doi:10.17659/01.2024.0026

Journal of Case Reports 2024;14(4):97-101

Integrative Treatment with Gamma-aminobutyric Acid and Phosphatidylserine in a Patient with Childhood Absence Epilepsy Treated with Ethosuximide

Jonathan E. Prousky

Canadian College of Naturopathic Medicine, 1255 Sheppard Avenue East, Toronto, Ontario, Canada M2K 1E2.

Corresponding Author:
Dr Jonathan E. Prousky
Email: jprousky@ccnm.edu

Received : December 9, 2023
Accepted : August 6, 2024
Published : November 25, 2024

Abstract

Background: A 6-year-old girl was diagnosed with childhood absence epilepsy (CAE) based on clinical history and video-recorded electroencephalogram (EEG). She was started on ethosuximide (ES; 150 mg twice daily), with a gradual increase over two weeks to a target dose of 250 mg twice daily. *Case Report*: The patient maintained a daily ES dose of 300 mg, supplementing it with gamma-aminobutyric acid (GABA; 3000 mg) and phosphatidylserine (PS; 200 mg from a liquid fish oil product). A follow-up EEG, done 23 months later, showed normal results. During nearly two years of integrative treatment, the patient experienced no seizures despite growth in height and weight. The integrative approach also improved her focus, reduced shyness, and promoted social engagement. *Conclusion*: This integrative approach, combining GABA and PS with ES, may have enhanced treatment effectiveness, maintained a low ES dose, and possibly minimized pharmaco-resistance. These positive outcomes suggest that a similar approach may benefit other patients with newly diagnosed CAE.

Keywords: Electroencephalography, Epilepsy, Gamma-aminobutyric acid, Glutamate, Seizure.

Introduction

When a child experiences an absence seizure, there is a sudden and brief lack of consciousness lasting about 10 seconds "often accompanied by simple automatisms, or clonic, atonic, or autonomic components" [1]. These observable changes arise when there is a brain milieu of reduced inhibitory activity of the gamma-aminobutyric acid (GABA) system and increased excitatory activity brought on by glutamate [2]. The frequency of absence seizures can range from 10 to more than 30 times each day [3].

The onset of typical absence seizures is normally around 6-7 years of age [4]. When untreated, absence seizures result in problems related to a child's physical safety, educational attainment, and quality of life [1]. An electroencephalography (EEG) is the main tool used for evaluating typical absence seizures and will show generalized spike and wave complexes that are greater than 2.5 Hz (Hertz), most notably 3 to 4.5 Hz [5] of a duration of 3 or more seconds [6,7]. Once the patient's clinical history is correlated with the aforementioned EEG findings, a diagnosis of childhood absence epilepsy (CAE) is made.

Treatment involves the use of monotherapy with an anti-epileptic drug (AED), using ethosuximide (ES) as the main first-line treatment, and depending on efficacy, it may be replaced with valproic acid (VA) or lamotrigine (LT). Unfortunately, a significant percentage of patients do not achieve freedom from seizures [8,9]. Seizure freedom has been reported in 57% to 74% of epileptic patients [4]. In a randomized clinical trial evaluating ES, VA, and LT among patients

with CAE, there was an overall treatment failure of 42% to 71% after week 16 [8]. In an extension clinical trial, patients that were seizure-free from the aforementioned clinical trial [8] were evaluated to determine how many remained seizure-free at 12 months on their initial AED. Only 37% remained seizure-free at the 12-month mark [9].

Integrative options may be capable of bettering the clinical outcomes from AED monotherapy treatment. Here, I present a case of a child that was experiencing typical absence seizures, and was subsequently diagnosed with CAE. The integrative approach combined GABA and phosphatidylserine (PS) supplementation with ES. This resulted in the immediate cessation of seizure activity and psychosocial improvement over the almost 24-month treatment duration.

Case Report

In January 2016, a 6-year-old female was having staring episodes for several seconds at a time during the day. From January to March of that year, her parents thought that she was not paying attention. They responded by talking more loudly, which did not capture their daughter's attention. In March the frequency of the staring spells increased, as they were happening upwards of 5 times each hour. The patient's teachers were unaware that anything unusual was happening, but surprisingly her good friend noticed that she was spacing out many times during the day. The parents did their own research and were convinced that their daughter had CAE. They estimated that their daughter was having upwards of 5 seizures per hour and approximately 40 seizures each day. During the seizures she would blink or lick her lips, and then at other times she might walk a little or speak incoherently.

The video EEG done on April 7, 2016 recorded generalized 3/s spike and slow wave activity which were enhanced during hyperventilation and accompanied clinically by staring and unresponsiveness. There was also a prolonged event which could have been triggered by photic stimulation at 8 Hz. The overall findings are in keeping with primary generalized epilepsy and the more prolonged events recorded, with absence seizures. On April 21, 2016, they had their first visit with the pediatric neurologist who correlated the video EEG with the patient's history, and confirmed that she had a diagnosis of CAE. The pediatric neurologist prescribed ES at an initial dose of 3 ml (150 mg) twice daily, with instructions to increase the dose over a 14-day period to 5 ml (250 mg) twice daily. Information about supplemental GABA and PS was discussed at the appointment, but the pediatric neurologist was unwilling to support an integrative approach. On April 22, 2016, the patient began the ES at 3 ml twice daily (300 mg per day), along with GABA (1,500 mg twice daily), and a liquid fish oil product that contained 100 mg of PS per teaspoon (5 mL twice daily). Each teaspoon of the liquid fish oil product contained 100 mg PS, 350 mg docosahexaenoic acid, 150 mg eicosapentaenoic acid, 1,000 IU vitamin D_3, 4 mg lutein, and 2 mg zeaxanthin. The patient also continued with supplements that were taken regularly before being diagnosed with CAE and continued thereafter, which included a chewable multiple vitamin/mineral supplement and 500 mg or more of vitamin C several times each week. The parents noticed an immediate response; the seizures stopped on the first day they started the integrative treatment approach.

The parents consulted a second pediatric neurologist on August 15, 2016. The new pediatric neurologist was open-minded about the integrative approach, and expressed no concerns about keeping the patient on such a low dose of ES as long as there were no reports of seizure activity. The patient had another video EEG done on March 19, 2018, which was normal. This routine video EEG, performed during awake, drowsy and sleep states, was within normal limits for age. Compared to her previous recording, there has been considerable improvement.

The patient remained on the integrative approach until April 17, 2018. During the duration of integrative treatment, the parents never saw any seizure activity. They also noticed psychosocial improvements in their daughter that included better focus, less shyness, and increased social engagement at school. The dose of ES remained unchanged during the active treatment period.

Discussion

Tower may have been the first clinician to report on the putative anti-seizure effects of oral GABA in humans [10]. His 1960 report involved a total of 11 patients that were given oral GABA each day; some were followed for 3 months, and others as long as 2 years. Of the 11 patients, 4 had notable therapeutic responses to oral GABA with seizure types described as "minor or petit mal types". Eventually, other reports were published that evaluated GABA's anti-seizure effects. These were animal studies that also involved co-administration with PS [11-14]. When PS was co-administered with GABA, there was a resultant increase in the synaptic availability of GABA, and an increased supply to GABA-ergic nerve endings [14]. This data suggests that GABA mediates inhibitory control within the brain, and diminishes seizure activity by overcoming the excitatory influences brought on by glutamate.

A human study, published in 1987, evaluated the co-administration of GABA and PS among teenage and adult patients (age range: 15-65; n=42) with various forms of epilepsy [15]. Only 34 patients completed the study. All patients in this study were on 1-3 AEDs. Only the patients with absence seizures (n=12) showed statistically significant differences from the reference and treatment periods, and clinically significant differences in monthly seizure frequency. The results demonstrated a statistically significant drop in the mean numbers of seizures per month during the reference (29±18) and treatment periods (12±13). The combined use of GABA and PS "brought about a significant decrease in absence seizures, while complex partial seizures showed no significant changes"

GABA may also reduce seizures by modulating alpha brain waves though there is speculation that it acts indirectly on the brain through the enteric nervous system [16]. A study on epileptic patients (age range: 5-17 years) showed a statistically significant correlation between the presence of seizure activity and the absence of alpha wave activity in EEG recordings [17]. A mere 100 mg of oral GABA when given to healthy human subjects increased alpha waves while simultaneously decreasing beta waves [18], and also prevented alpha and beta brain waves from declining following mental stress [19]. One hundred milligrams of GABA is rapidly absorbed, peaks at 30 minutes following oral administration, and then will decrease over the course of 60 minutes to a level that remains above the baseline measurement [20]. PS appears to augment the effects of GABA and assist in its cerebral utilization [11-14]. PS is also an integral part of the fatty components of cell membranes, and possesses broad-spectrum effects that influence nerve cell membrane functionality [21].

A particularly unusual aspect of this case involved the low daily dose of ES that remained unchanged at 300 mg until it was tapered down and eventually discontinued. When patient was first evaluated by the second pediatric neurologist on August 15, 2016, her weight was 46.3 lbs (21 kg) and height was 49 inches. On April 17, 2018, her weight had increased to 62 lbs (28.12 kg) and height to 53 inches. In a previously cited study, the mean dose of ES at week 16 of the trial was 33.5±15.3 mg per kilogram per day [8]. This suggests that the patient's daily dose of ES should have been somewhere between 675 mg and 1000 mg before the daily dose was tapered down and eventually discontinued. Both the pediatric neurologist and receptionist commented during the April 2018 visit that she had actually gone through a natural taper

because her ES dose remained unchanged during the active integrative treatment period despite gaining weight. The patient did not experience any significant adverse effects, except for rare stomach upset and/or burping episodes, which did not impact her compliance. The reported adverse effects from GABA are not serious and may include neurologic tingling and cutaneous flushing [22], as well as sedation since GABA has been shown to facilitate sleep onset [20]. Numerous clinical trials involving more than 800 patients have shown PS to be extremely safe and well tolerated [21]. Rarely, it causes stomach upset, and if high doses such as 600 mg are taken close to bedtime, sleeplessness may ensue [21].

The addition of GABA and PS might have also helped to reduce pharmaco-resistance. Pharmaco-resistance means a failure to control seizures despite "accurate diagnosis and carefully monitored pharmacologic treatment," and happens in some 30% of epileptic patients [23]. Pharmaco-resistance arises from the associated brain changes induced by some combination (or interplay) of genetics and medication effects, and from problems in getting medication to specific areas of the brain where seizure activity occurs [24,25]. The mere fact that the patient did so well on such low doses of ES suggests that GABA and PS possibly reinforced the anti-seizure effects of ES, allowing for smaller daily doses to be clinically effective, thereby lessening brain perturbations implicated in pharmaco-resistance.

Either the patient's form of CAE was unusual in that her seizures responded extraordinarily fast to such a low daily dose of the ES despite her weight gain, or it was the integrative treatment that allowed the daily ES dose to remain low and for the clinical outcome to be so positive. As mentioned previously, the liquid fish oil contained 100 mg of PS and 1,000 IU of vitamin D_3. The patient's total amount of vitamin D_3 from 2 daily teaspoons of the liquid fish oil was 2,000 IU. Vitamin D_3 has been shown to lessen seizure frequency in humans regardless of seizure type [26], and may be a protective factor in adolescent absence epilepsy [27]. Thus, vitamin D_3 could have been partly or entirely responsible for the observed anti-seizure effects from the integrative treatment. Lastly, it is possible that the addition of GABA, PS, and vitamin D_3 possessed no therapeutic or augmentative effects on their own, and all of what happened was purely the result of ES.

Conclusion

The patient experienced immediate and complete seizure control on the integrative approach that enabled an unusually small daily dose of ES to be effective. The patient also experienced an improved quality of life during the active treatment period. Given the positive outcome here, there is certainly the possibility that other pediatric patients might specifically benefit from this integrative approach for newly diagnosed CAE.

Contributors: JEP: manuscript writing, editing, and patient management. The author will act as a study guarantor, approved the final version of this manuscript and is responsible for all aspects of this study.
Funding: None; *Competing interests*: None stated.

References

1. Posner E. Absence seizures in children. BMJ Clin Evid. 2013;12:317.
2. Segan S. Absence seizures. Medscape. Updated September 25, 2018. Available from: https://reference.medscape.com/article/1183858-overview. Accessed on August 4, 2024.
3. Albuja AC, Khan GQ. Absence seizure. Updated 2022 Oct 10. Treasure Island, FL: StatPearls Publishing; 2023 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499867/. Accessed on August 4, 2024.
4. Loiseau P, Duche B, Pedespan JM. Absence epilepsies. Epilepsia. 1995;36(12):1182-1186.
5. Panayiotopoulos CP. Typical absence seizures and related epileptic syndromes: assessment of current state and directions for future research. Epilepsia. 2008;49(12):2131-2139.
6. Frank LM, Enlow T, Holmes GL, Manasco P, Concannon S, Chen C, *et al*. Lamictal (lamotrigine) monotherapy for typical absence seizures in children. Epilepsia. 1999;40(7):973-979.

7. Holmes GL, McKeever M, Adamson M. Absence seizures in children: clinical and electroencephalographic features. Ann Neurol. 1987;12(3):268-273.
8. 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;362(9):790-799.
9. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, *et al*. Childhood Absence Epilepsy Study Team. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: Initial monotherapy outcomes at 12 months. Epilepsia. 2013;54(1):141-155.
10. Tower DB. The administration of gamma-aminobutyric acid to man: systemic effects and anticonvulsant action. *In*: Roberts E, Baxter CF, Harreveld AV, Wiersma CAG, Adey WR, Killam KF, editors. Inhibition in the nervous system and gamma-aminobutyric Acid. New York: Pergamon Press Inc; 1960. pp.562-578.
11. Toffano G, Mazzari S, Zanotti A, Bruni A. Synergistic effect of phosphatidylserine with gamma-aminobutyric acid in antagonizing the isoniazid-induced convulsions in mice. Neurochem Res. 1984;9(8):1065-1073.
12. Loeb C, Bo GP, Scotto PA, Benassi E, Besio G, Mainardi P, Faverio A. GABA and phospholipids in penicillin-induced seizures. Exp Neurol. 1985;90(1):278-280.
13. Loeb C, Besio G, Mainardi P, Scotto P, Benassi E, Bo GP. Liposome-entrapped gamma-aminobutyric acid inhibits isoniazid-induced epileptogenic activity in rats. Epilepsia. 1986;27(2):98-102.
14. Benassi E, Besio G, Cupello A, Mainardi P, Patrone A, Rapallino MV, *et al*. Evaluation of the mechanisms by which gamma-amino-butyric acid in association with phosphatidylserine exerts an antiepileptic effect in the rat. Neurochem Res. 1992;17(12):1229-1233.
15. Loeb C, Benassi E, Bo GP, Cocito L, Maffini M, Scotto P. Preliminary investigation of the effect of GABA and phosphatidylserine in epileptic patients. Epilepsy Res. 1987;1(3):209-212.
16. Boonstra E, de Kleijn R, Colzato LS, Alkemade A, Forstmann BU, Nieuwenhuis S. Neurotransmitters as food supplements: the effects of GABA on brain and behavior. Front Psychol. 2015;6:1520.
17. Aich TK. Absent posterior alpha rhythm: An indirect indicator of seizure disorder? Indian J Psychiatry. 2014;56(1):61-66.
18. Abdou AM, Higashiguchi S, Horie K, Kim M, Hatta H, Yokogoshi H. Relaxation and immunity enhancement effects of γ-Aminobutyric acid (GABA) administration in humans. BioFactors. 2006;26(3):201-208.
19. Yoto A, Murao S, Motoki M, Yokoyama Y, Horie N, Takeshima K, *et al*. Oral intake of γ-aminobutyric acid affects mood and activities of central nervous system during stressed condition induced by mental tasks. Amino Acids. 2011;43(3):1331-1337.
20. Hepsomali P, Groeger JA, Nishihira J, Scholey A. Effects of oral gamma-aminobutyric acid (GABA) administration on stress and sleep in humans: a systematic review. Front Neurosci. 2020;14:923.
21. Kidd PM. Phosphatidylserine: membrane nutrient for memory. A clinical and mechanistic assessment. Altern Med Rev. 1996;1(2):70-84.
22. Bronson, PJ. A biochemist's experience with GABA. J Orthomol Med. 2011;26(1):11-14.
23. Wahab A. Difficulties in treatment and management of epilepsy and challenges in new drug development. Pharmaceuticals (Basel). 2010;3(7):2090-2110.
24. Pati S, Alexopoulos AV. Pharmacoresistant epilepsy: from pathogenesis to current and emerging therapies. Cleve Clin J Med. 2010;77(7):458-467.
25. Sharma AK, Rani E, Waheed A, Rajput SK. Pharmacoresistant epilepsy: a current update on the non-conventional pharmacological and non-pharmacological interventions. J Epilepsy Res. 2015;5(1):1-8.
26. Holló A, Clemens Z, Kamondi A, Lakatos P, Szűcs A. Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. Epilepsy Behav. 2012;24(1):131-133.
27. Luo X, Ruan Z, Liu L. The causal effect of serum 25-hydroxyvitamin D levels on epilepsy: A two-sample Mendelian randomization study. Epilepsia Open. 2023;8(3):912-917.

