Annual Conference of The Israeli League Against Epilepsy
March 27, 2024, Daniel Hotel, Herzliya
הכנס השנתי של הליגה הישראלית למניעת אפילפסיה
27 במרץ, 2024 | מלון דניאל הרצליה

**Session I**
**BASIC SCIENCE AND RESEARCH IN EPILEPSY**
**ABSTRACT PRESENTATION**
**Chair: Tawfeeq Shekh-Ahmad**

## Computational Biology and Artificial Intelligence for Classifying Genetic Variants in Epilepsy Genes- a Project

**Andreea Nissenkorn**[1], Nir Ben Tal[2]
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**Introduction:** Pathogenic variants in genes encoding voltage gated sodium and potassium channels (SCN1a, SCN2a, SCN8a, KCNQ2, KCNQ3) cause autism and epilepsy. The phenotype and correct treatment depend on the effect of the mutation (gain-of-function or loss-of-function), but tools predicting functional significance are lacking for clinicians. Molecular dynamics (MD) simulation uses mathematical equations to determine the position of atoms at each point in time, predicting proteins' motion, and inferring their mechanism of action.
Aim: Here we propose to present a project dedicated to the development of a tool integrating MD and deep learning to categorize the impact of variants in these channels.
**Methodology:** We will use the Boltzmann generators framework to properly sample the conformational space of the above wild-type channels, and representative mutants. The framework is based on transforming this many-body system into a low dimensionality 'latent' space, capturing the essence of channel function and action mechanism. We will explore the possibility of using the latent space to cluster variants based on functional phenotypes. We will examine this hypothesis with over 100 variants with known electrophysiological significance, calibrate and revise the model as needed.
**Significance:** The pipeline based on MD/deep learning will be used by clinicians to classify uncharacterized genetic variants, as a cornerstone to personalized medicine.

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**Analyzing Power Spectral Characteristics of EEG Signals during Complex Tasks in Epilepsy Patients: Unveiling Altered Brain Mechanisms in Drug-Resistant Epilepsy**

Inbal Maidan[1], **Sara Leviashvili[2],** Firas Fahoum[2]
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**Background:** Juvenile Myoclonic Epilepsy (JME) is one of the most common epileptic syndromes. Although many patients respond well to medication, up to 30% are drug-resistant. To date, no biomarkers for drug resistance in JME patients have been identified. This study aims to identify drug-resistant patients using a novel approach to analyze the spatio-temporal characteristics of event-related potentials (ERPs) during complex task recorded by EEG in JME patients.
**Methods:** Eighteen JME patients (aged 28.7±5.6 y/o) and 13 healthy controls (aged 30.1±3.4 y/o) participated in a Visual Go No-Go (VGNG) task, performed during sitting (simple task) and while walking (complex task). Frequency-domain analysis, including spectral and wavelet analysis, were utilized to investigate the EEG signals. Specifically, we focused on extracting features from the delta, theta, beta, and gamma frequency bands. To assess group differences, we performed t-tests between JME and healthy controls, comparing a series of EEG features during simple task and complex task. The same analysis was then performed between the JME groups, to compare drug-responding and drug-resistant subgroups.
**Results:** JME patients showed lower theta power and higher beta power compared to healthy controls only during the complex-task ($p=0.02$). Further analysis between the JME groups revealed that non-responders exhibited higher theta power and lower beta power compared to responders during the complex-task ($p=0.03$). No differences between the groups were found during the simple-task.
**Conclusions:** Differences in frequency oscillatory patterns during complex tasks among responders and non-responders JME patients could serve as discriminative markers, potentially elucidating variations in the underlying pathophysiology or mechanisms of drug response. These insights enhance our understanding of JME and may aid in the development of personalized treatment approaches.

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**Exploring Cognitive Neural Mechanisms Using Intracranial Event-Related Potentials (ERPs) in Epilepsy Patients**

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**Background:** Cognitive impairment is a prevalent comorbidity in epilepsy, impacting attention, perception, and memory. This study utilized intracranial electroencephalography (iEEG) to explore event-related potentials (ERPs) during the GO/NOGO task in drug-resistant epilepsy patients. By examining specific local field potentials (LFPs) at cortical and subcortical levels during the performance of cognitive task, the research aims to uncover neural mechanisms linked to inhibitory control and cognitive processes.
**Methods:** iEEG recordings were performed in six patients, undergoing invasive pre-surgical evaluation for drug resistant epilepsy, while they were engaged in a visual GO/NOGO task. The iEEG signals were pre-processed into event epochs, corresponding to both GO and NOGO events, and were subsequently clustered using the k-means algorithm to identify similar activation patterns in different brain regions. In addition, permutation-based statistical testing was used to assess if the cluster properties remained consistent and reflect patterns related to the Visual Go NoGo events.
**Results:** Preliminary results revealed a trend at both the individual and group levels that could have implications for cognition. Specifically, for GO events, we found involvement of the Left precentral gyrus, left hemispheric white matter, left amygdala, left entorhinal area, left hippocampus, left middle temporal gyrus, and left supplementary motor area. On the other hand, for NOGO events, the implicated brain areas were left precentral gyrus, left middle cingulate gyrus, left hemispheric white matter, left middle frontal gyrus, left middle temporal gyrus, and left supplementary motor area.
**Conclusions:** This study provides unique insights into ERPs using iEEG, contributing to our understanding of cognitive functions in epilepsy. To validate the findings, more subjects should be enrolled in the study. This rigorous approach will determine the significance of the clustering outcomes and shed light on the contribution of different brain areas to basic cognitive processing.

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**Exploring Ictal Dynamics in Patients with Epilepsy through fNIRS Coupled with Stereotactic Electroencephalography or Video Electroencephalography**

**Netaniel Rein**[1,2], Oshrit Arviv[1,2], Dana Ekstein[1,2], Tal Benoliel[1,2], Diya Doufish[1,3], Guy Rosenthal[2,4], Sami Heymann[4,2], Leah Morihon[4,2], Zvi Isreal[4,2], Tal Gilboa[5,2], Naomi Froimovich[1], Yulia Katz[1], Revital Shechter[6], Michal Balberg[6], Mordekhay Medvedovsky[1,2]
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**Background:** Functional near-infrared spectroscopy (fNIRS) assesses cerebral cortex activation through measurement of changes in oxyhemoglobin (HbO2) and deoxyhemoglobin (HHb) concentrations using light. It is used in many fields of research and clinical practice, including Neurology, Psychiatry, Psychology, Intensive Care and basic research. In previous studies, fNIRS has been demonstrated to

detect, lateralize and sometimes localize epileptic seizures and pre-ictal changes, as deflections of cerebral HbO2 and HHb levels. In the past, pre-ictal changes were defined compared to scalp electroencephalography (EEG).
**Methods:** A group of 10 adult (18 years old or above) patients with epilepsy, admitted for either video EEG (VEEG) (3) or stereotactic EEG (SEEG) (7), were additionally connected to fNIRS monitoring (6-32 channels). Peri-ictal and ictal changes in level of HHb and HbO2 were examined for changes relating to epileptic seizures.
R**esults:** Seizure onset was detected by standard VEEG and SEEG in 8 patients. Clear changes in HbO2 and HHB levels were detected during and prior to seizures by fNIRS. In at least four patients, these changes occurred over a minute before the clinical and electrical onset of seizures in both VEEG and SEEG. Furthermore, very low frequency reciprocal oscillations in HbO2 and HHb levels were seen in 2 patients, suggesting obstructive sleep apnea during sleep.
**Conclusion:** This study includes previously unreported simultaneous monitoring with SEEG and fNIRS. Changes in fNIRS preceded electrographic onset of epileptic seizures, during both scalp video-EEG and intracranial monitoring. These findings open new horizons to understanding the pathophysiology of seizure onset, seizure detection and prediction and therapeutic possibilities.
This study was supported by the Israeli Innovation Authority.

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**Efficacy of a combined anti-seizure treatment against cholinergic established status epilepticus following a sarin nerve agent insult in rats**

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The development of refractory status epilepticus (SE) following sarin intoxication presents a therapeutic challenge. Here, we evaluated the efficacy of delayed combined double or triple treatment in reducing abnormal epileptiform seizure activity (ESA) and the ensuing long-term neuronal insult. SE was induced in rats by exposure to 1.2 LD50 sarin followed by treatment with atropine and TMB4 (TA) 1 min later. Double treatment with ketamine and midazolam or triple treatment with ketamine, midazolam and levetiracetam was administered 30 min post-exposure, and the results were compared to those of single treatment with midazolam alone or triple treatment with ketamine, midazolam, and valproate, which was previously shown to ameliorate this neurological insult. Toxicity and electrocorticogram activity were monitored during the first week, and behavioral evaluations were performed 2 weeks post-exposure, followed by biochemical and immunohistopathological analyses. Both double and triple treatment reduced mortality and enhanced weight recovery compared to TA-only treatment. Triple treatment and, to a lesser extent, double treatment significantly ameliorated the ESA duration. Compared to the TA-only or the TA+ midazolam treatment, both double and triple treatment reduced the sarin-induced increase in the neuroinflammatory marker PGE2 and the brain damage marker TSPO and decreased gliosis, astrocytosis and neuronal damage. Finally, both double and triple treatment prevented a change in behavior, as measured in the open field test. No significant difference was observed between the efficacies of the two triple treatments, and both triple combinations completely prevented brain injury (no differences from the naïve rats). Delayed double and, to a greater extent, triple treatment may serve as an efficacious delayed therapy, preventing brain insult propagation following sarin-induced refractory SE.

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**Coherence Based Analysis of Information Transfer Along The Hippocampal Axis**

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**Background:** Patients with temporal lobe epilepsy often suffer from hippocampal disfunction, which is in part attributed to structural and network level changes in the hippocampus. It is unclear whether and how changes in excitation – inhibition balance, thought to play a major role in epilepsy pathophysiology, affect hippocampal function. Here, we implemented a method of coherence based multivariate analysis of neuronal ensembles to study the communication between areas along the hippocampal axis, and extracted the 1/f power spectral density slope as a measure of excitation inhibition balance to identify similarities and differences in these measures in the hippocampi of epilepsy patients undergoing stereo-EEG.
**Methods:** Intracranial electroencephalography signals recorded from five hippocampi of three neurosurgical epileptic subjects were used to calculate mutual coherence between four time-series using a multivariate analysis to identify functional directed pathways. The slope of the 1/f fit of the power spectral density as a measure of excitation inhibition balance was calculated for each pathway node in wakefulness and sleep states.
**Results:** In wakefulness and sleep, four node pathways were obtained across alpha to gamma range (7 to 100Hz) though the number of pathways found per hippocampus and the peak pathway frequencies differed between hippocampi. Averaged 1/f slope varied widely between hippocampi and state (range: -0.94 to -3.4). The majority of the pathways demonstrated a posterior to anterior (P-A) direction (60.4% during wakefulness, 86% in sleep. Prominent pathway frequencies were lower in sleep compared to wakefulness (26. 62±5 and 41.22±11.4, p=0.07) as was the slope of the 1/f curve (-2.8±0.88 and 3.16±0.52, p=0.0088) showing a shift towards inhibition.
**Conclusions:** Directionality of information transfer along the hippocampal axis and E/I pattern are preserved across wakefulness and sleep and disease states, illuminating a basic attribute of hippocampal information transfer. However, the variance observed between patients in the number of pathways, peak frequencies, directionality and 1/f slopes highlights possible functional disease dependent differences between hippocampi. These measures warrant further investigation as potential biomarkers of hippocampal function and disfunction, to be combined with behavioral and structural methods.


**Session II**
**EPILEPSY AND NEUROSURGERY**
**ABSTRACT PRESENTATION**
**Chairpersons: Ido Ben Zvi, Ido Strauss**

**When Infantile Spasms are Treated with Surgery; A Case of Mild Malformation of Cortical Development with Oligodendroglial Hyperplasia and Epilepsy (MOGHE)**

**Aida Hleihil**[1], Ido Ben-Zvi[2], Hadassah Goldberg-Stern[1], Amir Pshytycky[1], Amir Kershenovich[2], Dror Kraus[3]
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**Background:** Mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy (MOGHE) is a rare, recently discovered epilepsy syndrome. Interestingly, epileptic spasms are its most common initial seizure type, occurring in about 40% of patients. We present a case of MOGHE that presented with modified hypsarrhythmia and infantile spasms that did not respond to conventional medications. Surgical resection of the malformation resulted in significant clinical and developmental improvement.
**Case Presentation:** A female infant presented at 9 months of age with developmental regression, motor difficulties, and inability to hold objects. She was diagnosed with modified hypsarrhythmia and infantile spasms that were refractory to ACTH, Vigabatrin, and Topiramate, among other anti-seizure medications. The initial MRI was interpreted as normal; however repeat imaging demonstrated extensive structural changes in the left frontal lobe, with features suggestive of MOGHE. Video electroencephalography (VEEG) demonstrated bi-frontal onset of ictal events with suggestion of left frontal dominance, as well as interictal multifocal discharges. A fluoro-deoxyglucose positron emission tomography (FDG-PET) scan demonstrated subtle metabolic abnormalities in the left frontal lobe.
The patient underwent stereo-EEG to delineate the seizure onset zone, to determine resection margins and to specifically rule out involvement of the motor strip. The study revealed an epileptogenic focus in the left frontal lobe with anterior insular extension and sparing of the motor strip. Given these findings, she underwent an extensive left frontal resection that included the anterior insula. Biopsy demonstrated a mild cortical dysplasia, albeit without oligodendroglial hyperplasia. Genetic testing of the brain tissue is pending. Her postoperative recovery was uneventful, with complete cessation of seizures and significant developmental progress.
**Discussion/Conclusion:** This case report increases awareness of MOGHE, a relatively new type of malformation of cortical development. It highlights the importance of a multimodal approach in the diagnosis and management of MOGHE in pediatric patients and the opportunity for curative epilepsy surgery.

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**MRI-Guided Laser Interstitial Thermal Therapy for Treatment of Hypothalamic Hamartoma – TLVMC Experience**

**Lottem Bergman**[1], Orna Aizenstein[2,3], Lilach Goldstein[4,3], Firas Fahoum[4,3], Anat Gauzman[5,6], Miryam Attias[5], Shimrit Uliel-Sibony[7,3], Jonathan Roth[6,3], Ido Strauss[8,3]

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**Purpose:** Hypothalamic hamartomas (HH) are rare developmental malformations within the brain, often causing drug-resistant epilepsy. MR-guided laser interstitial thermal therapy (MRgLITT) is a promising minimally invasive neurosurgical treatment option. This study retrospectively evaluates our initial experience with MRgLITT for HH treatment, focusing on lesion size, ablation accuracy, safety, and patient satisfaction.

**Method:** We reviewed clinical and imaging data of all patients who underwent MRgLITT for HH at the Tel-Aviv Medical Center (TLVMC) between 2019 and 2023. Data collection included demographics, seizure characteristics, complications documented in medical records, and patient satisfaction assessed through phone interviews.

**Results:** Six patients underwent MRgLITT for intractable epilepsy due to HH. Four were children (average age at surgery: 12 ± 2.23 years) and two young adults (20 and 32 years old). The median follow-up period was 20 months (range 5-51 months). The average pre-op lesion volume was 0.3±0.32 $cm^3$. We were able to target all lesions using a single optic fiber. The average enhancing post ablation volume was 0.4±0.3 $cm^3$ There were no bleeding complications during the procedures. No serious adverse events or neurological deficits were reported during or after the procedure. Two patients experienced minor electrolyte disorders, one exhibited transient polyuria, and another presented with transient anisocoria that resolved spontaneously. Most patients were discharged on POD 1 (median 1 day, range 1-6 days).

3/6 patients of patients (50%) achieved seizure freedom (Engel class I), while the remaining 2/6 (50%) experienced a significant reduction in seizure frequency (Engel class II). All 6 patients and their families expressed high satisfaction with the procedure, willingness to repeat the treatment and would recommend it to others. Additionally, all patients are currently undergoing gradual tapering of their anti-seizure medications.

**Conclusion:** Our initial experience suggests that MRgLITT is a safe and effective minimally invasive treatment for HH in children and young adults. It demonstrates promising results in terms of ablation accuracy, seizure control, and patient satisfaction.

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**Learning Curve in Robotic Stereoelectroencephalography – Single Center Experience**

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Robotic-assisted Stereoelectroencephalography (SEEG) is an emerging technology that will gradually replace the manual frame-based technique for depth electrodes implantation in refractory epilepsy patients. Adoption of a new surgical technology always involves a period of adjustment for the surgical team. Challenges discovered during first cases are investigated and workflow modifications made based on clinical experience and intuition.

This study demonstrates the operative workflow evolution and learning curve for the Medtronic Stealth Autoguide robotic SEEG system. We will present a retrospective analysis of the first 6 robotic-assisted SEEG ceases in a single institution. The criteria to evaluate the improvement over time will be: mean entry point error, mean target point error, mean depth point error, total operative time and operative time per electrode.

The lessons learned from these first cases may facilitate incorporation of this robotic platform in other institutions, to improve operative efficiency and safety.

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**Quality of life of children with surgically treated epilepsy-the patient's perspective**

**Ido Ben Zvi**[1,2], Noa Schwartz[2], Aswin Chari[1], Martin Tisdall[1]
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**Background and Aim:** Clinical trials and studies in epilepsy surgery commonly use the seizure outcome (Engel or ILAE Classification) as the primary outcome measure, with the focus being on the proportion of patients achieving seizure freedom. However, little data exists as to what outcomes are important to patients and their carers. We sought to ascertain the most important outcomes for patients and their carers.
**Method:** An international online anonymous survey was conducted through patient advocacy groups. The survey consisted of 18 multiple choice questions. In addition to demographic questions about the patient and the management of their epilepsy, the survey asked what the most important outcomes were across multiple domains including seizure-related, cognition and developmental, quality of life and other long-term outcomes.
**Results:** 204 patients or parents/carers responded to the survey. 61% were children or their carers. 72% report focal seizures (30% of them have generalized seizures as well). 53.4% currently have more than one seizure a month (23.5% daily). 37.2% of patients had undergone surgery. Half of them reported seizure freedom, and 90% reported postoperative improvement. When asked what outcome measure was most important, 44.6% responded being seizure free and 26% desired improvement in quality of life. When asked about the timing of potential surgical treatment, 64.7% would consider having surgery soon after the diagnosis of epilepsy; this percentage was higher among operated patients (72%), but without statistical significance ($p = 0.077$).
**Conclusions:** More than third of our cohort had an operation, with half reporting seizure freedom. Across this large sample, the most important outcome measure is being seizure-free, reinforcing focus on seizure freedom in clinical trials. The second most important outcome measure was quality of life, emphasizing the need to measure these outcomes in clinical studies of epilepsy and epilepsy surgery. Many would consider early surgery and the risks and benefits of this warrant further study.


**Session III**
**CLINICAL SESSION**
**ABSTRACT PRESENTATION**
**Chairpersons: Shmuel Appel, Veronika Chernuha**

**"Status Non-Epilepticus"**

**Ronen Spierer**[1], Moshe Herskovitz[2]
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**Background and purpose**: Status non-epilepticus is characterized by recurrent or prolonged psychogenic non-epileptic seizures (PNES), which often mimic status epilepticus (SE). This study focuses on the misdiagnosis of convulsive SE in patients whose seizures were of psychogenic origin.
**Methods:** We analyzed eight patients (and 13 events) initially misdiagnosed as having convulsive SE. The diagnostic evaluation included a review of their clinical presentation, treatment, and treatment response. Results: The patients in this study were predominantly treated with Benzodiazepines (BZD). However, this treatment was mostly ineffective, leading to the need for tracheal intubation in many cases.
**Conclusion:** The poor response to BZD emphasizes the functional nature of PNES and further supports our previous research indicating that PNES stems from the reactivation of the freeze discharge reaction, implicating amygdalar dysfunction as its cause. In addition, the ineffectiveness of BZD in these cases highlights the importance of considering a differential diagnosis of PNES in patients presenting with these convulsive events. We also wish to emphasize the need for careful clinical assessment to avoid misdiagnosis and inappropriate treatment.

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**Analysis of Targeted Epilepsy Gene Panel Sequencing Suggests That Variants Previously Classified As Uncertain Significance In QARS1 And SCN9A Genes May Play An Important Role In Epilepsy**

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**Background:** Epilepsy, a chronic neurological disorder marked by seizures or epileptic syndrome, encompasses various etiologies, and carries implications for neurological, cognitive, psychological, and social well-being. There are over 500 genes associated with epilepsy occurrence. Therefore, Next-Generation Sequencing (NGS) epilepsy gene panels are commonly employed for patients with epilepsy. However, a substantial proportion of results remains uncertain and is not considered directly causative.
**Methods:** Between the years 2018-2022, a commercial epilepsy gene panel testing was conducted on pediatric patients at a single large tertiary health center. Utilizing NGS technology, the panel analyzed 187 genes associated with epilepsy, categorizing variants according to The American College of Medical Genetics and Genomics (ACMG) guidelines. A retrospective analysis of 156 probands and 74 parents delved into prevalence, population comparisons, and protein network path analysis, enhancing genetic comprehension. Advanced tools were employed for identifying notable variant combinations and calculating genetic correlations.
**Results:** Targeted gene panel sequencing revealed 18% negative, 22% positive and 60% uncertain outcomes among probands. Frequently implicated genes in which pathogenic variants were noted, included SCN1A, MECP2, and CDKL5. Notably, two distinct variants, c.2133G>C in the SCN9A gene and c.316G>A in the QARS1 gene, were identified as likely pathogenic in contrast to their formal interpretation as variants of uncertain significance.
**Conclusion:** Epilepsy gene panel enables targeted gene analysis, emphasizing its clinical significance. The study elucidates the intricate genetic landscape of infantile and childhood epilepsy, with approximately 60% uncertainty in test results. We suggest an interpretation of two clinically significant variants in the QARS1 and SCN9A genes.
**Grants:** This work received support from the Zuckerman STEM Leadership Program and Israel Science Foundation grants 1994/21 and 352/21.

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**Treatment of Infantile Spasms using Oral Steroids (UKISS Protocol)-the Experience of a Single Centre**

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Infantile epileptic spasms syndrome (IESS) is a severe (developmental and) epileptic encephalopathy in infancy with variable etiology leading to global developmental impairment. Prompt treatment of spasms and suppression of the epileptic activity (hypsarrhythmia) diminish the effect of cognitive impairement. Several treatment regimens were developed, including high dose steroids (ACTH) and vigabatrin. Recently, a short duration high dose oral steroid (prednisolone) regimen has been validated , the UKISS (United Kingdom infatile spasms syndrome) protocol. However, this protocol is underused in Israel. Here we present our experience with the UKISS protocol in five patients between the years 2019-2023.

Five patients (3 males) were enrolled in this study. The etiology was hypoxic ischemic encephalopathy in one, one gene variant in one (PMM2) and unknown in three. Treatment commenced with prednisolone 40mg/d, at a mean age of 7 months (4 month-14 months). Treatment started immediaty after diagnosis in four patients, but in two of them, clinical spasms with developmetal regression were present over one month. Hypsarrhythmia cleared in all patients within two weeks of treatment, and did not reccurr after tapering down. In a 14-month old patient with long-standing spasms, there was still multifocal epileptic activity on EEG after two weeks, therefore vigabatrin was added. One patient with hypoxic ischemic encephalopathy developed Lennox Gastaut syndrome. Three patients had no epilepsy and EEG normalized. Developmental outcome was good in two. Side effects like restlesness were minimal.

In conclusion: Our successfull experience treating IESS with oral steroids reinforces the need for dissemination of the UKISS protocol among other centers in Israel.

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**Seizure frequency during different trimesters in pregnancy**

**Yusef Najjar**[1], Tal Benoliel[2,3], David Mankuta[4,5], Dana Ekstein[2,3]

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**Background:** Treating women with epilepsy (WWE) during childbearing age is challenging and requires maintaining a careful balance between control of maternal seizures and the potential effects of anti-seizures medications (ASMs) on the developing fetus. The anagement of pregnant WWE is further complicated by the effects of hormones on ASMs pharmacokinetics.
**Methods:** A retrospective study of women seen at Hadassah WWE and pregnancy clinic between 2020-2022 was performed. Data on demographics, epilepsy, medications, blood tests and seizure frequency before conception and during each of the trimesters of pregnancy were acquired from the electronic medical records.
**Results:** 76 pregnancies of 46 WWE, 23 having two pregnancies and two - three pregnancies, were included. Most pregnancies (69, 91%) were exposed to ASM monotherapy - 38 lamotrigine, 28 levetiracetam and 3 carbamazepine. No seizures were recorded during 41 (54%) pregnancies, 31 out of 41 (76%) of the pregnancies that were preceded by at least one year of seizure freedom and 11 of 35 (31%) pregnancies with at least one seizure during the year prior to conception. More pregnancies were free of seizures during the first and third trimester – 54 (71%) and 53 (69%), respectively, than during the second trimester (41, 54%; p=0.003). In 10 of the 41 pregnancies beginning after well controlled epilepsy there were seizures: 4 during the first trimester, 9 during the second (including three of the pregnancies with seizures during the first) and 5 in the third trimester (all had also seizures during the second trimester), although the most pronounced decrease in ASM levels were seen in the first trimester. Of 35 pregnancies that began out of not well controlled epilepsy, in 17 (49%) there were no seizures during the first trimester, in 16 (46%) in the second trimester and in 18 (51%) in the third trimester.
**Conclusion:** Our study suggests that in most WWE the tendency for seizures may be lower during the first trimester of pregnancy, possibly related to relatively higher progesterone concentrations, and favoring a delay in ASMs increase after organogenesis. Further prospective studies could validate our findings, determine their causes and their impact on clinical practice.

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**A Case Series of Defects in Various AMPA Receptor Subunits and Their Genotype-phenotype Association**

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AMPA ionotropic glutamate receptors are formed by four subunits encoded by autosomal and x-linked genes GRIA1-4. While mutations in GRIA2, GRIA3 and GRIA4 have been associated with a wide spectrum of neurodevelopmental disorders and developmental epileptic encephalopathy (DEE), GRIA1 mutations were not linked to DEE until now. We present a case series of patients with defects in three different AMPA receptor subunits, including the first reported GRIA1 related DEE. We delineate their phenotypes and discuss the correlation between the genotype and therapeutic strategies.

**Patient 1.** A 3-month-old boy, born after an uneventful pregnancy and delivery, presented at day 4 with epileptic events. EEG showed bilateral, non-synchronized epileptic activity with multiple focal ictal electrographic events and a normal background activity in-between. Neurological examination demonstrated microcephaly, hypotonia and developmental delay. A comprehensive metabolic and infectious workup was negative. Brain MRI demonstrated a mildly small vermis. Trio whole exome sequencing (WES), found a de-novo heterozygous c.1915G>T, p.(Ala639Ser) variant in GRIA2, which at-the-time was previously unrelated to human disease. Intractable epilepsy persisted despite multiple anti-seizure medications including Perampanel and the patient passed away at 3 months of age.

**Patient 2.** A20-years-old female presented with severe developmental delay, hypotonia, hand stereotypes and absent hand usage accompanied by aphasia, sleep and behavioral disorder but no seizures. The general phenotype was consistent with Rett like syndrome. MECP2 sequencing and MLPA were negative, but single WES (unknown biological parents) revealed a heterozygous GRIA3 variant c.1994T>C, p.(ile665Thr).

**Patient 3.** A 4-month-old girl with unremarkable perinatal history was admitted to our hospital due to recurrent seizures since 2 months of age accompanied by developmental delay, microcephaly and hypotonia. EEG showed diffuse slowing and disorganized background activity without epileptiform activity. Brain MRI demonstrated diffuse atrophy, hyper-intensities of the white matter and dysplastic lateral ventricles. Comprehensive metabolic and infectious workup were negative. WES revealed a heterozygous missense GRIA1 variant c.1600C>T, p.(Pro534Ser) and Perampanel reduced seizure frequency.

To summarize, defects of AMPA receptor subunits are correlated with a wide neurodevelopmental phenotype including DEE. Prompt recognition and precision medicine treatment strategies may greatly improve these patients' quality of life and seizure control.

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**Is it autoimmune encephalitis?**

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Acute behavioral changes, with or without seizures is a common cause for admission to the neurology unit, with the possible explanation of autoimmune encephalitis. We present two cases of unrelated children with an acute change in behavior, seizures, and a new onset movement disorder.

A 3-year-old toddler with normal development was admitted to the emergency room with an acute change in his behavior; within several days he became extremely hyperactive, with repeated episodes of staring. His neurological examination was normal. EEG in sleep showed multifocal epileptic activity of high frequency and high amplitude. He did not respond to anti-seizure medication. Further on he stopped talking, had a severe sleep disorder, and recurrent dystonic and chorea-like movements. Brain MRI was normal; CSF workup came back positive for NMDA receptor antibody. He was treated with high dose corticosteroids, IVIG and due to his severe manifestations and slow recovery, Rituximab was initiated during his hospitalization.

A second 9-year-old child, with normal development, was admitted after an acute change in his behavior including severe irritability and impulsiveness, a profound sleep disorder and recurrent episodes of shouting and kicking. His neurological examination was normal. EEG in sleep showed bilateral central epileptic activity of moderate frequency, and he was treated with anti-seizure medication with no improvement. Video EEG showed inter-ictal and ictal activity, with over 20 episodes of behavioral change in correlation with electrographic changes of bilateral frontal activity. MRI was normal and so was CSF analysis. With a working diagnosis of seronegative immune encephalitis, he received high dose corticosteroids treatment with only slight improvement. IVIG was initiated simultaneously with a change in the anti-seizure treatment, with a marked decline in seizure frequency. Whole exome analysis was sent, and was positive for a missense mutation on SEMA6B gene. Pathogenic variants on SEMA6B are known to cause developmental and epileptic encephalopathy. Further analysis is needed.

Autoimmune encephalitis is an emerging diagnosis in pediatric neurology. However, many cases are treated without evidence of a specific antibody. As we described, additional testing, including genetic analysis, can assist in studying seronegative cases.

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**Sleep And Depression Habits In Patients With Epilepsy (PWE)**

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**Introduction:** Epilepsy exhibits a bidirectional relationship with sleep and depression. This intricate interplay is evident as sleep deprivation can precipitate seizures, while the use of anti-seizure medications (ASMs) can significantly affect sleep components and overall quality. Epilepsy is linked to depression, a condition that is notably prevalent among PWEs.
In this study, we aim to delve into the intricate relationship between sleep, depression, and epilepsy, seeking to unravel the complexities of their interplay and the implications for the management of epilepsy.
**Methods:** We recruited patients from the Epilepsy Outpatient Clinic at Rabin Medical Center (RMC). Patients were included that were diagnosed with epilepsy and are over eighteen years of age. We recorded patient characteristics along with details regarding their epilepsy history. Additionally, we utilized two questionnaires: the Pittsburgh Sleep Quality Index (PSQI) for sleep assessment, and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) for evaluating depression.
**Results:** Our study, which is still in progress, has currently recruited 30 patients from the Epilepsy Outpatient Clinic at RMC. The preliminary results offer intriguing insights, particularly in the relationship between seizure frequency and depression among patients with epilepsy. We observed a notable correlation between the frequency of seizures and depression levels, as measured by the NDDI-E. Specifically, patients experiencing weekly seizures reported an average NDDI-E score of 10 (±5.6), indicative of higher depression levels. In contrast, patients with less frequent seizures, occurring once a year, demonstrated significantly lower NDDI-E scores, averaging 6.33 (±2.95). This difference was statistically significant ($p<0.05$), suggesting a direct relationship between the regularity of seizures and the severity of depressive symptoms.
**Conclusion:** Despite the ongoing nature of our research and the relatively small sample size of 30 patients, the preliminary results are revealing. They underscore a significant connection between the frequency of seizures and the prevalence of depression in patients with epilepsy. This finding highlights the importance of managing seizure frequency not only for the direct benefits of reducing epileptic episodes but also as a potential strategy for mitigating depression in this patient population. Our study continues to explore these dynamics further.

**Session IV**
**DRUG TREATMENT AND DRUG RESEARCH**
**ABSTRACT PRESENTATION**
**Chairpersons: Tal Benoliel, Lilach Goldstein**

## Management of Antiseizure Medications Shortages In Israel

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Drug shortages (DSs) pose a global challenge, significantly affecting patient care and healthcare costs. This study investigated temporary distribution interruptions of antiseizure medications (ASMs) in Israel. The primary objective was to determine if ASMs difficult to replace with generics ("non-switchable") were more affected by drug shortages. The secondary objective was to determine whether drug shortage frequency increased during local and global emergency situations.

Methods: Data from the Israeli Ministry of Health (MoH) Database documenting supply shortages from 2013 to 2023 were analyzed by a clinical pharmacist. ASMs were categorized by the active substance, drug type, and the period of the shortage. Each case was assessed for available replacements and the issue of management guidelines by the MoH. The Chi-square test was utilized to determine significance.

Results: Over the 10-year study period, 117 shortages of ASMs were identified, with 52% involving medications not typically requiring therapeutic monitoring during generic switches. Notably, pregabalin and lamotrigine-containing preparations experienced more frequent interruptions. During the first and second waves of the Covid-19 pandemic in 2020, and the" Swords of Iron" war, there were noticeable peaks in drug shortages, accounting for 27% of the total drug shortages over a total of less than a year. Among ASMs requiring monitoring during generic switches, 10 shortages occurred during emergencies, while 45 did not. Conversely, among ASMs not requiring monitoring, 22 shortages occurred during emergencies, and 40 did not ($p = 0.03612$).

Conclusion: The findings of this study suggest that distributors of ASMs challenging to replace should maintain larger stocks, potentially mitigating the effects of emergencies on their supply chains. Additionally, the research underscores the importance of effective management strategies for ASMs shortages, offering possible guidelines for future ASMs shortage.

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**The Influence of Valproic Acid Amide Derivative: sec-Butylpropylacetamide, and its Stereoisomers on Folate Transporters in Human Placental Cell Line, an in vitro Study**

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**Purpose:** *sec*-Butylpropylacetamide (SPD), and its stereoisomers (2S,3S)-SPD, (2R,3S)-SPD and (2R,3R)-SPD are CNS-active compounds, closely related amide derivatives of valproic acid (VPA). In contrast to VPA, in SWV mice, SPD, (2S,3S)-SPD, (2R,3S)-SPD and (2R,3R)-SPD did not cause neural tube defects at therapeutic doses. High dose of (2R,3R)-SPD were associated with higher teratogenicity incidence. In this study, our goal was to characterize the effects of sub-chronic exposure to SPD and its enantiomers, on the expression of folate carriers, to evaluate the expression of these transporters as a major congenital malformation marker. We focused on *FOLR1* (encoding the folate receptor alpha), *SLC19A1* (reduced folate carrier) and *ABCG2* (breast cancer resistance protein) in a human placenta cell line *in vitro*, under controlled conditions.

**Methods:** BeWo cells were incubated for two or five days with SPD, (2S,3S)-SPD, (2R,3S)-SPD, (2R,3R)-SPD, VPA, or their vehicle at concentrations that mostly represent VPA's therapeutic range (0.5 mM [79 and 72 µg/mL for SPD and VPA, respectively]) and one supratherapeutic concentration (1 mM [157 and 144 µg/mL, respectively]). RT-PCR analysis was utilized to study the effects of the entities on carriers' mRNA expression (n=6/treatment group).

**Results:** Racemic SPD caused 2-fold elevation in the mRNA levels of *FOLR1* after 2 days of incubation ($p<0.05$), while the other SPD enantiomers did not significantly affect *FOLR1* expression. After 5 days, 1 mM SPD, (2S,3S)-SPD, and (2R,3S)-SPD reduced 2-fold *SLC19A1* expression ($p<0.001$), whereas (2R,3R)-SPD caused a non-significant elevation. Racemic SPD treatment caused up to 2-fold elevation ($p<0.001$) in *ABCG2* levels. (2R,3S)-SPD and (2S,3S)-SPD did not affect this transporter, while 0.5 mM (2R,3R)-SPD caused a non-significant elevation by 50%.

**Conclusions:** The most teratogenic SPD enantiomer, (2R,3R)-SPD, did not demonstrate exceptional effects on the expression of any of the three studied folate transports. These findings are in line with the results of our previous analysis using other VPA derivatives. It can be inferred that none of these folate carriers by itself can serve as a marker of VPA teratogenicity of in vivo. Yet an ongoing study assesses cellular folate levels, to clarify the cumulative effects of each enantiomer on folate handling by placental trophoblast cells.

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**CBD Effects on the Biophysical Properties of Cell Membrane**

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**Objective:** Cannabidiol (CBD) is the most lipophilic antiseizure medication (ASM; LogP=6.3). Lipophilicity considerably affects CBD's bio-disposition. For instance, it leads to CBD accumulation in adipose tissue and the placenta. Here, our aim is to investigate whether CBD lipophilicity can affect the biophysical properties of cell membranes.

**Methods**: CBD uptake and release kinetics were assessed in RAW 264.7 cells and isolated human white blood cells using LC-MS/MS. CBD's impact on RAW 264.7 cell membrane fluidity was examined using a fluorescence assay, with the generalized polarization (GP) value calculated as an indicator of fluidity. Trans-epithelial electrical resistance (TEER) was measured to evaluate membrane resistance in MDCK cells. We additionally evaluated the effects of CBD on the activity of the uptake and efflux transporters Glut1 and P-glycoprotein (P-gp) using 2-NBDG and calcein AM, respectively. CBD's effect on Glut1, Glut4 mRNA expression was analyzed via RT-PCR in RAW 264.7 and BV2 cells.

**Results:** CBD was uptaken into both RAW 264.7 and human cells. Changes in membrane fluidity were observed in RAW 264.7 cells at concentrations 5 µg/mL and 500 ng/mL (-1.8% and 15.2% of control GP value), respectively (*$p<0.01$). TEER values 78 ± 22% at 50 µg/mL CBD (*$p<0.05$) compared to control. Despite increases in Glut1 and Glut4 expression, these changes did not translate to an increase in the uptake of 2-NBDG. P-gp inhibition, but not CBD, affected cellular calcein accumulation.

**Conclusions**: Our findings indicate that CBD can enter myeloid cells and affect their membrane properties, including fluidity and epithelial resistance. This did not translate to significant changes in the activity of glucose transporters and P-gp. These findings call for further research to enhance our understanding of the mechanisms of action of lipophilic antiepileptic drugs and explore the therapeutic potential of these drugs in modulating cellular function and managing epilepsy.

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**Enzyme Inducers: A Pilot Analysis of the Relationships between Their Effects on Exposure to Sensitive CYP3A4 Substrates or UGT substrates and the Effects on Moderately Sensitive CYP3A4 or CYP3A4/UGT Substrates**

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**Background and purpose:** Enzyme inducers, including antiseizure medications (ASMs), are involved in many pharmacokinetic drug-drug interactions. Cytochrome P450 (CYP)3A4 is co-induced with several other drug-metabolizing enzymes, including -UDP-glucuronosyltransferase (UGTs), expanding the DDI potential. Yet data on the magnitude of many potential interactions are often scarce. During the process of drug approval, the manufacturer may provide information on the interaction of the drug with oral contraceptives and sensitive CYP3A4 substrates, but not less sensitive substrates. Given this knowledge gap, we intend to analyze systemically, for the first time, the potential of using these data to estimate the effects of enzyme inducers on a multitude of other drugs.
**Methods:** PubMed and Embase were searched up to December 2023, without date restrictions, to identify works in humans that indicate a change in the AUC (AUCR) of CYP3A4 sensitive substrates, CYP3A4 moderately sensitive substrates, ethinylestradiol (a CYP3A4/UGT substrate), and valproate (a UGT substrate) when given in combination with enzyme inducers. Indirect comparisons were performed based on AUC and Cmax ratios [substrate+Inducer]/[substrate only].
**Results:** A linear correlation was found between the effect of inducers on sensitive and moderate substrates; R squared=0.96, Y=1.243X-0.04151 (95% CI for the slope, 1.07 to 1.42). Michaelis–Menten kinetics performed better than linear correlation for the association between ethinylestradiol and CYP3A4 sensitive substrates, with R squared=0.72, Vmax=3.08 (95%CI, 2.281 to 4.754) and Km=0.29 (95%CI, 0.13 to 0.57). Michaelis-Menten kinetics also characterized the relationships between ethinylestradiol and valproate (R squared=0.99, Vmax=1.14, 95%CI, 0.88 to 1.73, Km=2.20, 95%CI, 1.41 to 3.86).
**Conclusion:** This pilot study provides a proof-of-concept for the ability to use data obtained with sensitive CYP3A4 substrates for predicting the effects of enzyme inducers, including ASMs, on other medications. These associations can be used for assessing the magnitude of ASM effects on multiple medications, including direct-acting oral anticoagulants (DOACs), statins, and antiviral medications, in the absence of direct studies. This allows for establishing TDM recommendations and/or improving drug selection when only scarce data are available. This is a preliminary study, and a systematic review is planned in the future.

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**Dose Adjustment of Anti-seizure Medications Levetiracetam And Lamotrigine During The Postpartum Period. Schedule Plan, Safety and Efficacy.**

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**Introduction:** Lamotrigine (LTG) and Levetiracetam (LEV) are anti-seizure medications (ASMs) widely used for the treatment of women with epilepsy (WWE) of childbearing age due to low teratogenic potential. Physiological changes during gestation alter the pharmacokinetic properties of these drugs and enhance their clearance. Hence, drug level monitoring and frequent dose adjustments are required to avoid a decline in serum levels that could result in poor seizure control. During the postpartum period, the physiological changes are reversed. A delay in dose reduction could result in drug toxicity. The ideal rate of dose reduction following delivery is yet to be determined.
**Methods:** We retrospectively examined the medical records of pregnant WWE who were followed at Tel Aviv Medical Center between the years of 2018-2023. At the beginning of the study period, patients were instructed to continue drug blood monitoring of ASMs following delivery. Starting 2020, an empiric taper down regimen following delivery was implemented with dosing adjustments scheduled for 1 day, 1 week and 3 weeks postpartum. Individualized regimen was provided for each patient. We recorded ASM dose, serum levels, side effects, and self-reports of seizures frequency.
**Results:** Eighty-nine pregnancies of 79 WWE were included. Forty-five were treated with LEV, 38 with LTG and 6 with a combination of both ASMs. In 29 pregnancies, patients continued *therapeutic drug monitoring* during the post-partum period and in 60, patients were instructed to follow an *empiric shedule down titration regimen*. There was no seizure relapse among WWE who received *dose reduction schedule*. Five of 29 among *empiric dose reductiongroup* reported having side effects, vs. 6 of 60 among *schedule dose reductiongroup*.
**Conclusion:** Empiric schedule for postpartum dose reduction of Lamotrigine and Levetiracetam was not associated with increased risk of seizure exacerbation and was well tolerated with minimal side effects.