ABSTRACTS

Special issue: 32nd International Epilepsy Congress
Barcelona, Spain
2nd – 6th September 2017

Epilepsia, 58(Suppl. 5):S5–S199, 2017
doi: 10.1111/epi.13944

Platform Sessions

Basic Sciences 1
Sunday 3rd September, 2017

0001
PRORESOLVING ANTIINFLAMMATORY MECHANISMS ARE NOVEL POTENTIAL TARGETS AGAINST EPILEPTOGENESIS
E. Frigerio*, R. Colas1, S. Marchini1, E. van Vliet2, P. Foerch2, E. Aronica3-5,6,7, M. Perretti3, J. Dalli2, R. Kaminski6,8, A. Vezzani4
*IRCCS-Mario Negri Institute for Pharmacological Research, Department of Neuroscience, Milan, Italy, 1William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom, 2IRCCS-Mario Negri Institute for Pharmacological Research, Department of Oncology, Milan, Italy, 3Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 4UCB Biopharma SPRL, Braine l’Alleud, Belgium, 5Stichting Epilepsie Instellingen Nederland, Heemstede, Netherlands, 6Stichting Epilepsie Instellingen Nederland, Heemstede, Netherlands, 7Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, Netherlands

Purpose: Resolution of inflammation is an active homeostatic process controlled by proresolving lipids and peptides. We characterized this process during epileptogenesis to test whether boosting resolution mechanisms prevents epileptogenesis or mediates disease modifications.

Method: Our analyses were done in the hippocampus of mice exposed to status epilepticus (SE) and their sham controls, and patients who died 5 or >27 days from SE and autopsy controls. Mice were studied 2 h, 24 h and 72 h after SE (epileptogenesis) evoked by intrahippocampal injection of kainic acid. We measured by RTRqPCR and/or immunohistochemistry: proinflammatory cytokines (IL-1β; TNF-α), proresolving lipid’s biosynthetic enzymes (LOX5; LOX15), key proresolving receptors (ALXR; ChemR23) and peptides (AnnexinA1; IL-1Ra). Proresolving lipids and related molecules were measured in mouse hippocampus by LC-MS/MS lipidomic analysis. The AnnexinA1 fragment Ac2-50, BML111 or PD1n-3DPA-Me, stable analogues of LipoxinA 4 and neuroprotectin PD1 n-3DPA, or their respective vehicles, were injected individually icv in mice twice/day for 4 days starting 1 h post SE, then mice were killed for neuroinflammation analysis.

Results: IL-1β and TNF-α mRNA levels increased by 2 h and remained elevated for 72 h post SE. LOX5 and LOX15 mRNA levels were induced 72 h post SE. ALXR and ChemR23 expression was limited to pyramidal cells and hilar interneurons in sham mice and autopsy controls while it was induced in activated astrocytes 72 h post SE in mice and in patients; AnnexinA1 and PD1n-3DPA were upregulated by 2- and 20-fold, respectively. PD1n-3DPA-Me injection abolished IL-1β increase during epileptogenesis while BML111 and Ac2-50 were ineffective.

Conclusion: The activation of proresolving mechanisms occurs with a delay after the onset of neuroinflammation during epileptogenesis. The anticipation and potentiation of the resolution response with PD1n-3DPA-Me inhibited neuroinflammation. PD1n-3DPA-Me is an ideal candidate for testing potential neuroprotective and anti-epileptogenic actions by boosting resolution mechanisms of neuroinflammation.

0002
NOVEL DRUG-SCREENING IN “EPILEPTIC” ZEBRAFISH UNCOVERS HISTONE DEACETYLASE (HDAC) 1 AND 3 AS A NOVEL ANTICONVULSANT TARGET
K. Ibhaizehiebo*, C. de la Hoz*, C. Gavrilovic†, J.M. Rhö, D.M. Kurkasch‡
*University of Calgary, Medical Genetics, Calgary, AB, Canada, †University of Calgary, Department of Pediatrics, Calgary, AB, Canada

Rationale: Epilepsy is a common neurological condition that affects approximately 1–2% of the general population. 30–40% of patients are unresponsive to drugs and continue to suffer from unremitting recurrent seizures, suggesting a need for drugs with new mechanisms of action. We created a drug-screening platform that harnesses the power of zebrafish (ZF) genetics and the measurement of whole animal bioenergetics to unbiasedly uncover novel agents with unexpected mechanisms of action. Previously, we identified vorinostat (a broad HDAC-inhibitor) as a potent and efficacious anticonvulsant agent. In the present study, we further investigated class I, IIa, IIb, and IV HDAC inhibitors to identify the specific class of HDACs that might be responsible for the anticonvulsant properties observed with vorinostat.

Methods: We introduced mutations into the zebrafish ortholog (kcnal1) of Kv1.1 epilepsy-associated gene, and analyzed their bioenergetics profile using the XF24 Extracellular Flux analyzer. Systematic analysis of bioenergetics activities of 26 HDAC inhibitors in kcnal-null zebrafish was conducted. All HDAC inhibitors that restored mitochondrially-mediated bioenergetics to baseline levels were further validated using video electroencephalogram (EEG) recording in Kv1.1 mutant rodent models.

Results: HDAC 1 and 3 inhibitors (class I HDAC) effectively restored elevated mitochondrially-mediated bioenergetics (p < 0.01), and reversed the abnormal metabolic bioenergetics profile observed in kcnal-null zebrafish. Also, treatment of the spontaneously seizing Kv1.1 mutant mice with HDAC 1 and 3 inhibitor led to >50% (p < 0.01) in the frequency of seizures observed in these mice. This further suggests that inhibition of HDAC 1 and 3 activity can serve as a potential anticonvulsant target.

Conclusions: Our metabolic approach to drug screening represents a new direction that could be used to identify therapeutics with novel mechanisms of action, which might be effective for the treatment of monogenic intractable epilepsy.
 Purpose: To retrospectively evaluate atypical MR images in three cases of Rasmussen’s encephalitis (RE) with clinical and histopathology findings fulfilling Part B diagnostic criteria of the disease as proposed by the European consensus (2005). We present MR findings that may assist radiologist to consider RE in the differential diagnosis of epilepsy patients and eventually aid in the early recognitions of this condition.

Method: All patients underwent at least one contrast enhanced brain MRI at 1.5T including T1, T2, FLAIR and DWI sequences. Diagnosis was established based on clinical features and histology findings after brain biopsy or surgery samples.

Results: Age at onset was 9 years (7-13y), all patients showed icatal semiology of focal origin before the development of epilepsy partial continua (EPC). Two patients presented with unilateral, transitory and isolated clonic movement of limbs and absent gaze. One patient evidenced ictal hypersalivation, absent gaze, ocular and head version with further development of behavior disturbances and hallucinations. EEG during clinical episodes was characterized by unilateral fast activity spikes, acute waves or spike-waves without hemispheric slowing in all cases. Average time to EPC was 9 months in all patients (3-12 m). All patients had histo-pathology findings compatible with active RE. During the acute stage all patient had subcortical FLAIR/T2 hyper-intensities with partial collapse of subarachnoid spaces. Lesions were initially unilateral in all cases (one or two lobes affected) with further involvement of the contralateral hemisphere in one patient. Two patients had five follow-up MRI during 18 and 7 months respectively. Lesions progressed in both cases after brain biopsy involving previously unaffected regions (within 3 months). Patient showed no evidence of brain atrophy.

Conclusion: MRI evidence of brain atrophy is not required for the definitive diagnosis of RE. Non typical initial neuro-imaging or unusual progression are not sufficient to exclude the diagnosis.

p0744 PAROXYSMAL NON EPILEPTIC EVENTS IN PEDIATRIC EPILEPSY CLINIC: A DESCRIPTIVE STUDY OF ETOLOGY, PROPORTION AND THERAPEUTIC IMPLICATIONS AT A TERTIARY HEALTH CARE CENTRE

A. Mandli*, N. Desai*, R. Badheka*, V. Udani*, D. Mhatre*
*P. D. Hinduja National Hospital & Medical Research Centre, Pediatric Neurology, Mumbai, India

Purpose: To study the proportion of paroxysmal non-epileptic events in pediatric patients presenting with history of paroxysmal events in epilepsy clinic.

Objectives:
1. To determine the age (<5 years, 5 to <12 years, ≥12 years) and gender distribution of different paroxysmal non-epileptic events in pediatric patients.
2. To evaluate the therapeutic implications of correct diagnosis (modification/withdrawal of drugs).
3. To determine the existence of true epilepsy in this population.
4. To evaluate for psychological co-morbidities in patients with psychogenic non-epileptic seizures.

Method: All new patients of 1-month to 18-year of age attending the Pediatric epilepsy clinic were included if they presented with history of paroxysmal events. Patients were assessed by history and clinical evaluation by pediatric neurologists. Sometimes aided by recorded videos of these events. If the diagnosis was not confirmed by this preliminary evaluation, further investigations like EEG/videoEEG, ECG and neuroimaging were advised.

Results: In this study of 200 new patients presenting with paroxysmal events in the pediatric epilepsy clinic, 19% had nonepileptic events, 80% had epileptic events, and 1% remained undiagnosed. Physiological or organic non-epileptic events were more common in patients less than 5 years of age and psychogenic non-epileptic events were more common in more than 5 years of age. Syncope was more common in adolescents. There was no statistically significant gender predilection for different paroxysmal non-epileptic events. 34.2% of patients with nonepileptic events were on AEDs. After confirming non-epileptic attacks, only 2.6% patients needed AEDs for coexisting true epilepsy. 31.6% of patients received unnecessary AEDs. The change in treatment with correct diagnosis was statistically significant (p = 0.0001).

Conclusion: Mimickers of epilepsy are common in pediatric practice and are often a cause of drug refractoriness and side effects of antiepileptic drugs (AEDs) and mental and financial burden to entire family. Correct diagnosis leads to correct management, commencing new treatment for the specific diagnosis if needed and appropriate referrals to other health care providers as indicated.

p0749 EEG CAN PREDICT NEUROLOGIC OUTCOME IN CHILDREN RESUSCITATED FROM CARDIAC ARREST

H.J. Kim*, D.H. Yang*
*Gachon University Gil Medical Center, Incheon, Korea

Purpose: Early prediction of prognosis of children resuscitated from cardiac arrest is a major challenge. We investigated the utility of EEG for predicting of neurologic outcome in children resuscitated from cardiac arrest.

Method: We retrospectively analyzed medical records of patients who were resuscitated from cardiac arrest from 2006 to 2015 at the Gil Medical Center. Patients aged one month to 18 years were included. EEG analysis included background scoring, reactivity and seizure burden. EEG background scoring classified 0(normal/organized), 1(slow and disorganized), 2(discontinuous or burst suppression), 3(attenuated). Neurologic outcome was evaluated by Pediatric Cerebral Performance Category(PCPC) at least 6 months after cardiac arrest.

Results: Among 166 patients who had cardiac arrest, 109 death of arrival patients were excluded. Among resuscitated 57 patients, 26 patients who had performed EEG were evaluated. The mean age was 5.0 ± 5.5 years. Nine patients showed good neurologic outcome(PCPC 1,2,3) and 17 patients showed poor neurologic outcome(PCPC 4,5,6). Good neurologic outcome group patients’ mean arrest duration was 10.4 ± 8.3 minutes, percent of treated with hypothermia was 44.4%. Poor neurologic outcome group patients’ mean arrest duration was 17.5 ± 11.1 minutes, percent of treated with hypothermia was 29.4%. EEG background scores in good neurologic outcome group were consist of 1(11.1%) in score 0, 2(22.2%) in score 1, 1(11.1%) in score 2, 5(55.6%) in score 3. Four patients (44.4%) of good neurologic outcome group showed reactivity and seizure burden. EEG background scores in poor neurologic outcome group were consist of 0(0%) in score 0, 1(5.4%) in score 1, 1(5.4%) in score 2, 15 (75.7%) in score 3. Five patients(29.4%) and 4 patients(23.5%) of good neurologic outcome group showed reactivity and seizure burden each.

Conclusion: EEG background patterns may be used to support prognostic decision in children resuscitated from cardiac arrest.

p0751 EARLY ELECTROCLINICAL FEATURES AND OUTCOME AT 6 YEARS OF AGE OF 61 SUBJECTS WITH DRAVET SYNDROME BORN BETWEEN 1972 AND 2010

*University of Verona, Life and Reproduction Sciences, Verona, Italy

Purpose: The correlations in DS between type of mutation and phenotype are unknown and the definition of the early electroclinical features having a prognostic meaning remains debated. In order to evaluate which findings can be predicting and/or conditioning the outcome and if it has modified during the years we analyzed comparatively the electroclinical features of 61 DS cases (aged 7 to 65 years) born between 1972-1990 (Group 1: 20), 1991-2000 (group 2: 22), 2001-2010 (Group 3: 19).

Method: They have been analyzed demographic and electroclinical findings at onset and during the evolution, age at diagnosis, kind of genetic disorder, treatment and the epilepsy, neurological and cognitive outcome at the age of 6 years. According to the cognitive outcome the
Abstracts

subjects have been divided un two groups: Normal/Mild ID (18), Moderate/Severe ID (43).

Results: The incidence of cases showing a moderate/severe ID is greater (80%) in group 3 than in group 1, 2 (53%). The findings statistically related with a worse neurological and cognitive outcome are: age at onset < 6 months, significant and persistent myoclonic manifestations (absences with myoclonias and massive myoclonias), photosensitivity, self-induction. No correlations have been found according to type of genetic disorder, first seizure semiology, partial or generalized seizures occurrence and frequency. Diagnosis in the first year is more frequent in group 3 and long-lasting treatment with phenobarbital and phenytoin more frequent in groups 1,2 without reaching statistical significance.

Conclusion: The electroclinical features occurring during the first years constitute the only significant prognostic factors, having myoclonic manifestations, photosensitivity and self-induction a poorer significance. The relatively lower incidence of subjects with a poorer outcome in group 3 is only related to the expanded phenotypic spectrum of DS. Only future long-term studies concerning cases born in the last years can evidence if earlier diagnosis and different treatments can modify the prognosis.

p0754
INTERICTAL DYSPHORIC DISORDER AND QUALITY OF LIFE IN PATIENTS WITH EPILEPSY
G.M. Tedrus*, R. Lima Silva*
*Pontificia Universidade Católica de Campinas, Faculdade de Medicina, Campinas, Brazil

Purpose: Intercital dysphoric disorder (IDD) is described in patients with epilepsy (PWE), but the associated factors remain controversial.

Objective: To analyze the occurrence of IDD in PWE and its relationships with the clinical and cognitive aspects of epilepsy and quality of life (QoL).

Method: The study included 117 consecutive PWE from the neurolology outpatient clinic of PUC-Campinas. Possible associations of IntercitalDysphoric Disorder Inventory (IDDI) data with the clinical aspects of epilepsy and QOLIE-31 were investigated at a significance level of 5% (p < 0.05).

Results: The patients had a mean age of 42.9 (±16.2) years; mean education level of 6.4 years; mean age at first seizure (ES) of 19.5 (±14.5) years; 45.7% of the patients were female; and 40.2% of the PWE had psychiatric disorders. Twenty-five (21.4%) patients had idiopathic generalized epilepsy, 29 (24.8%) had symptomatic focal epilepsy, and 63 (53.8%) had probably symptomatic focal epilepsy. IDD was found in 25 (21.4%) PWE. IDD was significantly more common in patients with psychiatric disorders (χ²; p = 0.021) and those with Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) scores >15 (χ²; p = 0.039).

The presence of IDD did not vary significantly by epileptic syndrome, hemispheric lateralization, seizure frequency, and type of seizure. PWE with IDD had significantly lower QOLIE-31 scores (dimensions and total score). The total QOLIE-31 score was negatively correlated (Spearman’s correlation; p < 0.05) with total symptomatology, labile depressive symptoms, labile affective symptoms, and specific IDDI symptoms.

Conclusion: IDD was found in 21.4% of the cases and occurred in different epileptic syndromes. Worse QoL (dimensions and total score) was associated with the presence of IDD.
Early electro-clinical features and outcome at 6 years of age of 61 subjects with Dravet syndrome born between 1972 and 2010


* Child Neuropsychiatry, Department of Surgery, Dentistry, Pediatrics and Gynecology, University of Verona, Italy
* University Hospital of Verona, § CREP Dravet Italia ONLUS

Purpose
It is unknown whether a correlation exists in Dravet Syndrome (DS) between the patient clinical phenotype and the kind of SCN1A gene mutation identified. Moreover, the definition of early electro-clinical features with a prognostic value in DS is still debated. Herein, we analyze electro-clinical features of 61 DS patients born between 1972 and 1990, in order to evaluate if any findings may predict and/or modify the cognitive outcome, and whether the overall clinical outcome changed over time, when stratifying patients for year of birth.

Methods
Sixty-one DS patients were stratified for year of birth in 3 groups: born in year 1972-1990 (Group 1, 20 pts), born in year 1991-2000 (Group 2, 22 pts), born in year 2001-2010 (Group 3, 19 pts). The age range at last follow-up evaluation was 7-45 years. Demographic and electro-clinical findings were evaluated at epilepsy onset and during evolution. Age at diagnosis, antiepileptic drugs administered, and kind of SNC1A gene mutation were registered for all patients. The epilepsy, neurological and cognitive outcome were analyzed at the age of 6 years. The cognitive outcome was stratified for IQ, estimated with scales appropriated for age.

Results
Comparing features of patients in 3 groups, we observed:
- Male/female ratio is similar in all group (12/8, 13/9, 9/10, respectively).
- Mean seizure at onset: 5.6 months in all groups; onset within the age of 5 months is similar in all groups (60%, 59%, 63%).
- First seizure in fever in 49% cases, without significant differences in groups. Seizure semiology at onset: no significant differences (Fig. 1).
- Frequency of convulsive seizures (generalized/unilateral) within 3 years: no significant differences (Fig. 2-3).
- "Partial complex" seizures occurred in 43 pts (74%), without significant differences in 3 groups (60%; 82%; 68%).
- No differences were observed in the incidence of convulsive Epileptic Status or prolonged Epileptic Status, whereas the occurrence of recurrent epileptic status and status requiring admission in I.C.U. is lower in Group 1 (Tab.1).
- Absence seizures occurred in 43 pts (70%) and Massive Myoclonias in 37 pts (61%), both less frequent in Group 3 (Fig. 4).
- Photo/pattern-sensitivity with self-induction was less frequent in Group 3 (Fig. 5).
- Ataxic gait was present within 3 years was less frequent in Group 3 (Fig. 6).
- Regarding treatment, only 4 subjects (7%) were in monotherapy during first 6 years of life (5% in Group 1, 5% in Group 2, 11% in Group 3). Major changes in time in treatment options were significant reduction of therapy with PB, CBZ, LTG, DPH, and the increasing use of TPM and Stiripentol. Continuous PB treatment was less frequent in Group 3 (Fig. 7).
- Clinical diagnosis was given earlier in Group 2-3; 63% cases in Group 3 had diagnosis before the age of 12 mths (Fig. 8).
- The genetic analysis performed in 58 patients documented a SCN1A gene missense mutation in 27 cases (47%), a truncating mutation in 25 (43%), deletion in a patient; no mutations were identified in 4 patients (7%).
- Cognitive functioning at 6 years: normal/borderline in 7 pts (11,5%), mild ID in 10 (16%), moderate ID in 21 (34,5%), severe ID in 23 (38%). Patients with moderate or severe ID predominated in Group 1-2 (Fig. 9).

In order to analyzed correlations between genotype and early phenotype and cognitive outcome at 6 years, the population was stratified for Intelligence Quotient (IQ≥50, normal functioning or mild ID; IQ<50, moderate or severe ID).
- There is a statically significant association between a worse cognitive outcome and:
  - Absence seizures (with/without myoclonias) and Massive Myoclonias (Fig. 10-11);
  - Photo/pattern-sensitivity + self-induction (Fig. 12);
  - Ataxic gait within 3 years (Fig. 13).
- There is not a statically significant association between cognitive outcome and onset before 5 months, seizures semiology and frequency other than Absence seizures and Myoclonias in first 3 years, recurrence of prolonged Epileptic Status even if needing I.C.U. admission, kind of treatments, kind of SCN1A genetic mutation.

Conclusion
Major electro-clinical features in DS appeared to be stable along time, as well as the globally unfavorable long-term outcome. Up to day only electro-clinical features observed in first years of life may represent relevant prognostic factors. Myoclonic seizures, photosensitivity and seizure self-induction resulted to be correlated with a worse cognitive outcome at 6 years of age, regardless the year of birth. The higher incidence of favorable cognitive outcome in the group of patients born in year 2001-2010 is due to the higher proportion of subjects without Absence seizures (with/without myoclonias), Massive Myoclonias, photo/pattern-sensitivity + self-induction (Fig. 4-5). This is probably due to the expanded phenotypic spectrum of DS.

Future long-term studies on DS pts born in the last decade are needed to establish whether a confirmed diagnosis of DS soon after the epilepsy onset, and/or a different treatment approach in the first years of life, might really relevantly modify the cognitive and epilepsy outcome in DS.