

# HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS

## *9th European Congress on Epileptology Rhodes, Greece, 27th June to 1st July 2010*

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The 9th European Congress on Epileptology was conducted in the sunny island of Rhodes in Greece from 27th June to 1st July 2010. The congress presented recent scientific developments in epilepsy to allow those working in all fields of epilepsy to update their knowledge. The topics selected for the main sessions included "Predicting Epileptogenesis," "Advances in Imaging Techniques," "Idiopathic Epilepsies" and "AED Development." Those sessions were followed by related discussion groups or workshop sessions. In addition, parallel platform and poster sessions were included to present recent epilepsy research updates. In this syllabus, we present the highlights from the 9th European Congress on Epileptology.

### **Genetics**

#### ***Identification of a 15q13.3 microdeletion in clinically affected and unaffected members in a pedigree with idiopathic generalized epilepsy.***

Seizures will recur in most patients presenting with their first postoperative event. The period of highest risk is within the few subsequent months. A third will become seizure-free with the risk for refractoriness assessed by easily ascertainable measures at 6 postoperative months.

Chowdhury FA, Hindocha N, Flomen R, Richardson MP, Nashef L, Makoff A. Identification of a 15q13.3 microdeletion in clinically affected and unaffected members in a pedigree with idiopathic generalized epilepsy. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

#### ***The association between carbamazepine induced cutaneous adverse drug reactions with HLA-B\*1502 allele in mainland of China.***

The HLA-B\*1502 allele frequency was 100% (6/6) in patients with carbamazepine (CBZ)-induced SJS/TEN, 13.6% (3/22) in patients with CBZ-induced MPE, frequency was 6.7% (3/45) in CBZ-tolerant subjects, and 7.25% (5/69) in the healthy volunteers. All the six patients with SJS/TEN were found positive with HLA-B\*1502 allele (100%, OR = 168), and there was no difference in the frequency of patients with HLA-B\*1502 allele between MPE and control group (13.6% vs. 6.7%;  $p=0.629$ , OR=2.2). The patients with CBZ-induced SJS/TEN, but not the MPE, have the significant association with HLA-B\*1502. The test of HLA-B\*1502 allele is essential for the Chinese Han people before taking CBZ treatment if it is possible.

Wu X, An D, Hu F, Stefan H, Zhou D. The association between carbamazepine induced cutaneous adverse drug reactions with HLA-B\*1502 allele in mainland of China. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### **Pediatric Epileptology**

#### ***Immune-mediated and inflammatory disease in etiology of epilepsy parialis continua in children***

Epilepsia parialis continua (EPC) was diagnosed in 19 children: acute (7) and subacute viral encephalitis (5), subacute sclerosing panencephalitis (2), limbic encephalitis (1), CNS tuberculosis (3), sclerosis multiplex (1). The EPC appeared in the first (11), second (6), and in the terminal (2) phase of disease. Mean EPC duration was 10.4 days. Ictal EEG showed focal in 10, generalized epileptic discharges in 5 and generalized abnormal background activity in 4. The EPC was resistant to antiepileptic drugs and the best response was observed to midazolam in continuous intravenous infusion combined with high dosage of corticosteroids (11) and plasmapheresis in one case. Epilepsia parialis continua is more frequent in the subacute than in the acute form of encephalitis and appears often

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in the later phases of disease. It might suggest that not only inflammation but also immunological processes play a role in its pathogenesis. Good response to corticosteroids and plasmapheresis even in acute disease supports such a mechanism. On the other hand, ictal scalp EEG in numerous cases showed generalized abnormalities implying that EPC is a very focal manifestation of diffuse brain disorder.

Kravljanac R, Jovic N, Djuric M, Pekmezovic T. Immune-mediated and inflammatory disease in etiology of epilepsy parialis continua in children. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### *Early prognostic factors in patients with severe myoclonic epilepsy in infancy (SMEI).*

The SCN1A analysis by dHPLC/sequencing revealed 14 mutations (case group) comprising missense and truncating mutations. The MLPA showed genomic deletions/duplications in only one of 6 patients (control group) in whom no mutation of SCN1A had been identified previously by direct DNA sequencing. The phenotype of patients with SCN1A mutation was characterized by a number of seizures  $\geq 5$  before one year of age ( $p=0.02$ ) and the presence of epileptic status ( $p=0.03$ ) with a worse prognosis. Other clinical features (gender, seizure type, family history, mean age seizure onset) were not associated with the gene mutation. These findings suggest that the seizure number and the presence of epilepticus status are associated to SCN1A gene mutation and represent negative prognostic factors in the natural history of patients with early complex febrile seizures. This phenotype-genotype correlation confirms the high sensitivity of genetic approach in the diagnosis of SMEI.

Petrelli C, Passamonti C, Cesaroni E, Zamponi N. Early prognostic factors in patients with severe myoclonic epilepsy in infancy (SMEI). *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### *Risk factors for seizure prognosis in myoclonic-astatic epilepsy*

Age at onset of myoclonic-astatic epilepsy (MAE) varied from 9 months to 3 years. Female/male ratio was 7/9. Myoclonic and/or myoclonic-astatic seizures were observed in all patients. Fourteen patients had more than 2 seizure types. Rare GTCS in 12 patients, absences in 6, brief tonic seizures during sleep in 9, stupor like state or nonconvulsive status in 7, photosensitivity in 11. Stormy like onset was found in 9 patients. Six patients evolved to MAE from West syndrome. After one year from onset remission of all seizure types was observed in 56%, after 4 years in 44%. Decline in IQ appeared in 31%. Stormy onset, initial resistance to treatment, number of seizure types, photosensitivity did not influence prognosis ( $p<0.01$ ). Predictors of unfavorable outcome (1) for seizures, evolution from West syndrome ( $p<0.05$ ), sleep tonic seizures ( $p<0.01$ ), early onset off syndrome, (2) for cognition, existence of nonconvulsive status. Evolution from West syndrome, tonic seizures in sleep are predictors of resistant seizures, nonconvulsive status leads to decline of IQ.

Tatishvili N, Kipiani T, Japaridze N, Tatishvili S. Risk factors for seizure prognosis in myoclonic-astatic epilepsy. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### *Epileptic encephalopathy – seizure and developmental outcome after functional hemispherotomy*

Data from 28 children (11 girls; age at surgery: median: 6.0 years, range: 1 year–17 years) were analyzed for this report. Fourteen patients had perinatal strokes, 12 had cortical dysplasias, one patient had a hypothalamic harmartoma and one patient suffered from Rasmussen encephalitis. Postoperative follow-up was up to 11 years (median 2.0, range: 6 months–11.0 years). Twenty-three children were long time seizure-free after surgery. Thirteen patients showed a significant EEG improvement (especially with respect to continuous spike and wave during sleep). All these children were free of seizures, none of the children with continuous seizures showed an improvement in the EEG. Seizure freedom after surgery and improvement in the postoperative EEG were correlated with a neuropsychological progress. Results were best, but not statistically significant, in young children with perinatal stroke. Functional hemispherotomy should be performed early in the course of drug-resistant epileptic encephalopathies to improve the neuropsychological development in children.

Groppe G, Dressler A, Muhlechner A, Pahs G, Porsche B, Czech T, Kasprian G, Prayer D, Feucht M. Epileptic encephalopathy – seizure and developmental outcome after functional hemispherotomy. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

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## *Epilepsy Surgery*

### *The TimeToStop study II. The relation between timing of antiepileptic drug withdrawal and seizure recurrence after childhood epilepsy surgery*

TimeToStop is an international multicenter retrospective cohort study of 759 children, operated between 2000 and 2008 in 15 participating centers from 8 countries, who reached postoperative seizure freedom and in whom AED reduction was started. Four hundred and thirty-nine of 759 children completely stopped medication, 93 had seizure recurrences during or after AED withdrawal. At latest follow up, only 25 patients were not seizure-free. Shorter I\_stop, but not I\_start, was independently related to seizure recurrences after withdrawal, as were bilateral MRI abnormalities, and incomplete resection of the anatomical lesion ( $p < 0.05$ ). I\_start and I\_stop did not affect eventual seizure freedom. The number of preoperative AEDs, left sided surgery, and incomplete resection of the structural lesion predicted seizure outcome. Early start of AED withdrawal does not independently increase the risk of seizure recurrences. Early complete AED discontinuation predicts seizure recurrences but not eventual seizure outcome. Early AED withdrawal may unmask surgical failure, but not at the cost of permanent loss of seizure freedom.

Boshuizen K, Uiterwaal CSPM, van Nieuwenhuizen O, Braun KPJ, the TimeToStop Study Group. The TimeToStop study II. The relation between timing of antiepileptic drug withdrawal and seizure recurrence after childhood epilepsy surgery. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### *Effectiveness of neurosurgical treatment for seizure control in patients with cerebral arteriovenous malformation*

Complete microsurgical excision of arteriovenous malformation (AVM) was performed in all 18 cases. Seizure-free observed in 4 patients, rare seizures in 5 patients. Worthwhile decrease in 5, insignificant reduction in 4 cases. Total endovascular embolization achieved in 2 cases. Epileptic fits stopped in one case, in 3 cases seizure frequency reduced significantly, in 7 cases no changes was observed, and one patient had seizure worsening. After Gamma knife treatment complete AVM obliteration was achieved in 9 patients, 2 refused control angiography. Seizure-free observed in 4 patients. In 5 cases seizure frequency reduced significantly, in 3 patients seizures decreased and in 2 cases seizure frequency did not change. Best seizure control in patients with cerebral AVM was achieved after open microsurgical excision or Gamma knife irradiation when the malformation was completely eliminated. Management needs to be individualized to each patient and requires careful assessment of surgical risks and expectation of positive results.

Kostiuk K, Tsymbaliuk V, Tsimeyko O, Yakovenko L. Effectiveness of neurosurgical treatment for seizure control in patients with cerebral arteriovenous malformation. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### *Hypermotor seizures in patients with temporal lobe epilepsy: a retrospective analysis of clinical features and outcome after temporal lobe resection*

Among 293 patients who were resected exclusively in the temporal region we identified 16 (5.5%) who presented with hypermotor semiology such as violent vocalization, complex movements of the proximal segments of the limbs, rotation of the trunk, pelvic thrusting, early tonic or dystonic posturing. Most of the patients had a preceding aura. Ictal EEG activity was located in the corresponding temporal region, usually with a wide distribution over anterior or posterior temporal electrodes with fast propagation to unilateral frontal electrodes and to the other side. Neuroimaging revealed extended lesions in the temporal lobe involving mesial and neocortical structures. Most of the patients underwent classical 2/3 temporal lobe resection plus amygdalo-hippocampectomy leading to seizure freedom. Histology showed mainly focal cortical dysplasia plus hippocampal sclerosis. Hypermotor seizure semiology is no contradiction to the hypothesis of temporal lobe epilepsy when scalp EEG patterns and neuroimaging are corresponding. The seizure outcome is favorable.

Staack AM, Bilic S, Scholly J, Steinhoff BJ. Hypermotor seizures in patients with temporal lobe epilepsy: a retrospective analysis of clinical features and outcome after temporal lobe resection. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

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## *Neuroimaging of Epilepsy*

### *Reorganization of language in temporal lobe epilepsy and prediction of effects of temporal lobe resection*

In controls and right temporal lobe epilepsy (TLE), better preoperative naming correlated with greater left frontal and left hippocampal fMRI activation with verbal fluency. In left TLE, naming correlated with greater right than left frontal activation and no such correlation was seen in the left hippocampus. Greater preoperative fMRI activation in the dominant frontal lobe (FL) correlated with greater naming decline after ATR. Postoperatively, greater fMRI activation in the nondominant FL correlated with higher postoperative naming scores. Controls and right TLE patients show similar patterns of activation of left FL and hippocampus on verbal fluency. In left TLE, there was evidence for reorganization of naming function to the nondominant FL, in compensation for the diseased left fronto-temporal system preoperatively, and after dominant ATR. Preoperative language fMRI may be a useful predictor of postoperative naming deficits in patients undergoing ATR in the dominant hemisphere.

Bonelli S, Powell R, Yogarajah M, Focke N, Thompson P, Symms M, Koeppe M, Duncan J. Reorganization of language in temporal lobe epilepsy and prediction of effects of temporal lobe resection. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### *Reliability of MRI findings in temporal lobe epilepsy associated with focal cortical dysplasia*

There was relatively low agreement when assessing white matter (WM) T2 signal increase and atrophy, with full agreement in 67% and 57% respectively. However, these were the most frequently identified characteristics— 54% and 26% respectively. There was relatively higher agreement in assessment of abnormal gyral/sulcal pattern and increased cortical thickness. However, investigators fully agreed mostly on the absence of this finding. This study indicates high interrater variability in assessment of subtle MRI characteristics in TLE patients with FCD. White matter T2 signal increase was the most frequent and consistently identified MRI finding.

Marusic P, Fauser S, Krysl D, Schulze-Bonhage A. Reliability of MRI findings in temporal lobe epilepsy associated with focal cortical dysplasia. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

## *Drug therapy: Pregnancy and AED adverse effects*

### *Developmental abilities of children exposed in utero to antiepileptic drugs: A comparison between sodium valproate and levetiracetam*

On overall developmental ability children exposed to valproate (VPA) differed significantly from both levetiracetam (LVT) ( $p < 0.001$ ) exposed children and the control group ( $p = 0.001$ ). Levetiracetam did not differ significantly from controls ( $p = 1.0$ ). Maternal IQ, social economic status, maternal epilepsy type, gestational age, and age of child at assessment were all controlled for using a linear regression analysis. When compared with controls LVT exposure was not associated with overall developmental outcome ( $p = 0.88$ ). When compared with LVT exposure, VPA exposure was negatively associated with overall developmental outcome ( $p = 0.02$ ). Children under the age of 2 years, exposed to LVT in utero did not differ from control children on developmental scores. When compared to LVT, VPA exposure is negatively associated with developmental outcome. The results support the notion that LVT may be a preferable alternative drug choice for WVE of childbearing age, in regards to cognitive developmental outcomes in the child. Caution is needed interpreting the preliminary results of this study due to the young age of the children.

Shallcross R, Bromley RL, Irwin B, Morrow JI, Baker GA. Developmental abilities of children exposed in utero to antiepileptic drugs: A comparison between sodium valproate and levetiracetam. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

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## *Malformation risks after monotherapy exposure to antiepileptic drugs: First report from EURAP*

Of 5,707 pregnancies, 39 ended in induced abortions for fetal abnormalities, 43 perinatal deaths, 88 stillbirths, and 5,537 in live births. The major congenital malformations (MCM) rate (95% CI) associated with monotherapy with lamotrigine was 2.9% (2.1-4.1), carbamazepine 5.7% (4.6-7.1), valproate 9.3% (7.6-11.3), phenobarbital 7.5% (4.6-12.0), other monotherapies combined 3.4% (2.2-5.3). A multivariate analysis, including 12 covariates in addition to type of treatment in the entire population, revealed that the risk of MCM was significantly associated with family history of MCM ( $p < 0.0001$ ), family history of epilepsy ( $p = 0.017$ ), folic acid use (higher with “appropriate use,”  $p = 0.040$ ), and with gender of offspring (higher in males,  $p = 0.006$ ). Compared with lamotrigine monotherapy, MCM risks were significantly higher with: valproate, odds ratio (95%CI) 3.4 (2.1-5.7); phenobarbital, 2.7 (1.3-5.5); and carbamazepine, 2.1 (1.3-3.5). Our results indicate that risk of MCM is influenced not only by type of AED, but also by other variables. Findings with individual AEDs should be interpreted cautiously because dose-effect relationships have not yet been analyzed.

Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, Sabers A, Tomson T, Vajda F, on behalf of the collaborative EURAP study group. Malformation risks after monotherapy exposure to antiepileptic drugs: First report from EURAP. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

## *Epilepsy Syndromes in Adults*

### *Does it exist a subgroup of juvenile myoclonic epilepsy patients with a self-limited course? Supporting evidence from a longterm clinico-EEG study*

There were 151 (98 women; 53 men) consecutive patients meeting the inclusion criteria for (juvenile myoclonic epilepsy) JME. Their mean  $\pm$  SD age is  $31.3 \pm 9.8$  (range: 15–72) years. Mean  $\pm$  SD follow-up has been  $6.6 \pm 4.6$  (range: 0.2–21) years, with 93 and 46 patients being followed for at least 10- and 5-years, respectively. The majority (137 patients) showed the typical course: good response to treatment (mainly valproate), and frequent seizure relapses due either to poor compliance or abnormal life-style. Six patients showed true drug-resistance (inadequate control despite AED combinations). Eight patients (5.3%) showed complete and prolonged seizure remission (of mean duration 12.8; range: 9–25 years), despite treatment discontinuation (after an average of 4.4 years from seizure freedom onset). Their mean age at seizure cessation onset was 21.0 years. The characteristics of that group did not differ from those of the whole JME population. A short, self-limited course may be seen in some JME patients, probably indicating a milder phenotypic expression. Some patients in this category probably remain undetectable because of the tendency to put JME patients under long-term treatment.

Giannakodimos S, Alexoudi A, Karageorgiou CE. Does it exist a subgroup of juvenile myoclonic epilepsy patients with a self-limited course? Supporting evidence from a longterm clinico-EEG study. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

## *Clinical Epileptology*

### *EEG patterns in nonconvulsive status epilepticus on the intensive care unit*

Thirty-seven patients (1.2%) were found to have non-convulsive status epilepticus (NCSE). The EEG demonstrated focal or lateralized epileptiform discharges in 24 patients (64.9%): in 14 rhythmic sharp-waves, in 2 repetitive spikes, in 8 PLEDs. In 13 patients (35.5%) EEG showed generalized or bilateral epileptiform discharges: in 7 rhythmic sharp-waves, in one repetitive spikes, in 5 rhythmic delta with intermittent spikes. Encephalitis was the most frequent etiology of NCSE in our population (21.6%). The largest group of patients (81.1%) had no previous diagnosis of epilepsy. The majority of the patients (56.8%) had isolated seizures or convulsive status epilepticus prior to the onset of NCSE. Twenty-six (70.3%) of the patients were comatose, while 11 (29.7%) of the patients

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were obtunded or confused. All patients were treated with intravenous anticonvulsants, mostly PHT and MDZ. Four patients (10.8%) died of their underlying illness, and 33 (89.2%) patients survived to discharge. Hospital outcome was not related to specific EEG patterns. On the basis of EEG, NCSE in patients on the ICU may be classified as generalized or lateralized. Prognosis of NCSE appears to be more related to underlying conditions rather than to EEG patterns.

De Maria G, Perone G, Guarneri B, Antonini L. EEG patterns in nonconvulsive status epilepticus on the intensive care unit. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

## *Drug therapy: Miscellaneous*

### *Antiepileptic drug-induced osteopathy*

More than half of the examined epilepsy patients showed pathological bone mineral density (BMD) with osteopenic or osteoporotic T-values. Among these patients only a few individuals had additional causes for secondary osteopathy. There was a significant difference of BMD values in epileptic patients compared to the control group. We could demonstrate that long-term treatment with AEDs clearly affects BMD. These results underline the need of a careful monitoring of bone health in epileptic patients in order to identify and treat an AED-associated osteopathy in time.

Graf W, Harsch IA, Kerling F, Wenzel E, Stefan H. Antiepileptic drug-induced osteopathy. *Epilepsia* 2010; 51 (Suppl 4): 1-189.

### CONSULTANT NEUROSURGEON

Candidates should possess a Standard International qualification in Epilepsy Surgery. Should have at least 3-5 years experience as a Neurosurgeon.

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**For interested applicants, please send detailed curriculum vitae, 3 references, copies of professional qualifications, and passport photo, by post or by fax to:**

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