LONG-TERM COGNITIVE CONSEQUENCES OF SELF-LIMITED EPILEPSIES OF CHILDHOOD - ARE THEY REALLY SO BENIGN?

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Introduction: The self-limited epilepsies of childhood are common and were historically considered benign.We sought to determine whether cognitive function in young adults who experienced self-limited epilepsy as children and are now seizure-free and unmedicated differs to the general population.

Methods: We performed a cross-sectional population-based study using data obtained from the Israel Defense Forces compulsory program for conscription from 1980-2018. Participants were defined as having a self-limited epilepsy of childhood if they had a previous diagnosis of epilepsy but were > 5 years following the last seizure and > 2 years without anti-seizure medication.The main outcome was the odds ratio for having low cognitive function defined as being >1.5 SD below the mean in those with previous self-limited epilepsy of childhood vs. their peers without a history of epilepsy, using an unadjusted multinominal regression model. Separate analyses were performed for three sub-periods to assess potential impact of changes in management over time. A similar analysis was performed in participants following remission of a non-neurological chronic disease of childhood, asthma.

Results: Following exclusion criteria, 2,124,871 men and women aged 16 to 19 years were included in the analysis, of whom 3,452 (0.16%) met the criteria of having had a self-limited epilepsy of childhood. 346 (10.0%) participants from the self-limited epilepsy group had low cognitive function vs. 160,133 (7.5%) in the other participants. The odds ratio of having low cognitive function in the self-limited epilepsy of childhood group was 1.43 (95% CI 1.28-1.59, p<.001). Correcting for gender and socioeconomic status did not attenuate the statistical significance and was unchanged during the three sub-periods. We did not demonstrate similar findings in the resolved asthma cohort .

Conclusions: Cognitive outcomes in young adults with previous self-limited epilepsies of childhood are more likely to be poor. Our results support that this is not merely due to the burden of dealing with chronic illness and underlie the need to avoid the term “benign” for these epilepsies. Further research should delineate the role of seizure burden vs. other possible contributing factors such as long-term effects of anti-seizure medications or genetic variations in epilepsy patients.

READING DIFFICULTIES AMONG CHILDREN WITH SELF-LIMITED ("ROLANDIC") EPILEPSY WITH CENTROTEMPORAL SPIKES: AN FMRI STUDY

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Introduction: Self-limited Epilepsy with Centrotemporal Spikes (SeLECTS) has been traditionally regarded as a benign epilepsy with no associated comorbidities. The current ILAE new nomenclature recognized a growing body of evidence challenging this assumption, and abandoned the descriptor "benign" to this epilepsy syndrome (formerly known as benign rolandic epilepsy).

Reading was shown to be one of the cognitive domains impacted by SeLECTS. Affected children have been repeatedly shown to have increased rates of technical and reading comprehension difficulties. Yet, the mechanisms underlying these challenges remain poorly understood. The aim of the current study is to characterize reading abilities among 8-14 y.o. Hebrew-speaking children with SeLECTS vs healthy age-matched typical readers.

Methods: All participants underwent a comprehensive reading assessment and an fMRI reading task. Clinical data were collected for the test group.

Results: Initial results show differences in reading scores between both populations. We will present data from five patients with SeLECTS who completed the study, and highlight differences from results obtained in healthy typical readers.

Conclusion: This study should raise awareness of mild cognitive deficits among children with SeLECTS, and inform educators and other professionals regarding reading interventions to ameliorate this effect.

DEP SCORE - A SIMPLE BEDSIDE TOOL TO DIAGNOSE PSYCHOGENIC NON EPILEPTIC SEIZURES

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Background: As of today, efficient bedside tools for differentiating psychogenic non-epilpetic seizures (PNES) from epileptic seizures (ES) haven't been found. The study aimed to build and validate a clinical tool that will allow a good differentiation between PNES and ES.
Methods: We constructed a 4-dimensional scale that included: 1. The absence of global dynamics of the movement type 2. The absence of global dynamics of the movement rhythms. 3. Eyes closure during an event. 4. The absence of rotational pelvic movements.
Each dimension received a score of 1- if it met the above conditions or 0- if not. The total score ranged from 0-4. The score was named DEP (Dynamics of movements, Eyes closure, and Pelvic rotation).
Two junior residents in their first months of residency underwent practice on a series of video footage that we had used in a previous study. Subsequently, each rater was given 20 video footage and had to score each case.
We hypothesized that a low score would indicate an ES attack and a high score would indicate a PNES attack.
Results: Intraclass correlation between raters was high (r=.87). The ES group (M=0.80, SD=1.11) was rated lower compared to the PNES group (M=2.95, SD=0.76) (t(18)=5.05, p<.01). A ROC analysis showed a statistically significant AUC (.93). Youden index J showed a 90% sensitivity and 80% specificity for a 1.5 score cutoff.
Conclusions: High DEP score >1.5 has high sensitivity and specificity for PNES diagnosis and can serve as a simple bedside tool for PNES diagnosis.

WHICH PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES) PATIENTS ARE MORE LIKELY TO BE TREATED WITH ANTI-SEIZURE MEDICATIONS?

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Background: The average time for psychogenic non-epileptic seizures (PNES) diagnosis is about 7.5 years. During this time, many patients receive inadequate treatment, and sometimes even life-threatening treatments such as tracheal intubation.
Purpose: To determine the risk factors for misdiagnosis of PNES as epilepsy.
Methods: The medical records of patients that underwent video-electroencephalogram (EEG) monitoring were reviewed retrospectively. Patients that had PNES without epileptic seizures (ES) were included in this study. Baseline personal and monitoring characteristics were collected. The patients were then divided into two groups based on their therapeutic status. Patients in the treatment group were again divided into two groups based on the number of anti-seizure medications (ASM) they were treated with.
Results: Fifty-seven patients diagnosed with PNES were included in this study. Thirty-seven patients were under treatment and 20 patients weren't under treatment at the time of monitoring. Convulsive seizures, abnormal interictal EEG patterns, and pathological brain imaging findings were more frequent among patients in the treatment group ($p<0.05$). Patients with convulsive seizures were more likely to be treated with multiple ASM in comparison to patients with only dialeptic seizures ($p<0.05$). Lastly, patients in the treatment group were monitored longer and had fewer seizures during monitoring ($p<0.05$).
Conclusion: PNES patients with abnormal EEG patterns and pathological brain imaging findings are more likely to be treated with ASM. Pure dialeptic nature of seizures is less likely to be misdiagnosed as ES. In addition, patients with such seizures are less likely to be treated with multiple treatment lines.

RATE OF COGNITIVE DECLINE BEFORE SEIZURE DIAGNOSIS IN INDIVIDUALS WITH DEMENTIA AND SEIZURES

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Seizures and epilepsy occur frequently in individuals diagnosed with dementia. While previous studies report highest incidence in advanced disease stages, emerging studies suggest subclinical seizures noted only on EEG occur frequently in early stages. Such recorded subclinical seizure activity is associated with a more rapid course of cognitive decline on longitudinal assessment. We thus hypothesized individuals with dementia who are diagnosed with seizures in any stage experience a rapid cognitive decline before they are diagnosed with seizures.

Method: Study design is a retrospective case-control study, assessing clinical data from 24142 research subjects evaluated longitudinally from the National institute of health Alzheimer Coordination Center, years 2006-2019. Exclusion criteria included individuals with seizures on their first visit or unknown seizure status, unknown APOE genotype or without longitudinal data. Cognitive decline as an outcome was defined with annual Mini Mental State Exam (MMSE) and Clinical Dementia Rating Sum of Boxes (CDR-SB). Individuals were dichotomized to with or without seizure diagnosis during follow up. The decline was assessed using a linear mixed effects models adjusting for other variables known to alter decline rate such as age at onset of symptoms, sex and ApoE4 genotype and included a random effect for time between visits within patients.

Results: We identified 139 and 2819 individuals with and without seizures respectively on follow up. Seizure group was on average younger at symptom onset (65+11.3 vs 70+10.0), and remained longer on follow up (5+3 vs 3+2years). While baseline MMSE and CDR-SB was similar, The seizure group experienced a rapid annual decline in CDR-SB(0.98 , SE 0.24, 95% CI 0.51-1.46, p<.0001) and MMSE(-1.8, SE=.40, 95% CI -1.4 and -2.6, p<0.00001).

Conclusions: A rapid rate of decline can be observed in individuals with dementia prior to seizure diagnosis. Our study suggests undiagnosed seizures or seizures activity on EEG should be suspected in individuals who experience a rapid rate of cognitive decline.

IDENTIFYING PRE-ICTAL PATTERNS USING EEG ANALYSIS

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Background: Epilepsy is a common neurological disease characterized by sudden seizures. Prediction of upcoming seizures long enough before their onset will allow warning the patient to prevent seizure-associated injuries, and will even allow intervention by administration of preventive treatments such as benzodiazepines. Therefore, identifying patterns preceding seizure onset and localization of the area most prominent for seizure prediction are important for better understanding of the currently concealed mechanisms of seizure initiation.
Methods: Long-term scalp electroencephalography (EEG) recordings of 4 patients with focal epilepsy were analyzed, two seizures were included for each patient. Ten commonly used features for EEG analysis were extracted from the signals in a moving-window fashion. For each seizure, a localization algorithm classified the EEG channels that show maximal separation between pre-ictal and interictal states, and a feature-importance algorithm chose the features most important to such separation.
Results: In each patient, the best separation between pre-ictal state and interictal state was shown in specific electrodes. Those were chosen by a localization algorithm. The most prominent EEG channels were similar in both seizures for all 4 patients. The electrodes chosen by the localization algorithm did not always match with the epilepsy localization.
Furthermore, the features most prominent for pre-ictal to interictal separation were similar in all 4 patients.
Another important finding was that the Hjorth mobility, spectral entropy and power in the delta band were found to be important for separation between pre-ictal to interictal states in all patients.
Conclusions: First, the preictal state and interictal state have different electrophysiological features and can be detected by multifeatured analysis in focal epilepsy with scalp EEG. Second, similar features characterize the preictal state in different seizures of the same patient. Third, electrodes that show the most prominent differentiation between preictal and interictal states can be located outside the ictal onset zone and sometimes even in the contralateral hemisphere, implying seizure organization in focal epilepsy is network based and not a local event.

EEG QUANTUM POTENTIAL CHANGES DUE TO VAGUS NERVE STIMULATION (VNS) AND PREDICTION OF VNS EFFICACY

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Vagus nerve stimulation (VNS) is an important therapeutic tool in the management of drug-resistance epilepsy1,2 and has been shown to reduce mortality in patients with epilepsy3 and is effective on other neuro-psychiatric diseases like depression.4 Efficacy is highly variable, and a substantial portion of patients report no alleviation in seizure frequency. Currently there are no clear pre-implantation indicators predicting VNS benefits, and patients undergo implantation with a degree of uncertainty. This is partly due of the fact that the mechanism behind the anti-seizure effect of VNS is still not entirely understood. Contemporary research indicates a diffuse effect on brain-wide network connectivity as the VNS mechanism of action, but there is plenty yet to be discovered.

Our previous work showed high prediction accuracy in determining neuro-psychiatric diseases using our mathematical model of the p-adic quantum potential5 and thus we here aim to detect EEG changes brought about by the VNS stimulation in an attempt to differentiate between VNS responders and non-responders using pre-implantation EEG parameters. Specifically, we intend to use the promising field of quantum potential mean and variability score (qpmvs) algorithms, which utilize a holistic and integrative view of the brain and thus seems ideal to portray the suspected diffuse changes in brain functionality.

We included 24 patients who underwent EEG at the Rabin medical Center, Petach Tikva, Israel before and after VNS implantation (2015-2021). Patient age at VNS implantation was 41.1 ±16.4 years. Of the 24 patients, 14 patients underwent an EEG examination both before and after a VNS implantation. EEGs were analyzed using standard frequency spectrogram and our newly developed the qpmvs algorithm.

Our p-adic quantum potential algorithm shows clear changes in patients undergoing VNS implantation. In addition, using receiver operating characteristics (ROC) we present a highly accurate differentiation between patient's EEGs of those responding and non-responding to VNS treatment. Our newly developed EEG analysis method using p-adic quantum potential might be useful to select those patients with intractable epilepsy which will respond to Vagus Nerve Stimulation using a routine EEG.

CORTICOTROPIN RELEASING FACTOR MEDIATES KCA3.1 INHIBITION, HYPEREXCITABILITY, AND SEIZURES IN ACQUIRED EPILEPSY

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Introduction: Temporal lobe epilepsy (TLE), the most common focal seizure disorder in adults, can be instigated in experimental animals by convulsant-induced status epilepticus (SE). Principal hippocampal neurons from SE-experienced epileptic male rats (post-SE neurons) display markedly augmented spike output compared with neurons from nonepileptic animals (non-SE neurons). This enhanced firing results from a cAMP-dependent protein kinase A-mediated inhibition of KCa3.1, a subclass of Ca2+-gated K+ channels generating the slow afterhyperpolarizing Ca2+-gated K+ current (IsAHP). The inhibition of KCa3.1 in post-SE neurons leads to a marked reduction in amplitude of the IsAHP that evolves during repetitive firing, as well as in amplitude of the associated Ca2+-dependent component of the slow afterhyperpolarization potential (KCa-sAHP).

Results: Here we show that KCa3.1 inhibition in post-SE neurons is induced by corticotropin releasing factor (CRF) through its Type 1 receptor (CRF1R). Acute application of CRF1R antagonists restores KCa3.1 activity in post-SE neurons, normalizing KCa-sAHP/IsAHP amplitudes and neuronal spike output, without affecting these variables in non-SE neurons. Moreover, pharmacological antagonism of CRF1Rs in vivo reduces the frequency of spontaneous recurrent seizures in post-SE chronically epileptic rats. These findings may provide a new vista for treating TLE.

Conclusion: Epilepsy, a common neurologic disorder, often develops following a brain insult. Identifying key cellular mechanisms underlying acquired epilepsy is critical for developing effective antiepileptic therapies. In an experimental model of acquired epilepsy, principal hippocampal neurons manifest hyperexcitability because of downregulation of KCa3.1, a subtype of Ca2+-gated K+ ion channels. We show that KCa3.1 downregulation is mediated by corticotropin releasing factor (CRF) acting through its Type 1 receptor (CRF1R). Congruently, acute application of selective CRF1R antagonists restores KCa3.1 channel activity, leading to normalization of neuronal excitability. In the same model, injection of a CRF1R antagonist to epileptic animals markedly decreases the frequency of electrographic seizures. Therefore, targeting CRF1Rs may provide a new strategy in the treatment of acquired epilepsy.

DIMETHYL FUMARATE EXERTS A DISEASE MODIFYING EFFECT IN A RAT MODEL OF TEMPORAL LOBE EPILEPSY

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Strong evidence suggests that oxidative stress plays a key role in neurological disease including in prolonged seizures and epilepsy. In recent years, the nuclear factor erythroid 2-related factor 2 (Nrf2), described as the "master regulator" of the anti-oxidant response, has emerged as an important therapeutic target for various diseases. In animal epilepsy models, Nrf2 has been shown to increase in kindled animals and overexpressing Nrf2 showed a neuroprotective effect in chemical kindling in rats and SE in mice.

The fumaric acid ester, dimethyl fumarate (DMF) was approved by the FDA for the treatment of multiple sclerosis in 2013, and its application in the treatment of various tumors and inflammatory diseases has been reported in subsequent studies. Although its exact mechanism of action is unknown, orally administered DMF is thought to exert its therapeutic (e.g., neuroprotective, anti-inflammatory) effects via activation of the Nrf2 antioxidant response pathway. We here aim to evaluate the anti-epileptogenic and antiepileptic properties of DMF in a rat model of temporal lobe epilepsy.

We have found that DMF, when administered over 7 days following SE, significantly elevated Nrf2 activity and attenuated SE-induced neuronal cell death in CA1 and CA3 regions in the hippocampus of treated animals. Interestingly, DMF treatment significantly decreased the seizure frequency (per week) and total number of seizures compared to vehicle treated animals.

Importantly, we have also found that treatment initiated well after epilepsy diagnosis; i.e., 12 weeks post-SE, can still exert a disease modifying effect as observed from decreased seizure frequency during the treatment period, and up to 2 weeks after terminating the treatment. The neuroprotective effects observed in the CA1 and CA3 region of the hippocampus certainly supports the underlying hypothesis that DMF will mitigate or prevent the cognitive decline associated with epilepsy.

Collectively, these results with DMF suggest that Nrf2 activation is disease modifying because the effect of treatment long outlasted the presence of circulating drug.

SEMI-AUTOMATIC DETECTION OF PRE-ICTAL AND ICTAL CHANGES IN FUNCTIONAL NEAR INFRARED SPECTROSCOPY

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Background: Functional near-infrared spectroscopy (fNIRS) assesses cerebral cortex activation through measurement of changes oxyhemoglobin (HbO2) and deoxyhemoglobin (HHb) concentrations using light. It is used in many fields of research and clinical practice including Neurology, Psychiatry, Psychology, 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 oxygenation.
Methods: A twenty-year-old patient with focal onset epilepsy was admitted for video EEG (VEEG) monitoring. In addition to the standard EEG and telemetry, he was connected to an ETG-4000 fNIRS system using optical fibers. Peri-ictal fNIRS were examined for changes relating to seizures. Additionally, we created a semi-automated algorithm to detect epochs of suspected seizures in the fNIRS data. The algorithm calculated the variance in levels of HbO2 or HHb during a time window of 20s for every channel. This process was repeated at intervals of 10s. A correlation matrix of the variance vectors was calculated, where time windows of unusual variance can be easily detected and assessed for patterns of oxygenation relating to seizures. The data from the VEEG was used to confirm the presence of a seizure.
Results: Pre-ictal and ictal changes in HHb and HbO2 were identified in the averaged data of 23 seizures, preceding the VEEG onset of seizure by 30s. Our algorithm was able to detect epochs correlating with seizures seen both on EEG and video. The fNIRS changes were lateralized to the left hemisphere, which corresponded to the EEG lateralization.
Conclusion: The results of this study demonstrate the detection and lateralization of pre-ictal and ictal changes in fNIRS signals. Additionally, we developed an algorithm for semi-automatic detection of epochs of suspect seizures in fNIRS.

HIPPOCAMPAL RESECTION DURING HEMISPHEROTOMY - IS IT NEEDED?

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Introduction: Hemispherotomy is an effective surgery for pediatric intractable hemispheric epilepsy. Over the years, the surgical goal has shifted from a complete hemispheric resection (anatomical hemispherectomy), to a disconnective hemispherotomy. Several techniques for hemispherotomy have been described, and often hippocampal resection is concurrently performed. The goal of the current study is to question the need of hippocampal resection.

Methods: We retrospectively accrued all clinical data of children (<18 years old) that underwent hemispherotomy between 2001-2022 at the Tel-Aviv Medical Center and Baylor College of Medicine. Epilepsy outcome was compared based on whether the hippocampus was resected, or disconnected at the amygdala and atrial segment of the fornix.

Results: A total of 86 patients (32 females) were included. Most common epilepsy etiologies were Stroke (31), Rasmussen's encephalitis (16), Cortical dysplasia (10), and Hemimegaloencephaly (9). Age at surgery was 7±4.8 years. Median number of antiseizure medications (ADS) before surgery was 3. Hemispherotomy techniques included peri-insular (54), vertical (23=endoscopic 19 + parasagittal 4), and trans-sylvian (9). Follow-up was 41.5±38 months. 43 patients had hippocampal resection and 43 patients had hippocampal disconnection. Both groups had a mean Engel Outcome Scale of 1.2 (p=0.85, Student's t-Test), and there was no significant difference in the functional outcome status of the groups.

Conclusions: Disconnective hemispherotomy is highly effective for pediatric intractable hemispheric epilepsy. Our date suggests that there is no need for hippocampal resection if a complete disconnection is performed.

EPILEPSY AND FOCAL CORTICAL DYSPLASIA. SHOULD THE TWO MEDICATION FAILURE PARADIGM BE PURSUED?

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Objective: Focal cortical dysplasia (FCD) is a malformation of cortical development and is associated with drug-resistant epilepsy. Standard indication for epilepsy surgery is drug resistance (as defined by the ILAE). Given the high incidence of drug resistance in these children, this delay may not be warranted. The aim of the study was to determine the proportion of patients with a presumed FCD who develop drug resistance and evaluate post-operative outcomes.

Methods: This study incorporated a survey within a regional pediatric epilepsy network (to rule out a possible selection bias in our cohort), and a retrospective database review of a large, tertiary pediatric epilepsy surgery center serving the network to identify children with epilepsy and a presumed FCD on MRI.

Results: The survey revealed that 86% of the patients with epilepsy and presumed FCD on MRI within the network were referred to our center. Of 139 pediatric patients included in the study, 131 (94.2%) had drug-resistant epilepsy. One hundred and ten (83.9%) patients were referred to epilepsy surgery, of whom 97 underwent surgery. Of 92 with one-year postoperative follow-up, 59.8% had an Engel Class 1 (seizure-free) outcome. Concordance of location between MRI and ictal EEG was strongly associated with Engel Class 1 outcome ($p<0.001$), as was older age at seizure onset ($p=0.03$). Time from diagnosis to surgery, number of medications, type of surgery and histology were not associated with improved outcome.

Conclusions: Our data suggest that most children presenting with seizures and a radiological diagnosis of FCD will develop drug-resistant epilepsy and are candidates for epilepsy surgery. The main outcome predictors are the correlation between MRI and ictal EEG localization and age at onset. This suggests that patients with FCD and epilepsy may be considered for surgery before traditional criteria of drug resistance are met. This change in practice has the potential to improve quality of life and cognitive function and reduce burden on epilepsy services.

STIRIPENTOL (STP) ADD-ON THERAPY-BEYOND DRAVET SYNDROME

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Introduction: STP is a unique antiseizure medication (ASM). It has pharmacokinetic interactions due to inhibition of cytochrome P450 enzymes. STP is well established as add-on therapy to Valproate (VPA) and Clobazam in refractory seizures associated with Dravet syndrome (1).
BRAT1 gene has a role in initiating DNA repair (2) ,and mutations may cause a severe epileptic encephalopathy with rigidity and refractory seizures (3).
We report the dramatic effect of STP add-on therapy in control of refractory seizures in a case of BRAT1-related early onset epileptic encephalopathy.
Case Report: A 10-month-old baby with refractory epilepsy due to BRAT1 gene mutation was hospitalized with seizures despite polypharmacy. She received repeated IV VPA loads. VPA trough levels remained low despite maintenance doses up to 30 mg/kg/day QID, and she continued to experience seizures. On the 15th day STP was added. 2 days following STP initiation seizures ceased completely, IV VPA was discontinued, and levels rose and stabilized.
Discussion: In Dravet syndrome randomized placebo-controlled trials showed response rate of 66-71% with 36% seizure freedom (4-5). Similar response rates were reported in small series in other types of refractory epilepsy (6-8).
Our case report suggests the effectiveness of STP in epilepsy of infancy with migrating focal seizures due to a BRAT1 mutation. Our patient became seizure free, and we were able to reduce other ASMs. We also showed STP's effect on raising VPA trough levels.
Conclusions: STP is a unique ASM that may be a useful add-on therapy in drug-resistant epilepsies due to pharmacodynamic and pharmacokinetic effects. The current case as well as other limited case series implicate its possible effectiveness beyond Dravet syndrome

BEYOND THE ANTI-EPILEPTIC DRUGS - KETOGENIC DIET AS A SALVAGE THERAPY IN EPILEPSY

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Introduction: Ketogenic diet (KD) is a high fat and low carbohydrates diet, and is an established treatment for drug-resistant epilepsies. In several epilepsy syndromes, it has been recommended to begin KD early in the course of the disease, such as epilepsy with myoclonic atonic seizures (previously known as Doose syndrome), and glucose transporter type 1 (GLUT1) deficiency syndrome.
Methods: We retrospectively reviewed the charts of children (ages 0-18 years) with epilepsy treated with KD during the years 2010 to 2022 in a tertiary pediatric epilepsy center. Our aims were to evaluate its efficacy in different etiologies, as well as safety and compliance rates. The patients were evaluated for age, seizure semiology, epilepsy etiology, response rate and reasons for diet discontinuation.
Results: Our cohort included 100 patients treated with KD. The efficacy and retention rate of KD in various epileptic syndromes will be presented. Reasons for stopping the diet will be discussed. A special emphasis will be given to our unique experience in KD in very difficult cases such as secondary epileptic spasms and developmental and epileptic encephalopathies (DEE).
Conclusions: KD is an efficacious and safe treatment option in specific epilepsy syndromes, especially in difficult to treat cases including secondary epileptic spasms and developmental and epileptic encephalopathies.

THE DIFFERENT CLINICAL AND ELECTROPHYSIOLOGICAL EFFECTS OF CANNABIDIOL-ENRICHED OILS ON ADULT PATIENTS WITH DRUG-RESISTANT EPILEPSY

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Background: Cannabidiol (CBD)-enriched oils are being increasingly used to improve seizure control in adult drug-resistant epilepsy (DRE) patients, despite the lack of large-scale studies supporting their efficacy in this patient population. Furthermore, little is known about the brain-wide effects of CBD, and if there are patient characteristics that are associated with good clinical response to CBD. We aimed to assess the effects ofCBD on seizure frequency and to explore the motor, cognitive, and electrophysiological effects of CBD in responder and non-responder patients to CBD treatment.
Methods: We prospectively recruited 19 DRE patients who fulfilled the requirements of the Israeli MOH for medical cannabis treatment and were treated with add-on CBD. Patients were evaluated prior to treatment, and following 4 weeks of titration and 4 weeks of maintenance daily dose of 260mg CBD and 12mg THC. Response to CBD was defined as 50% decrease in debilitating seizures according to weekly seizure diaries. The evaluation included clinical assessment and EEG recording during rest as well as evoked potentials (EPs) during visual Go/NoGo task while sitting and walking. Wilcoxon-test was performed to examine the effects of CBD and Mann-Whitney to compare between groups.
Results: Seven patients (43.75%) were responders and nine (56.25%) were non-responders. Responders demonstrated an average *reduction* of 82.4%, while non-responders average *increase* of 30.1% in debilitating seizures. No differences in demographics and clinical parameters were found between responders and non-responders to CBD at baseline. However, responders demonstrated larger improvements in sleep quality, MOCA, and HADS anxiety/depression post-treatment. Post-CBD EPs during sitting showed increased P300 amplitude in responders ($p=0.046$) and decreased in non-responders ($p=0.028$). During walking, both groups showed a decrease in P300 amplitude (responders: $p=0.068$, non-responders: $p=0.043$).
Conclusions: CBD treatment can help reduce debilitating seizures in a subset of DRE patients. No specific motor, cognitive and electrophysiological characteristics can be linked to response to CBD. However, changes in EPs in response to CBD were found between the groups, demonstrating the different effects of CBD on motor and cognitive networks and suggesting promising direction to learn about the differences between responders and non-responders to CBD treatment.

HIGH DOSE DIAZEPAM TREATMENT IN ESES

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Background: ESES is an electrical status epilepticus observed in sleep during non-rapid eye movement . Continuous spikes and waves activity ranges between 50-85% in slow wave sleep and is associated with cognitive, behavior and development regression. Corticosteroids and benzodiazepines are the most commonly used treatments after failure of other anti-seizure medication. However, the long-term use of steroid is compromised by severe side effects and poor tolerability. Occasional reports of high doze Diazepam usage suggest possible long-term benefits. In order to verify the long-term effect and tolerability of high dose diazepam treatment and to further consider its use in our clinical practice, we treated a cohort of ESES patient with high dose diazepam protocol either before or after steroid treatment.
Methods: We included 21 patients with ESES who received two equal high doses of diazepam (1 mg/kg/d), 24 hours apart. Patients with good effect on EEG were further treated by slow tapering of diazepam to tolerable dose. EEG monitoring was repeated, 3 to 6 weeks after starting diazepam treatment.
Reduction of spike and wave frequency in sleeping EEG and its general effect according to the parent's reports were assessed.
Results: Mean age of ESES appearance was 5.2 years. All patients were resistant to at least 5 anti-seizure medications and 15 patients were treated with pulse steroids prior to diazepam treatment. 6 patients received high dose diazepam without preceding steroid treatment. Regarding high-dose diazepam effect, 9 patients (42%) had more than 50% reduction in epileptiform activity (spikes and waves) and 23% (5 patients) retained this improvement after 3 months while only one patient showed improvement after 6 months. Only 19% reported behavior and language improvement after treatment. 10 patients (47%) have stopped the treatment due to side effect.
Conclusion: in this cohort of patients, High-dose diazepam has shown a good short-term effect in patient with different etiologies. Further investigation is needed in refractory epilepsy (ESES) patients.

NEW ONSET REFRACTORY STATUS EPILEPTICUS : SUCCESSFUL TREATMENT WITH HIGH DOSE POTASSIUM BROMIDE

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Background: New Onset Refractory Status Epilepticus (NORSE), is a challenging medical condition, characterized by the occurrence of new onset prolonged seizures, resistant to treatment, in otherwise healthy individuals, without a clearly identifiable cause. Autoimmune Encephalitis was found to be the most frequently (identifiable) cause, but the vast majority of cases are still (cryptogenic) . Different treatment methods were tried with variable oOutcomes. The use of potassium bromide showed good outcome in the treatment of resistant epilepsy in the pediatric patients, but was not studied enough in the treatment of NORSE in the adult populations. Here we present a case of NORSE ,with significant seizure reduction after treatment with high dose potassium bromide after failure of many other treatment lines.

Case Description: a 30 year old previously healthy male, presented to our hospital with fever, altered mental status and seizures. Lumbar punctures showed pleocytosis with elevated protein. Brain MRI was inconclusive. Initial treatment with antibiotics, and several anti-seizure medications, followed by propofol induced coma, ketamine, high dose midazolam,and thiopental (limited use due to ileus) failed to show any clinical improvement. Thorough auto-immune,infectious and paraneoplastic panel was negative. Further and concomitant treatment with IV steroids, plasma exchange and IVIG didnt change the ictal status and was limited at some points by the septic profile of the patient.

Additional treatment lines like electroconvulsive therapy (ECT), and Vagal nerve stimulation (VNS) with rapid cycling were tried, with no change in the clinical course. Finally, a therapeutic trial with Potassium bromide, with targeting therapeutic level (80-150), and cautious monitoring of serum potassium level showed significant seizure reduction after around 2 months of continued status epilepticus.

Conclusion: Potassium bromide may have a role in NORSE treatment and improving clinical outcome, in patients where no clear identifiable autoimmune, paraneoplastic or infectious cause is found; which forms the vast majority of the cases. Prospective studies would be needed in order to evaluate and better assess its role in early seizure cessation and possible improvement in the clinical outcome.

LEVETIRACETAM THERAPEUTIC DRUG MONITORING IN PREGNANCY

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Background: Levetiracetam (LEV) is an anti-seizure medication (ASM), indicated for the treatment of generalized and focal seizures. LEV is mainly excreted by the kidneys. Due to its low teratogenic risk, LEV is frequently used in pregnant women. Physiological changes during different stages of gestation may affect the pharmacokinetic characteristics of LEV. The goal of our study is to characterize the magnitude and course of alterations in levetiracetam (LEV) clearance during pregnancy and the postpartum period and contribute to a rational treatment plan and dosing paradigm.
Methods: This retrospective, observational study included a cohort of women that were followed at the epilepsy in pregnancy clinic in Tel Aviv Sourasky medical center (TASMC). Individualized target concentrations were used for seizure control and an empiric postpartum taper was used to reduce the likelihood of maternal toxicity. Trough LEV blood levels were measured before conception, during pregnancy and postpartum. Measurements were preformed once every 1-2 months during pregnancy. All measurements were done at a single lab in TASMC. Week of gestation and LEV dosage at the time of level measurement were documented. Office visits during pregnancy occurred every 1 to 2 months with review of medication diaries and blood sampling. Total LEV concentration/dose were calculated based on LEV levels and dosage as an estimation of LEV clearance.
Results: A total of 244 samples were collected from 38 pregnant patients, between the years 2020-2022. We observed a decrease in LEV concentration/dose as the pregnancy progressed, followed by an abrupt post-partum increase in LEV concentration/dose. LEV dose was empirically gradually increased by 50% on average during pregnancy compared to pre-conception dosage. The mean serum levels (ug/ml) decreased from 19.15 before pregnancy to 12.1 13.04 and 16.3 at 1st 2nd and 3rd trimester respectively. Post-partum, there was an increase in average LEV level to 25.92 as the average dosage was decreased by 24%.
Conclusions: LEV serum level monitoring is essential for women with epilepsy upon planning pregnancy and during pregnancy. Our data contribute to a rational treatment plan and dosing paradigm for levetiracetam use during pregnancy, parturition, and the postpartum period.

PERAMPANEL AS PRECISION THERAPY IN RARE GENETICS EPILEPSIES

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Background and Aims: Perampanel, an antiseizure drug with AMPA-receptor antagonist properties, may have a targeted effect in genetic epilepsies with overwhelming activation of glutamate receptors. Special interest holds epilepsies with loss of GABA inhibition (e.g. *SCN1A*), overactivity of excitatory neurons (*e.g. SCN2A, SCN8A*), and variants in glutamate receptors (*e.g GRIN2A*). We aimed to collect data from a large rare genetic epilepsy cohort treated with perampanel, to detect possible subgroups with high efficacy.

Methods: A multicenter project based on the framework of NETRE (Network for Therapy in Rare Epilepsies), a web of pediatric neurologists treating rare epilepsies. Retrospective data from patients with genetic epilepsies treated with perampanel was collected. Outcome measures were responder rate (50% seizure reduction), and percentage of seizure reduction after 3 months of treatment. Subgroups of etiologies with high efficacy were identified.

Results: 137 patients, with 79 different etiologies, aged 2 months-61 years (mean 15.48±9.9) were enrolled. The mean dosage was 6.45±2.47 mg, and treatment period was 2.0±1.78 years (1.5 months-8 years). 62 patients (44.9%) were treated for >2 years. 98 patients (71%) were responders, and 93 (67.4%) choose to continue therapy. The mean reduction in seizure frequency was 56.61±34.36%. 60 patients (43.5%) sustained over 75% reduction in seizure frequency, including 38 (27.5%) with > 90% reduction in seizure frequency. The following genes showed high treatment efficacy: *SCN1A, GNAO1, PIGA, PCDH19, SYNGAP1, POLG1, POLG2, NEU1*. 1/17 (64.7%) of patients with *SCN1A* were responders, 35.3% had over 90% seizure reduction. Other etiologies remarkable for over 90% reduction in seizures were GNAO1 and PIGA. 14 patients had a CSWS EEG pattern and in 6 subjects perampanel reduced epileptiform activity.

Conclusions: Perampanel revealed a high safety and efficacy in patients with rare genetic epilepsies, especially in *SCN1A, GNAO1, PIGA, SYNGAP1, CDKL5, NEU1* and *POLG*, suggesting a targeted effect related to glutamate transmission.

CENOBAMATE FOR THE TREATMENT OF FOCAL EPILEPSY- A SINGLE CENTER REAL LIFE EXPERIENCE

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Introduction: Approximately one third of adult patients with epilepsy, are classified as having a Drug-resistant epilepsy (DRE) Hence there remains an unmet need for new antiseizure medications (ASMs) that can improve seizure control.

Cenobamate is a novel oral compound approved for the treatment of focal onset seizures in the United States and Europe. The drug exerts it's antiseizure effect by enhancing the inactivated state of voltage-gated sodium channels and positive allosteric modulation of GABA-A receptors.

To date, cenobamate appears to be a promising anticonvulsant drug. It has high responder rate and remarkable seizure freedom rate and is generally well tolerated. Nevertheless, data on long term sustainability of antiseizure effect is limited and originate mainly from extensions of the original regulatory trails that are limited by small sample size and treatment drop-outs.

The purpose of this cohort observational study is to evaluate the efficacy and safety of Cenobamate and asses it's clinical relevance based on long term follow-up in real-life experience.

Methods: This is a retrospective observational study. All adult patients that were prescribed Cenobamate at the Thomas Jefferson Epilepsy center in Philadelphia were enrolled. Patients who participated in the regulatory trails of the drug were excluded. Clinical and demographic characteristics, the use of concomitant ASMs and seizure frequency were obtained from the patient's electronic medical records. Retention rate was presented using a Kaplan–Meier curve. Response rates were calculated as proportion of patients who had at least 50%, 75% and 100% reduction in monthly convulsive and total seizure frequency compared to baseline. Treatment- emergent adverse effects (AEs) were recorded.

Results: 185 Patients were included. 174 had focal epilepsy and 11 generalized epilepsy. Retenetion rate at 2 years was about 70% for focal epilepsy and 45% for generalized epilepsy. Responder rate was over 50% with over 20% of patients becoming seizure free.

Discussion: The phase 2 and 3 regulatory trials showed high efficacy of Cenobamate. But to date, real life data is scarce. High rates of retention and sustained reduction in seizure frequency were observed with Cenobamate in a large cohort of adults during long term followup.

EPILEPSY FOLLOWING HERPES SIMPLEX ENCEPHALITIS - A CASE COHORT STUDY

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Background: herpes simplex encephalitis (HSE) is associated with severe mortality and morbidity rates. Its incidence is estimated as 1:250 000, and the typical symptomatology of the acute disease includes headache, mental state disturbance, confusion, sleepiness and acute symptomatic seizures. The chronic phase of the disease is characterized by epilepsy and neurological sequela. The present retrospective single-center study is aimed to identify risk factors for predicting the development of epilepsy (epileptogenesis) and sequela after HSE.
Methods: Medical records of patients aged 18 years and above, hospitalized and diagnosed between January 2005 and September 2019 with "encephalitis" and "herpes simplex virus, HSV" infection were screened. HSE diagnosis was based on analysis of cerebrospinal fluid with positive HSV testing. The follow-up period was 86.8 ±37.7 months. Patients lost to follow-up were excluded.
Results: We included 24 patients with HSE. The average age of these patients was 52.5 years. Symptomatic seizures during the acute phase of the disease occurred in 14 (58.3%) patients. Of these, 7 (50%) developed epilepsy.
Over the long term, 33.3% (8 patients) of the patients developed epilepsy. Of these, 62.5% (5 patients) and 37.5% (3 patients) developed epilepsy without and with acute symptomatic seizures, respectively. Of the former, 62.5% each had personality changes and imaging-positive encephalitis and 75% had fever; the average age of these patients was 52.5 years. Of the latter, 77.7% developed epilepsy in the long term.
Conclusion: This is the first study to report a possible association between epileptic seizures in the acute phase of HSE and epilepsy development on the long term.
Based on our results, we consider that the following are the risk factors for the development of epilepsy in HSE patients: age, <60 years; imaging results suggestive of encephalitis; seizures in the acute phase; and Behavioral changes.
This observation should be more extensively studied to establish its role in pathogenesis of epileptogenesis following HSE.

DRUG RESISTANT EPILEPSY FOLLOWING HERPES SIMPLEX VIRUS ENCEPHALITIS IN CHILDREN

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Introduction: The introduction of systemic anti-viral treatment acutely in the treatment of herpes simplex virus (HSV) encephalitis in children has vastly reduced mortality, yet long-term morbidity is common with poor outcomes reported. We aim to characterize epilepsy and neurodevelopmental outcomes in children following this debilitating disease.
Methods: We describe a retrospective review of case notes of children with a background of HSV-encephalitis followed-up by a tertiary hospital's pediatric epilepsy clinic. Data were collected on age of infection, duration of acyclovir treatment, presence of seizures or status epilepticus acutely, the latency period between acute infection and onset of drug-resistant epilepsy, anti-seizure medication used, steroid/IVIG administration, acute and follow-up MRI and EEG findings, epilepsy syndrome diagnoses and neurodevelopmental status.
Results: 11 children were identified, with age of infection ranging from 10 days to 6 years. 75% had status epilepticus acutely, with continued acyclovir treatment ranging from 3 weeks to 1 year. 10 of 11 patients had a latency period following acute infection with minimal or no seizures lasting between 8 months and 8 years. Neither HSV reactivation nor evidence of NMDA-encephalitis was identified in any patients. Most had EEG findings with generalized or multifocal spike-wave outbursts activated by sleep consistent with electrical status epilepticus in sleep. Over the course of their follow-up, one was treated for infantile spasms without hypsarrhythmia, and 2 progressed to Lennox-Gastaut syndrome. Of note, children with localized unilateral temporal changes on MRI had similarly pathological, and bilateral EEG findings. Over half were treated with steroids. One is in regular schooling, while all other patients have been diagnosed with autism spectrum disorder, cerebral palsy-like (quadriparesis/hemiparesis) and/or intellectual disability with prominent behavioral difficulties.
Conclusions: Survivors of HSV encephalitis during infancy and childhood often develop drug-resistant epilepsy with poor neurodevelopment outcomes, regardless of the age of the acute disease. We demonstrate that even those with more mild structural damage develop equally profound developmental and epileptic encephalopathy with spike-and-wave activation in sleep, and discuss the potential role of even late immunotherapy in these patients and propose a multicenter prospective study on this population for better understanding long term pathogenesis and optimal interventions.

THE EFFECTS OF SARS-COV-2 INFECTION AND VACCINATION ON DISEASE COURSE IN CHILDREN WITH EPILEPSY

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Background: Over the past year, a spectrum of neurological syndromes among patients with COVID-19 were reported. However, most of the reports do not specifically describe the effects of the infection on the course of epilepsy. Moreover, there is very little data on the effects of vaccination on the course of epilepsy. We conducted a cross-sectional study to evaluate the adverse events profile of the mRNA-based anti-COVID vaccination and to characterize the epilepsy course after acute infection with SARS-CoV-2

Methods: We conducted an observational cross-sectional study. The patient or their parent who visited our pediatric epilepsy center were offered to fill out an anonymous questionnaire on the effects of COVID-19 and the adverse events of the anti-COVID-19 vaccine. We included children with known epilepsy between the ages of 5 and 18 years. The questionnaire documented the date and clinical manifestations of each SARS-CoV-19 infection, dates and adverse events of each dose of the vaccination, and relevant clinical and demographic information.

Findings: One hundred and sixty patients with a mean age of 11·2 years completed the questionnaires. Seizures during the acute infection occurred in 17%, and the majority were a-febrile, with otherwise mild disease. No seizure exacerbation was noted over the week following 93 vaccination doses. The vaccination rate was lower than in the general population, especially in children under 12 years.

Interpretation: In contrast to the minimal risk for seizure exacerbation following the vaccination, the risk for seizure exacerbation during an infection is substantial. Clinicians should reassure patients, parents, and caregivers regarding the low risk of seizures with anti-Covid-19 vaccination.

Funding: This study had no funding.

EPILEPSY PREVALENCE AND TREATMENT GAPS IN MAMBWE DISTRICT, ZAMBIA

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Aim: Epilepsy is diagnosed in roughly 65 million people worldwide, with roughly 80% of those affected living in developing countries. In many developing countries patients with epilepsy are not medicated. Left underdiagnosed and untreated, epilepsy is severely debilitating and lead to cognitive decline, disability, increased risk of death—and, due to social stigma—unemployment.

Quantifying prevalence, causes, and types of epilepsy in Kakumbi Chiefdom, Mambwe District, Eastern Province, Zambia. In addition: (1) identify gaps in epilepsy prevention, diagnosis and treatment in the region; (2) promoting awareness and tolerance of the disease and (3) understand the natural history of untreated epilepsy

Methods: An extensive door to door survey throughout Kakumbi Chiefdom questioning 15,290 individuals to: 1) identify patients diagnosed of epilepsy, 2) identify undiagnosed patients who are experiencing one or more symptoms commonly associated with epilepsy. Detailed epilepsy and medical history including a full neurological examination, EEG, and blood sample by researchers and epileptologists of those patients selected from the survey who are diagnosed with epilepsy or with a high probability of suffering from epilepsy.

Results: The study was approved by University of Zambia Ethics Committee. Between March 2019 and February 2020, a total of 15,290 individuals living in the Kakumbi Chiefdom were surveyed. Of this group, 208 individuals (1.36%) reported being diagnosed with epilepsy. An additional 1,435 individuals (9.5%) reported having at least one symptom suggesting epilepsy as a possible diagnosis. Notably, 370 reported “loss of response” (2.5%), and 543 reported “convulsions” (3.6%), symptoms particularly suggestive of epilepsy. 318 respondents reported two symptoms suggestive of epilepsy (2.1%) and 136 reported three symptoms (0.9%). Detailed history, neurological examination and EEG study in 78 patients confirmed the diagnosis of epilepsy in all but one individual. In >90% seizures were not controlled. Together, these results strongly suggest the underdiagnosis of epilepsy in this population with a high treatment gap, stressing the need for additional tests (for accurate diagnosis) followed by prompt treatment and educational effort within the community.

MONITORING OF CHRONIC BRAIN INJURY PATIENTS WITH AMPLITUDE-INTEGRATED ELECTROENCEPHALOGRAPHY (AEEG)

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Purpose: To evaluate the feasibility and utility of aEEG monitoring of chronic brain injury patients in a pediatric rehabilitation center, including the frequency of abnormal background activity and seizures.
Methods: A total of 117 aEEG readings from 51 patients treated in a pediatric respiratory rehabilitation department over a period of 20 months were studied. Patients were included if they performed at least one aEEG exam and needed respiratory rehabilitation treatment. aEEGs were performed either upon admission or due to suspected seizures.
Results: More than 85% of exams were feasible for interpretation. The background activity and presence of seizures were clearly related to the clinical diagnoses and radiological findings. Seizures were noted in 32% of the aEEG readings. Most of the seizures were suspected clinically (79%). Twenty-one percent of seizures were unexpectedly detected during routine examinations. Treatment was modified following 38% of aEEG exams. A follow-up aEEG was performed after 68.9% of exams with 52% showing a pattern change.
Conclusion: Relatively short-term CFM monitoring was feasible, had a reasonable association to clinical diagnosis and radiological findings while effectively detecting seizures when used in chronic brain injury patients on a pediatric rehabilitation setting.