UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE
„CAROL DAVILA", BUCUREŞTI
ŞCOALA DOCTORALĂ
DOMENIUL MEDICINĂ

PHD THESIS
SUMMARY

Conducător de doctorat:
PROF. UNIV. DR.
ULMEANU CORIOLAN

Student-doctorand:
GHEORGHITA
KARINA LIDIA

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THERAPEUTIC APPROACH OF PATIENTS WITH EPILEPTIC ENCEPHALOPATHY ASSOCIATED WITH ELECTRICAL STATUS EPILEPSY DURING SLEEP

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CONTENT OF THESIS

INTRODUCTION

I. GENERAL PART

Epileptic encephalopathy associated with electrical status epilepticus during sleep, or ESES, is a rare epileptic encephalopathy, mainly observed in children, characterized by epileptic activity predominantly during non-REM sleep and associated cognitive and behavioral disorders.

The electrical status epilepticus in sleep pattern appears in clinical syndromes that present with three common features and varying degrees of severity: (1) epileptic seizures, (2) potentiation of epileptic electrical activity during sleep, and (3) cognitive regression. These common features follow an age-dependent course, with their onset in early childhood, a peak of severity during middle and late childhood, and spontaneous improvement before puberty. [1-4]

ESES is correctly diagnosed when the patient presents an association between epileptic seizures, either manifest or subclinical, during wakefulness and/or sleep, with abnormal electrical activity >85% recorded on an electroencephalogram (EEG) over at least one sleep cycle, and with signs of cognitive and neurodevelopmental regression. [1, 5-12]

1.1 Clinical Characteristics

Symptoms usually appear between the ages of 2 and 12. Initially, patients present with epileptic seizures, which can be accompanied by gradual or sudden cognitive deterioration. These patients may have concentration deficits, memory disorders, mild motor disturbances, and behavioral disorders. Typically, these patients had normal neuropsychomotor development before diagnosis. Initial epileptic seizures are often mild and may present polymorphism in manifestation. [1,7,10-15]

Usually, the improvement of clinical seizures and ESES is associated with cognitive improvement, although most patients continue to show some degree of impairment. It is currently believed that frequent EEG discharges and ESES patterns are associated with a poor neurocognitive outcome; thus, it is assumed that improving the EEG appearance might positively impact the cognitive outcome. According to some reports, the duration of ESES seems to be the main predictor of neurocognitive function [1,4,17-21].

1.2 Paraclinical Data

Electroencephalography highlights the characteristic discharges - spike-wave complexes, recorded in at least 85% of non-REM sleep, showing bilateral or sometimes unilateral continuous or near-continuous spike-wave complexes [1,11,17]. The discharges typically have a frequency between 1.5 and 3 hertz [1,4].

An EEG with a sleep cycle is enough to prove the diagnosis. In most cases, the localization of epileptic discharges is fronto or centro-temporal, both during wakefulness and sleep, although during sleep, the discharges tend to become much more widespread and frequent and often generalize [1,4]. Analysis of other sleep stages is not relevant for diagnosis. Interictal findings during wakefulness include focal or multifocal spikes or slow waves, sometimes appearing in salvos. With neurocognitive regression, interictal abnormalities during wakefulness become more prominent [1,4].

Typically, neuroimaging is not significant for diagnosis, its potential role being in determining a structural cause or identifying underlying structural abnormalities [1,3,7].

1.3 Pathophysiology

The pathophysiology of ESES is not fully understood. Studies on neuronal networks related to neuroconnectivity suggest an interaction between the medial parietal cortex, precuneus, thalamus, and fronto-temporal cortex [12]. Mechanisms involving hyperactivation of thalamic pathways related to GABA metabolism are considered.[18]

Autoimmune mechanisms have also been explored based on the response to steroids and immunosuppressants. [12].

1.4 Therapeutic Management

It is generally accepted that the drug approach to epileptic activity in ESES often leads to an improvement in associated cognitive and behavioral symptoms. Several antiepileptic drugs, including valproic acid, clobazam, ethosuximide, lamotrigine, and levetiracetam, have been tried with varying success rates in ESES. There are different treatment regimens for ESES, and studies to date have not proposed a clear diagnostic protocol.

Techniques such as neurofeedback, cognitive-behavioral therapy, and personalized educational support may benefit children presenting cognitive disorders associated with ESES.

Early recognition and strict therapeutic strategies, including both pharmacological and non-pharmacological interventions, are crucial to mitigate the impact on the patient's quality of life.

ESES Pharmacotherapy

Valproic Acid (Valproate)

Valproic acid is often considered a first-line treatment for ESES due to its broad-spectrum activity against various types of seizures. Its efficacy is not only in controlling associated seizures but also in its potential to reduce epileptic activity during non-REM sleep, characteristic of ESES. In some

cases, valproic acid can be combined with other antiepileptics to optimize treatment efficacy, given the refractory nature of ESES in some patients. The ultimate goal is not just to control epileptic seizures but also to reduce SWC discharges during sleep, potentially mitigating the cognitive and behavioral disorders observed in ESES.

Benzodiazepines

Among benzodiazepines, clobazam and clonazepam have been used either as monotherapy or in combination with other antiepileptic drugs. They can be particularly useful when epileptic seizures coexist with epileptic activity during sleep, but there's a risk of tolerance, sedation, and dependence.

Clobazam is a benzodiazepine derivative used for its antiepileptic properties. Unlike other benzodiazepines, clobazam was developed and used mainly for its antiepileptic effects. Clobazam has proven effective in various epileptic syndromes, including the Lennox-Gastaut syndrome, which has some similarities with ESES.

Clobazam can be an effective addition to the therapeutic protocol against ESES, especially in challenging or refractory cases.

Ethosuximide

Ethosuximide is a well-known antiepileptic drug, mainly used for managing absence seizures due to its specific mechanism of action on T-type calcium channels. Its role in ESES has been of interest, given the complex nature of ESES and its association with various types of seizures. Some ESES patients have shown a reduction in epileptiform activity and clinical seizures when treated with ethosuximide.

Lamotrigine

This antiepileptic has potential benefits in some ESES patients. It can help reduce the frequency of seizures and the characteristic EEG anomalies observed in this condition, though the drug's efficacy varies.

Levetiracetam

For levetiracetam, there are studies and case reports suggesting it might be effective in reducing both clinical seizures and characteristic EEG anomalies of ESES.

Corticosteroids

Corticosteroids offer another treatment option for ESES, especially in refractory cases. However, their use comes with challenges, considering the potential side effects. As always, a careful and individualized approach is essential.

Cannabidiol

Its potential therapeutic effects in various epileptic conditions have attracted significant attention, leading to its approval for specific severe forms of epilepsy, such as Dravet syndrome and Lennox-Gastaut syndrome. However, so far, the evidence regarding the use of cannabidiol specifically for ESES is still under research. Considering its broader role in treating refractory epilepsies, clinicians might consider it an option, especially for ESES cases resistant to standard treatments and to address comorbidities.

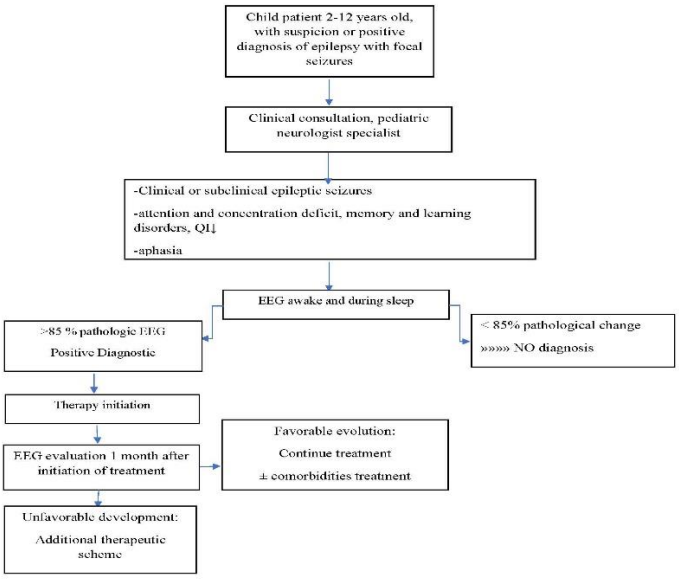
Therapeutic interventions for cognitive and behavioral symptoms of ESES

Early recognition of ESES and immediate intervention are vital to prevent long-term cognitive deficits and improve the quality of life for both patients and their families.

The ideal pharmacotherapy for ESES varies from one patient to another. Regular EEG monitoring and cognitive assessments guide the therapy's effectiveness. The primary objective is not just

seizure control (if present), but more importantly, EEG normalization, as the ongoing electrical pathological activity is directly linked to cognitive and behavioral disorders.

Given the above-discussed chapter, we propose a diagnostic and treatment algorithm for ESES.



I. PARTE ORIGINALA

1.1 Working Hypothesis and General Objectives

Within the research work, our objectives were:

- Determine the effectiveness of the VPA+ETH drug combination in patients diagnosed with ESES and ascertain how demographic profiles influence the establishment of a therapeutic regime.
- Establish the stability of the VPA+ETH combination, which was introduced at the time of diagnosis.
- Assess to what extent the VPA+ETH combination affects symptoms associated with ESES.

- Determine the effectiveness of using cannabinoids in controlling ESES comorbidities, specifically the alleviation of aphasia and attention and concentration deficits secondary to ESES.
- Monitor these patients and determine how the introduction of CBD oil has changed their health status and identify its stability.

2.2 General Research Methodology

In the observational study conducted, we enrolled 40 patients diagnosed at the pediatric neurology outpatient clinic, of which I am the head physician, between 2016 and 2023. At the time of inclusion in the study, all patients exhibited clinical epileptic seizures and had over 85% of their EEG recording pathologically altered, specifically presenting nearly constant generalized CVU. Electroencephalographic assessments made to determine therapeutic efficacy within the study were performed at diagnosis, one month after diagnosis and therapeutic regime introduction, and subsequently every three months. All patients underwent psychological evaluation to determine neurocognitive impairment at diagnosis, one month after treatment initiation, and three months from the initial presentation. As the patients are pediatric-aged, consent was obtained from both parents before therapeutic intervention and subsequently for the processing and analysis of personal data. For the electroencephalographic evaluation, we used the NEURON SPECTRUM system with an annual license, with evaluations done in the EDF- European Data Format, standard with 21 electrodes, double-banana assembly. All recordings were done as sleep-wake EEG and siesta with one sleep cycle. The evaluation of comorbidities for diagnostic purposes and post-drug intervention monitoring was carried out by a clinical psychologist collaborator of the medical clinic, a member of the psychologists' college. The assessments used were PORTAGE, NEPSY, and CONNERS, licensed and approved by the College of Psychologists in Romania. The therapeutic regime was tailored to each patient based on age, weight, detailed sleep electroencephalographic analysis and re-evaluated one month and three months after diagnosis. All patients received antiepileptic medication in the original formula, dosed according to the patient's weight, following current treatment protocols, presented in the general part of this research work. The CBD oil used was a unique formula, approved by current ANM and MS regulations, without THC in its composition, and concentration tailored to age and weight. The therapeutic dose used was determined individually for each patient and titrated based on age and

weight, with doses ranging from 1 to 3 mg/kg/day, a single dose in the morning. Appendix 1. For statistical analysis, we used the SPSS software, Microsoft Office Word, and Excel with a 2022-2023 license. The tests used were T-Test, with a 95% confidence level, p=0.05.

2.3 Study

2.3.1 Introduction

The objectives of this study were to determine the efficacy of the VPA+ETH drug combination in patients diagnosed with ESES in the studied group and to determine how the demographic profile influences the establishment of a therapeutic regime. This study aimed to ascertain the stability of the VPA+ETH combination, which was introduced at the time of diagnosis. Another goal was to establish the utility of cannabinoids in controlling ESES comorbidities, specifically alleviating aphasia and attention and concentration deficits secondary to ESES. Another objective of this study was to monitor these patients and determine how introducing CBD oil changed their health status and identify its stability. Patients coming to the clinic with ESES exhibited varying degrees of aphasia and attention deficit, ranging from mild to severe. The administration of VPA+ETH aimed to assess the extent to which this drug influenced these two medical conditions.

2.3.2 Materials and Methods

The observed patient group consisted of 40 children, evaluated neurologically, electroencephalographically, and psychologically at the pediatric neurology outpatient clinic, of which I am the head physician, between 2016 and 2023. The electroencephalographic evaluation system used was the NEURON SPECTRUM with an annual license, with which sleep siesta EEGs with one sleep cycle were recorded in EDF format, standard with 21 electrodes, double-banana assembly. EDF is a standardized format that allows data storage and interpretation in a way that's compatible with multiple other electroencephalographic reading systems. Comorbidities were evaluated by a clinical psychologist both for diagnostic purposes and as a follow-up post-drug intervention. Complex psychological assessments were used, namely PORTAGE, NEPSY, and CONNERS, licensed and approved by the College of Psychologists in Romania. For the treatment of comorbidities with cannabinoids, we used a unique formula, approved according to current ANM and MS regulations, without THC in its composition. Appendix 1. Statistical analysis was

carried out using SPSS, Microsoft Office Word, and Excel software with a 2022-2023 license. T-Test type tests were used, with a 95% confidence level, p=0.05.

2.3.4 Results and Discussions

The study sample consisted of children aged between 4 and 12 years. The gender distribution leaned more towards females, and for age categories, there wasn't a specific representation regarding the prevalence in the population with the conditions studied. Moreover, the study included 40 patients, and the comparisons made to highlight statistically significant differences should be approached with caution. The samples included in the analysis could have sizes even smaller than 20; hence significant tests were not elaborated due to a lack of statistical representativeness (T-test at a 95% confidence level, p=0.05%).

One of the objectives of this study was to determine if there's a significant difference between patients who were given AE at the time of ESES diagnosis - VPA+ETH - and those who did not receive this medication. It was also crucial to determine if this difference is influenced by the patient's gender or age. Additionally, the study aimed to determine the stability of VPA+ETH, which was added at the time of diagnosis.

Moreover, patients were given CBD oil a month after the ESES diagnosis was established. Another goal of this study was to monitor these patients and determine the extent to which the introduction of CBD oil led to changes in their health status and to identify its stability.

Patients who came to the clinic with ESES displayed varying degrees of aphasia and attention deficit, ranging from mild to severe. The administration of VPA+ETH aimed to evaluate the extent to which this medication influenced these two medical conditions.

The primary conclusion here is that patients who received VPA+ETH did not need any additional treatment after a month, unlike those who were given other drugs. This indicates the effectiveness and stability of VPA+ETH after just one month of treatment. Significantly fewer patients who received VPA+ETH needed additional medication after a month (T-test at a 95% confidence level).

Considering the gender and age analysis, it was observed that the effectiveness of VPA+ETH was more pronounced in females and younger children (under 8 years of age).

Additionally, by introducing CBD oil into the treatment plan, an improvement in the symptoms of patients who were given VPA+ETH at the time of diagnosis was observed, especially among females and the youngest children (aged between 4 and 6 years). For patients who received a different type of treatment other than VPA+ETH, the number who showed improvements is too small to draw a conclusion.

Comparing tables 2.7 and 2.8, which evaluated the efficacy of using CBD OIL without considering the basic antiepileptic regimen, it was observed that it is mainly effective when associated with the appropriate synthetic antiepileptics, specifically when combined with VPH + ETH in the presented case.

Significantly fewer patients who received VPA+ETH together with CBD oil had a relapse compared to those given a different treatment than VPA+ETH at the time of diagnosis (T-test at a 95% confidence level). Most patients who received VPA+ETH were mostly young females (under 8 years), while the other patients who got a different treatment than VPA+ETH were not differentiated based on gender or age.

For almost half of the patients who were given VPA+ETH, an improvement in aphasia and attention deficit symptoms was observed, unlike those given a different treatment than VPA+ETH where improvement was seen to a lesser extent.

As previously mentioned, the sample size introduced in the study is too small to develop a standard treatment protocol. However, these results reveal certain benefits that arose from the administration of these medications and could be the subject of a broader study.

It's recommended that objectives and hypotheses be formulated based on the results of this study. Additionally, it's advised to adopt a sufficiently large patient sample that allows relevant statistical analyses at the sub-sample levels, such as patient groups receiving different types of treatments, or an analysis based on socio-demographic profiles. Also, the patient sample should be statistically

representative of the population with the prevalence of conditions included in the study, both in terms of gender, age, or other socio-demographic dimensions that can add value to the final results.

It's worth noting that some of the statistical data presented in this research also appeared in the article "ROLE OF VARIOUS ANTIEPILEPTIC DRUGS IN ELECTRICAL STATUS EPILEPTICUS DURING SLEEP AND ITS COMPLICATIONS", authored by: Karina Lidia Gheorghita, MD, Acad. Prof. Alexandru Vlad Ciurea, MD, PhD, Assis. Prof. R. E. Rizea, MD, PhD.

2.3.4 Conclusions

Following the statistical analysis carried out with a 95% confidence level, all the working hypotheses included in the study were demonstrated.

The gender distribution showed a prevalence of females in the examined group, which contrasts with the studies presented in the general section that indicated a slight prevalence of males.

Patients who received VPA+ETH did not require any additional AE treatment after a month, unlike those who received other therapeutic regimens, such as CBZ, corticosteroids, or LTG. Significantly fewer patients who took VPA+ETH needed additional medication after one month (T-test at a 95% confidence level). The effectiveness of VPA+ETH was more pronounced in girls and in children under the age of 8. VPA+ETH treatment, introduced at the diagnosis of ESES, proved its effectiveness by improving the electroencephalographic trace, aphasia, and concentration and attention capacity one month after its addition. Its results were more stable over time compared to other therapeutic regimens.

Using CBD OIL, a natural product without THC, proved beneficial in treating ESES comorbidities. The therapeutic regimen made up of VPH+ETH+CBD OIL was shown to be maximally effective for the studied group, both in terms of controlling the classic symptoms of ESES and complications caused by this condition.

The number of patients who used the VPA+ETH treatment regimen and experienced an ESES relapse was significantly lower than patients who used other treatment regimens. Current study

data suggest the benefits of using the therapeutic regimen composed of VPA+ETH+CBD in treating pediatric neurology patients with epileptic encephalopathy associated with electrical status epilepsy in sleep.

The personal recommendation is to administer this therapeutic combination as a first-line treatment upon diagnosis. The personal recommendation to use this treatment regimen arises from personal experience accumulated over the past 10 years.

I believe the distinctive value of this work reflects the presentation of a stable therapeutic regimen, capable of preventing irreversible cognitive decline in children, unlike other therapeutic approaches previously proposed.

Comparisons made to highlight statistically significant differences should be approached with caution due to the small number of cases. We recommend conducting a larger study with objectives and hypotheses formulated based on the results of this study.

2.4 Conclusions and personal contributions

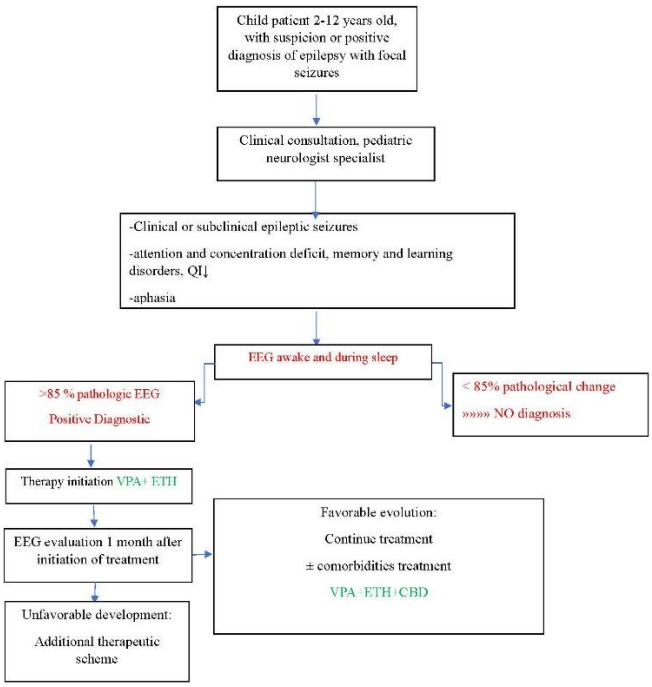
Epileptic encephalopathy associated with electrical status epilepsy in sleep is a rare, complex pediatric condition that requires immediate multidisciplinary intervention to prevent the onset and persistence of its complications, aphasia, and concentration and attention deficits. Since up to now a standard therapeutic protocol for treating this condition and its comorbidities was not clearly defined, despite the significance of the disease and its complications, I found a study demonstrating the effectiveness of valproic acid in combination with ethosuximide for these patients to be useful. The analysis revealed that the VPA+ETH combination provides good control over clinical and electrical epileptic seizures, as well as associated neurocognitive disorders.

I believe another significant contribution of this study is the demonstration of the effectiveness of a cannabis oil formula without THC and impurities, in accordance with current standards, in controlling the effects determined by electrical status in sleep, specifically concentration and attention disorders, learning disorders, and aphasia associated with electrical status epilepsy in sleep.

Using CBD OIL is novel in pediatric neurology since up to now, only synthetic cannabinoid studies have been conducted. Cannabinoids, especially cannabis oils, have been of great interest in recent years in medicine, with controversial and still incomplete ideas about their efficacy and safety in neuropsychiatric conditions. Even if there is evidence suggesting the benefits of cannabinoids for certain neuropsychiatric conditions, I consider further research essential to determine the proper titration of the substance.

Recent results suggest the benefits of adhering to a therapeutic regimen consisting of VPA+ETH+CBD for treating pediatric neurology patients diagnosed with epileptic encephalopathy associated with electrical status epilepsy in sleep.

Based on personal experience accumulated over the past 10 years, I strongly recommend adopting this therapeutic combination as a first-line treatment immediately upon diagnosis. From the results of personal research, I propose the following diagnostic and treatment algorithm for ESES.



I believe the main value of this work lies in proposing a set therapeutic regimen that offers the potential to prevent irreversible and debilitating cognitive decline in children, compared to other therapeutic approaches.

Given the results of the study, I believe it is appropriate to conduct a more extensive research study based on the findings presented above.

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ABREVIETIONS

ADD= attention deficit disorder, attention deficit disorder

AE = antiepileptic

ANM= National Medicine Association

CBD = cannabidiol

CBZ = clobazam

CVU= peak-wave complexes

DEXA = dexamethasone

EEG = electroencephalogram

ESES = encephalopathy associated with electrical status in sleep

ETH= ethosuximide

LTG= lamotrigine

MS = Ministry of Health

CanX
CBD PROCESSING CORP

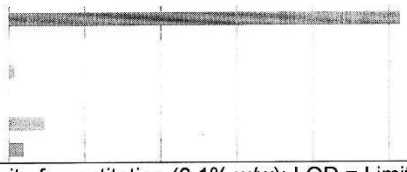
CERTIFICATE OF ANALYSIS

No.: 01/06.12.2021

Issued to	S.C. CanX CBD S.R.L.
Sample received	06.12.2021
Sample details	10% CBD oil, Full spectrum decarboxylate, THC Free, Hemp seed oil, Production date: 06.12.2021.
Sample batch	097C10
Sample type	CBD Oil
Sample delivery	-
Sample packing	Bottle
Sample size	10 mL
Appearance	Dark brown oil
Odour	Characteristic
Analysis date	06.12.2021
Method	PS-CC-05
Instrument	GC-FID

CANNABINOID PROFILE

Cannabinoid	**% w/w**
Cannabidiol (CBD)	10,27
Δ^9-Tetrahydrocannabinol (THC)	ND
Cannabidivarin (CBDV)	0,13
Cannabichromene (CBC)	ND
Cannabigerol (CBG)	0,92
Cannabinol (CBN)	0,37



Abbreviations: % w/w = weight percent; LOQ = Limit of quantitation (0.1% w/w); LOD = Limit of detection (0.05% w/w); ND = not detected; n/a = not available.

Performed: 06.12.2021
MENGHERES GABRIEL

Verified:
06.12.2021
ONARASU CONSTANTIN

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Anex 1 CBD Formula made for NaturHemp, produced for NaturWay by SC CanX SRL