Cavalieri method in combination with point counting**



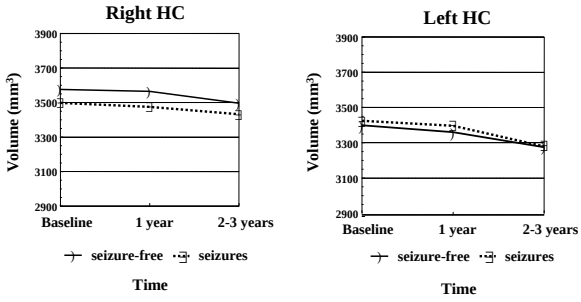
Hippocampal volumes

Follow-up



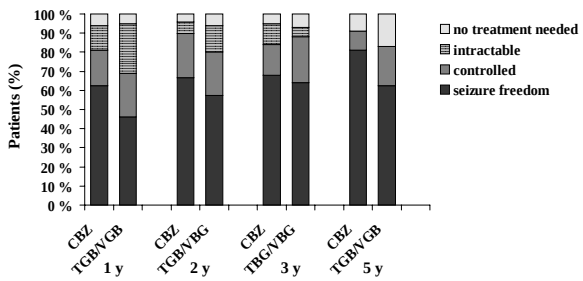
Hippocampal volumes

Follow-up



Clinical outcome

Efficacy of carbamazepine (CBZ) and tiagabine/vigabatrin (TGB/VGB) treatments after 1-, 2-, 3- and 5-year-follow-up



The Prognosis of the Epilepsies: lessons from the developing world

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Prognosis of the epilepsies: methodological problems I

- **Diagnostic accuracy**
  - **epilepsy can only be diagnosed by history or by chance observation of a seizure**
  - **diagnosis is discretionary depending on skill and quality of information**
- **10 - 20% of "chronic" cases referred to tertiary centres do not have epilepsy**
- **> 50% of cases suspected or diagnosed at primary care level do not have epilepsy**

The prognosis of the epilepsies: methodological problems II

- **The heterogeneity of the epilepsies**
  - **erroneous to regard epilepsy as one diagnosis**
    - **parallel would be to regard cancer or anaemia as a single condition**
  - **most outcome studies oversimplify classifying only by seizure type or broad aetiological categories**
  - **dearth of data on epileptic syndromes**
  - **molecular basis of the epilepsies still unknown**

Prognosis for seizure control in untreated epilepsy

- **The natural history of untreated epilepsy is largely unknown as effective treatment has long been available**
- **Based on circumstantial evidence from seizure pattern in newly-diagnosed patients, whom seem to have a short-lived condition after treatment it has been suggested that failure to provide early treatment may facilitate intractability**

Prognosis for seizure control in untreated epilepsy

- **In a truly chronic condition which never recovers, cumulative incidence rates approaches prevalence rates, the difference being differential mortality in cases**
- **In developed countries, the difference between the two rates is largely attributed to AED-induced remission**
- **Treatment gap: over 80% of people with epilepsy in developing countries not treated**

The incidence and prevalence of the epilepsies

- **Incidence in the developed world:**
  - **40 - 80/100,000/year (50/100,000/year)**
- **Incidence in the developing world:**
  - **80 - 190/100,000/year (120/100,000/year)**
- **Prevalence of active epilepsy (independent of location):**
  - **5 - 8/1,000**

Possible reasons for higher incidence in developing countries

- **CNS infections and parasites**
  - **tropics**
  - **ecological niches**
- **Social factors**
  - **poor sanitation**
  - **malnutrition**
  - **inadequate health delivery systems**

Discrepancy between incidence and prevalence rates

- **Methodological problems**
  - unlikely
- **Acute symptomatic seizures ?**
- **Role of mortality ?**
  - circumstantial evidence
- **Spontaneous remission ?**
  - circumstantial evidence

Prognosis for seizure control in untreated epilepsy

- **Clinical trials in untreated patients**
  - **Kenya**
  - **Ecuador**
  - **India**
  - **Over 50% became seizure free**
- **Neither duration or number of seizures prior to treatment were predictors of outcome**
- **Further trials are needed**

Conclusions

- No evidence from epidemiological data that failure to treat early will lead to chronicity
- Number of seizures of duration of epilepsy are not predictors of outcome
- Thus, seizure do not beget seizures in the generality of patients!

Evidence based treatment of newly diagnosed epilepsy in puberty

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Department of Pediatrics and Adolescence
Oulu University Hospital, Oulu, Finland

Generalized epilepsies, idiopathic generalized epilepsy syndromes with onset in puberty

- Juvenile absence epilepsy
- Epilepsy with grand mal seizures on awakening
- Juvenile myoclonic epilepsy
- Photosensitive epilepsies

Evidence based treatment of childhood absence epilepsy - may persist into puberty

- Many clinical reports of the efficacy of valproate for absence seizures
- Valproate and ethosuximide were equally effective for absences in a double-blind prospective randomized comparative study
  Sato S et al. Neurology 1982;32:157-163
- Lamotrigine was effective in one study; open-label dose escalation was followed by placebo-controlled double-blind study
  Frank LM et al. Epilepsia 1999;40:973-979

Evidence based treatment Childhood and Juvenile absence epilepsy

Therapy	Level of evidence
Ethosuximide	C
Lamotrigine	C
Valproate	C

Evidence based treatment Juvenile myoclonic epilepsy

- Valproate is the drug of choice
- Clinical reports of a dramatic response
- Valproate effective in 86% - 88% of patients with juvenile myoclonic epilepsy in two prospective follow-up studies, respectively
  Delgado-Escueta AV & fe Enrile B. Neurology 1984;34:285-294
  Panayiotopoulos CP, Obeid T and Tahan AR. Epilepsia 1994;35:285-296

Evidence based treatment Juvenile myoclonic epilepsy

- Lamotrigine
  - no randomized trials comparing its efficacy with valproate
  - lamotrigine was used in 12 patients who either had valproate side effects or did not wish to take valproate: 5 patients had seizures fully controlled
    Buchanan N Seizure 1996;5:149-151

Evidence based treatment
Juvenile myoclonic epilepsy

Therapy	Level of evidence
Lamotrigine	D
Valproate	C

Evidence based treatment
Side effects of drugs

- Clinical reports of valproate-related weight gain
- Valproate-related weight gain was found in a controlled longitudinal growth analysis of 40 girls with epilepsy
  Rättyä J et al. Pediatrics 1999;103:588–593
- Valproate monotherapy was associated with significantly greater weight gain than lamotrigine in one randomized, double-blind study in newly onset epilepsy
  Biton V et al. Neurology 2001;56:172–177

Evidence based treatment
Side effects of drugs

- Valproate may induce hyperandrogenism in girls with epilepsy during pubertal maturation – a controlled cross-sectional study
  Vainionpää L et al. Ann Neurol 1999; 45:444–450
- Careful endocrine observation of children and adolescents with epilepsy taking valproate is emphasized

Generalized seizures and idiopathic generalized epilepsies

Side effects of valproate vs. lamotrigine	Level of evidence
– weight gain	B
Side-effects of valproate	
– hyperandrogenism	C

Evidence based treatment of newly diagnosed epilepsy in puberty

- Childhood absence epilepsy
  - Ethosuximide, Valproate
  - Lamotrigine
- Juvenile absence epilepsy
  - Valproate
  - Lamotrigine
- Juvenile myoclonic epilepsy
  - Valproate
  - Lamotrigine

Evidence based treatment of newly diagnosed epilepsy in puberty

- Randomized controlled trials are needed in which only patients with specific epilepsy syndromes are recruited
- Newer drugs, lamotrigine and topiramate could be compared with valproate, which is the drug of choice at the present moment