Ref: Ro J Med Pract. 2023;18(2)
DOI: 10.37897/RJMP.2023.2.7

Role of various antiepileptic drugs in electrical status epilepticus during sleep and its complications

Karina Lidia GHEORGHITA[1], Alexandru Vlad CIUREA[2,4], Gelu ONOSE[3,4], Catalin NICOLAE[5], Radu Eugen RIZEA[3,4]

[1]Gheorghita Karina Lidia, Private Practice, Bucharest, Romania
[2]Sanador Hospital, Bucharest, Romania
[3]"Bagdasar-Arseni" Hospital, Bucharest, Romania
[4]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[5]Emergency County Hospital Oradea, Bihor, Romania

ABSTRACT

Electrical Status Epilepticus during Sleep (ESES) is an uncommon epileptic encephalopathy typically seen in children. It features pronounced epileptiform activity during non-REM sleep stages and is linked with behavioral and cognitive impairments. This article introduces a novel method for managing patients with ESES.

Keywords: ESES, treatment protocol, antiepileptic drugs, cannabidiol, comorbidities approach

INTRODUCTION

First identified in 1971, Electrical Status Epilepticus during Sleep (ESES) is recognized by persistent EEG irregularities coinciding with sleep onset [1,2]. ESES is diagnosed based on the combination of 85% abnormal EEG patterns during non-REM sleep and an accompanying decline in neurocognitive functions [3]. This condition often appears in male children and is age-related [1,4-9].

CLINICAL FEATURES

ESES generally emerges between the ages of 2 and 12. Initial symptoms include seizures, often paired with a sudden or progressive cognitive decline, attention lapses, memory issues, subtle motor coordination difficulties, and behavioral problems. Prior to the disease's manifestation, affected children typically display normal developmental patterns. The seizures they experience at the onset are generally mild, and can manifest as localized motor symptoms, generalized tonic-clonic seizures, or absences. Many patients experience multiple seizures daily. Typically, the cognitive and behavioral complications arise 2-3 years post the initial seizure episodes [1,6,10-14].

PARACLINICAL DATA

In ESES is the EEG recording shows over 85% complex spike-wave discharges between 1.5 to 3 hertz during non-REM sleep [1,3,10,15]. These spikes in the EEG are measured by the spike-wave index (SWI), representing the portion of non-REM sleep filled with spike waves [1,15]. While these discharges are generally localized in the frontotemporal or centrotemporal regions during wakefulness, they tend to become more generalized and frequent during sleep [1,3]. However,

Corresponding author:
Karina Lidia Gheorghita
E-mail: karina.gheorghita@gmail.com

Article History:
Received: 1 June 2023
Accepted: 12 June 2023

abnormal waves from other sleep stages aren't diagnostic. When awake, the patient may exhibit localized or multifocal spikes, occasionally in bursts, which become more evident with the emergence of comorbidities [1,3].

While neuroimaging doesn't directly assist in diagnosis, it can reveal potential structural anomalies.

PATHOPHYSIOLOGY

The exact cause of ESES remains elusive, but prevalent theories suggest the involvement of hyperactive thalamic pathways. This may be due to a shift from GABAA-related inhibitory postsynaptic potentials to GABAB-mediated potentials, leading to extended latency and reduced frequency [16].

OUTCOMES

Clinical seizures often resolve naturally around puberty. Nonetheless, some electrical irregularities might persist in EEGs post-puberty. An improvement in cognition often follows these electrical rectifications. Various reports suggest that the duration of ESES can significantly influence neurocognitive outcomes [1,3,17-19].

TREATMENT

There are various treatment approaches for ESES, with none definitively superior. Common treatments include valproic acid, benzodiazepines, ethosuximide, corticosteroids, lamotrigine, levetiracetam, and sometimes a combination of these. Valproic acid, given its broad-range efficacy, is often a first choice. It's especially potent in regulating non-REM sleep discharges and reducing ESES-associated comorbidities [20,21]. Despite the potential side effects like tolerance and sedation, benzodiazepines, including clobazam and clonazepam, are used either alone or in combination [22,23]. Ethosuximide, recognized for its efficacy against absences, might also benefit some ESES cases [24,25]. Lamotrigine, when introduced cautiously, serves as an option for complex cases [26,27], while levetiracetam is an alternative for those unresponsive to primary treatments [28,29]. Corticosteroids, given their immunomodulatory properties, also present a viable option for treatment-resistant cases [20,30].

In what follows, we will present the results of an observational research study on 40 ESES patients who received classic antiepileptic therapy in specific combinations in order to control the disease.

The study sample consisted of children aged between 4 and 12 years old. The gender distribution leaned more towards girls, and for the age categories, there was no specific representation regarding the prevalence in the population with the conditions under study. Furthermore, the study included 40 patients, and comparisons made to reveal statistically significant differences should be approached with caution. Samples included in the analysis can have sizes even smaller than 20; therefore, significant tests were not developed due to the lack of statistical representativeness (T-Test la 95% level of confidence).

One of the objectives of this study was to determine if there is a significant difference between patients who received AE at the time of ESES diagnosis - VPA+ETH - and those who didn't receive this medication. Additionally, it was important to establish whether this difference is influenced by the gender or age of the patients. Furthermore, the study aimed to ascertain if the stability of VPA+ETH, that was added at the time of diagnosis.

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

The main conclusion here is that patients who received VPA+ETH didn't require any additional

treatment after one month, unlike those who received other medication. This indicates the effectiveness of VPA+ETH and its stability after just one month of treatment. Significantly fewer patients who received VPA+ETH needed additional medication after one month (T-Test at 95% level of confidence).

Considering the gender and age analysis, the effectiveness of VPA+ETH was observed to be more pronounced in girls and younger children (under the age of 8).

The conclusion is that the treatment with VPA+ETH added at the time of ESES diagnosis, demonstrated its effectiveness by improving attention deficit conditions one month after their addition, as well as their stability over time. This symptom improvement was observed more prominently in girls and generally in younger children.

Limits and Recommendation

As previously mentioned, the sample size introduced in the study is too small to draw statistically significant conclusions. However, these results do reveal certain benefits that have emerged from the administration of these medications, and which could be the subject of a more extensive study.

The objectives and hypotheses are recommended to be formulated based on the results of this study.

CONCLUSION

The ideal pharmacotherapy for ESES varies from patient to patient. The association between VPA and ETH can be very effectiveness in cases of refractory to treat-

ment ESES. The primary goal is not only seizure control but, also improvement of cognitive and behavioral disturbances.

Acknowledgements
We thank families' patients for cooperation.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Nilika Shah Singhal, Joseph E. Sullivan, Continuous Spike-Wave during Slow Wave Sleep and Related Conditions. *ISRN Neurol.* 2014 Jan;2014:619079. https://doi.org/10.1155/2014/619079
2. Patry G, Lyagoubi S, Tassinari CA. Subclinical "electrical status epilepticus" induced by sleep in children. A clinical and electroencephalographic study of six cases. Arch Neurol. 1971;24(3):242-52. doi: 10.1001/archneur.1971.00480330070006
3. Loddenkemper T, Fernández IS, Peters JM. Continuous spike and waves during sleep and electrical status epilepticus in sleep. *J Clin Neurophysiol.* 2011 Apr;28(2):154-64. doi: 10.1097/WNP.0b013e31821213eb. PMID: 21399511
4. Eksioglu YZ, Tas E, Takeoka M, et al. Clinical presentation and acute treatment of electrical status epilepticus in sleep and sleep potentiated spikes. *Neurology.* 2009; pp. 72
5. Morikawa T, Seino M, Watanabe Y, Watanabe M, Yagi K. Clinical relevance of continuous spike-waves during slow wave sleep. In Manelis S, Bental E, Loeber JN, Dreifuss FE (Eds.), Advances in Epileptology. Raven Press; 1989. pp 359-363
6. Bureau M. Outstanding cases of electrical status epilepticus during sleep and LKS: analysis of the data sheets provided by the participants. In: Beaumanoir A, Bureau M, Deonna T, Mira L, Tassinari CA, editors. Continuous Spikes and Waves during Slow Sleep. Electrical Status Epilepticus during Slow Sleep: Acquired Epileptic Aphasia and Related Conditions. London, UK: John Libbey; 1995. pp. 213-6.
7. Inutsuka M, Kobayashi K, Oka M, Hattori J, Ohtsuka Y. Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders. *Brain Dev.* 2006;28(5):281–286. https://doi.org/10.1016/j.braindev.2005.09.004
8. Ohtsuka Y, Tanaka A, Kobayashi K et al. Childhood-onset epilepsy associated with polymicrogyria. *Brain Dev.* 2002;24(8):758-65. doi: 10.1016/s0387-7604(02)00099-2. PMID: 12453599
9. Van Hirtum-Das M, Licht EA, Koh S, Wu JY, Shields WD, Sankar R. Children with ESES: variability in the syndrome. *Epilepsy Res.* 2006 Aug;70 Suppl 1:S248-58. doi: 10.1016/j.eplepsyres.2006.01.020. Epub 2006 Jun 23. PMID: 16806829.
10. Bureau M. Continuous spikes and waves during slow sleep' (Electrical status epilepticus during sleep): definition of the syndrome. In: Beaumanoir A, Bureau M, Deonna T, Mira L, Tassinari CA, editors. Continuous Spikes and Waves during Slow Sleep. Electrical Status Epilepticus during Slow Sleep: Acquired Epileptic Aphasia and Related Conditions. London, UK: John Libbey; 1995. pp. 17-26.
11. Tassinari CA, Bureau M, Dravet C et al. Epilepsy with continuous spikes and waves during slow sleep-otherwise described as ESES (epilepsy with electrical status epilepticus during slow sleep) In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, editors. Epileptic Syndromes in Infancy, Childhood and Adolescence. 2nd edition. London, UK: John Libbey; 1992. p. 245-56.
12. Morikawa T, Seino M, Watanabe M. Long-term outcome of electrical status epilepticus during sleep syndrome. In: Beaumanoir A, Bureau M, Deonna T, Mira L, Tassinari CA, editors. Continuous Spikes and Waves during Slow Sleep. Electrical Status Epilepticus during Slow Sleep: Acquired Epileptic Aphasia and Related Conditions. London, UK: John Libbey; 1995. p. 27–36.
13. Sarco DP, Takeoka M. Epileptic and epileptiform encephalopathies. Emedicine, July 2009, http://emedicine.medscape.com/article/1179970-overview
14. Raha S, Shah U, Udani V. Neurocognitive and neurobehavioral disabilities in Epilepsy with Electrical Status Epilepticus in slow sleep (ESES) and related syndromes. *Epilepsy Behav.* 2012 Nov;25(3):381-5. doi: 10.1016/j.yebeh.2012.08.028. Epub 2012 Oct 24. PMID: 23103314.
15. Tassinari CA, Rubboli G, Volpi L, Meletti S, d'Orsi G, Franca M et al. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clin Neurophysiol.* 2000 Sep;111 Suppl 2:S94-S102. doi: 10.1016/s1388-2457(00)00408-9. PMID: 10996561.
16. Beenhakker MP, Huguenard JR. Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? *Neuron.* 2009 Jun 11;62(5):612-32. doi: 10.1016/j.neuron.2009.05.015. PMID: 19524522; PMCID: PMC2748990.
17. De Negri M, Baglietto MG, Battaglia FM, Gaggero R, Pessagno A, Recanati L. Treatment of electrical status epilepticus by short diazepam (DZP) cycles after DZP rectal bolus test. Brain Dev. 1995 Sep-Oct;17(5):330-3. doi: 10.1016/0387-7604(95)00076-n. PMID: 8579219.
18. De Negri M. Electrical status epilepticus during sleep (ESES). Different clinical syndromes: towards a unifying view? *Brain Dev.* 1997 Nov;19(7):447-51. PMID: 9408589.
19. Rousselle C, Revol M. Relations between cognitive functions and continuous spikes and waves during slow sleep. In: Beaumanoir A, Bureau M, Deonna T, Mira L, Tassinari CA, editors. Continuous Spikes and Waves during Slow Sleep. Electrical Status Epilepticus during Slow Sleep: Acquired Epileptic Aphasia and Related Conditions. London, UK: John Libbey; 1995. pp. 123-33.
20. Tassinari CA, Cantalupo G, Rios-Pohl L, Giustina ED, Rubboli G. Encephalopathy with status epilepticus during slow sleep: "the Penelope syndrome". *Epilepsia.* 2009 Aug;50 Suppl 7:4-8. doi: 10.1111/j.1528-1167.2009.02209.x. PMID: 19682041.
21. Nickels K, Wirrell E. Electrical status epilepticus in sleep. *Semin Pediatr Neurol.* 2008 Jun;15(2):50-60. doi: 10.1016/j.spen.2008.03.002. PMID: 18555191
22. Ng YT, Collins SD. Clobazam. *Neurotherapeutics.* 2007 Jan;4(1):138-44. doi: 10.1016/j.nurt.2006.11.002. PMID: 17199029; PMCID: PMC7479695.
23. Wheless JW, Isojarvi J, Lee D, Drummond R, Benbadis SR. Clobazam is efficacious for patients across the spectrum of disease severity of Lennox-Gastaut syndrome: post hoc analyses of clinical trial results by baseline seizure-frequency quartiles and VNS experience. *Epilepsy Behav.* 2014 Dec;41:47-52. doi: 10.1016/j.yebeh.2014.09.019. Epub 2014 Oct 2. PMID: 25282105.
24. Crunelli V, Leresche N. Childhood absence epilepsy: genes, channels, neurons and networks. *Nat Rev Neurosci.* 2002 May;3(5):371-82. doi: 10.1038/nrn811. PMID: 11988776.
25. Panayiotopoulos CP. Absence epilepsies. In: The Epilepsies: Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005.
26. Pisani F, Oteri G, Russo MF, Di Perri R, Perucca E, Richens A. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. *Epilepsia.* 1999 Aug;40(8):1141-6. doi: 10.1111/j.1528-1157.1999.tb00832.x. PMID: 10448829.

27. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D et al. Childhood Absence Epilepsy Study Group. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med.* 2010 Mar 4;362(9):790-9. doi: 10.1056/NEJMoa0902014. PMID: 20200383; PMCID: PMC2924476.
28. Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci USA.* 2004 Jun 29;101(26):9861-6. doi: 10.1073/pnas.0308208101. Epub 2004 Jun 21. PMID: 15210974; PMCID: PMC470764.
29. Guimarães CA, Li LM, Rzezak P et al. Temporal Lobe Epilepsy in Childhood: Comprehensive Neuropsychological Assessment. *J Child Neurol.* 2007;22(7):836-40. doi: 10.1177/0883073807304701
30. van den Munckhof B, van Dee V, Sagi L, Caraballo RH, Veggiotti P, Liukkonen E et al. Treatment of electrical status epilepticus in sleep: A pooled analysis of 575 cases. *Epilepsia.* 2015 Nov;56(11):1738-46. doi: 10.1111/epi.13128. Epub 2015 Sep 4. PMID: 26337159.
31. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R et al. Cannabidiol in Dravet Syndrome Study Group. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med.* 2017 May 25;376(21):2011-2020. doi: 10.1056/NEJMoa1611618. PMID: 28538134.
32. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C et al. GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2018 Mar 17;391(10125):1085-1096. doi: 10.1016/S0140-6736(18)30136-3. Epub 2018 Jan 26. PMID: 29395273.