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Efficacy of propofol and midazolam combination in managing refractory epileptic encephalopathy with spike-wave activation in sleep

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ABSTRACT

We presented a 7-year-old boy with refractory Epileptic Encephalopathy with Spike-and-Wave Activation in Sleep (EE-SWAS) successfully managed with a combination of propofol and midazolam. His seizures began at age 2, initially controlled by multiple antiseizure medications (ASMs) for almost three years. At age 5, seizures recurred with electroencephalography (EEG) showing electrical status epilepticus in sleep (ESES) and a spike-wave index (SWI) of 85 %. High-dose methylprednisolone pulse therapy initially reduced the SWI to 50 %, but it relapsed to 80 % within six months. Despite further treatments, including methylprednisolone, midazolam infusion, and four combined ASMs, the SWI persisted between 75 % and 85 %, leading to progressively worsening cognitive impairment and subsequently a somnolent state with nearly continuous discharges. During hospitalization, a combination of propofol and midazolam significantly improved the condition, reducing the SWI to 50 % upon completion of the treatment period. Over a three-year follow-up, no ESES or seizures were reported, and cognitive function notably improved. Currently, there is no consensus on the treatment of ESES, which is sometimes refractory to medication and can result in partially irreversible cognitive impairment. Propofol in combination with midazolam has demonstrated effective suppression of ESES phenomena, presenting a promising treatment strategy for refractory ESES.

1. Introduction

Electrical Status Epilepticus in Sleep (ESES) is characterized by nearly continuous spike-wave discharges during non-rapid eye movement (NREM) sleep on electroencephalography (EEG), typically seen in children and associated with various epilepsy syndromes, including Developmental and/or Epileptic Encephalopathy with Spike-and-Wave Activation in Sleep (D/EE-SWAS). While EEG abnormalities in ESES often resolve by puberty, cognitive and behavioral deficits persist. Earlier onset and prolonged duration are associated with poorer outcomes [1], highlighting the importance of early intervention to improve long-term prognosis. However, there is no consensus on the treatment of ESES and the current treatment paradigm is primarily based on retrospective studies, case series, and expert opinion, focusing primarily on corticosteroids, benzodiazepines (BZPs), other antiseizure medications (ASMs), and surgery. Despite these therapies, some patients remain refractory due to ESES's complex, heterogeneous nature [2]. Propofol combined with midazolam has shown rapid, effective suppression of epileptiform activity. Here, we present a case of refractory EE-SWAS where conventional therapies failed, but complete ESES resolution was achieved with intravenous propofol and midazolam, suggesting a potential alternative approach for managing refractory cases.

2. Case report

A 7-year-old boy, born at term with a birth weight of 2700 g, had a history of cerebral hemorrhage occurring 10 days after birth, primarily involving the right thalamus. Development was within normal parameters before the onset of the disease. At age 2, he experienced afebrile hemiclonic seizures, occurring approximately four times per year with durations lasting 30–50 min. He was initially treated with multiple ASMs (oxcarbazepine (OXC), levetiracetam (LEV), and nitrazepam (NZP)), which provided seizure control for almost 3 years.

However, at age 5, seizures recurred, occurring more than 10 times

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per day, and began to exhibit atypical absence seizures, characterized by impaired consciousness with limb movement stagnation. EEG recordings revealed ESES during NREM sleep with a Slow-Wave Index (SWI) of 85 %. High-dose intravenous methylprednisolone pulse therapy (20 mg/kg for 3 days, repeated after 4 days) reduced the SWI to 70 % and then to 50 % at the 2-month follow-up without any seizures when he received subsequently low-dose prednisone and a combination of four ASMs (valproate (VPA), LEV, lacosamide (LCM) , and clonazepam (CZP)).

However, seizures recurred after 6 months, in March 2020, presenting similarly, with a frequency of several episodes per day, and ESES reappeared with an increased discharge index of 80 %. High-dose methylprednisolone combined with intravenous midazolam infusion (0.5–1 μg/kg/min for 7 days) and the addition of perampanel (PER) and topiramate (TPM) failed to resolve ESES. A total of seven ASMs were tried, but the SWI remained fixed at 75–85 %, with progressive worsening of cognitive abilities and attention deficit. Additionally, he attempted the ketogenic diet for two weeks, but had to discontinue due to the development of hematuria and B-ultrasound indications of multiple kidney stones. At this time, the Raven's test score was 65, indicating mild cognitive impairment. Cranial magnetic resonance imaging (MRI) conducted in March 2020 revealed cerebral softening lesions in the right thalamus and posterior and splenium of the corpus callosum (Fig. 1), with no changes observed at the half-year follow-up.

Six months later, at the follow-up visit in November 2020, the patient had progressed to a somnolent state, unresponsive to verbal stimuli, and unable to engage in simple communication with a SWI of more than 85 %, nearly continuous discharges. Upon admission to the hospital, the patient was transferred to the intensive care unit for close supervision and mechanical ventilation. Intravenous midazolam drip (initially at 6 μg/kg/min for 3 days, followed by 4 μg/kg/min for 5 days) was administered in conjunction with intravenous propofol infusion (initially at 2 mg/kg/h for 4 days, then increased to 4 mg/kg/h for 4 days). Oral ASMs including VPA, topiramate (TPM), CZP, and PER were introduced during the infusion period. Simultaneously, continuous bedside EEG monitoring was performed, showing a marked reduction in continuous discharges, with the SWI decreasing to 50 % after treatment and no seizures observed.

Video EEG examinations were conducted after discharge. The SWI decreased to less than 50 % by December 2020, with complete resolution of ESES noted since January 2021, and maintained during subsequent multiple follow-ups at intervals of 3–6 months (Fig. 2). Throughout the follow-up period, CZP and TPM was gradually discontinued, and the patient currently takes VPA and PER orally. There have been no seizures for more than 3 years since discharge, and cognitive and motor functions have shown some improvement. At the last follow-up, at the age of 10 years and 7 months, the patient was in the first grade of primary school with normal motor function. The patient

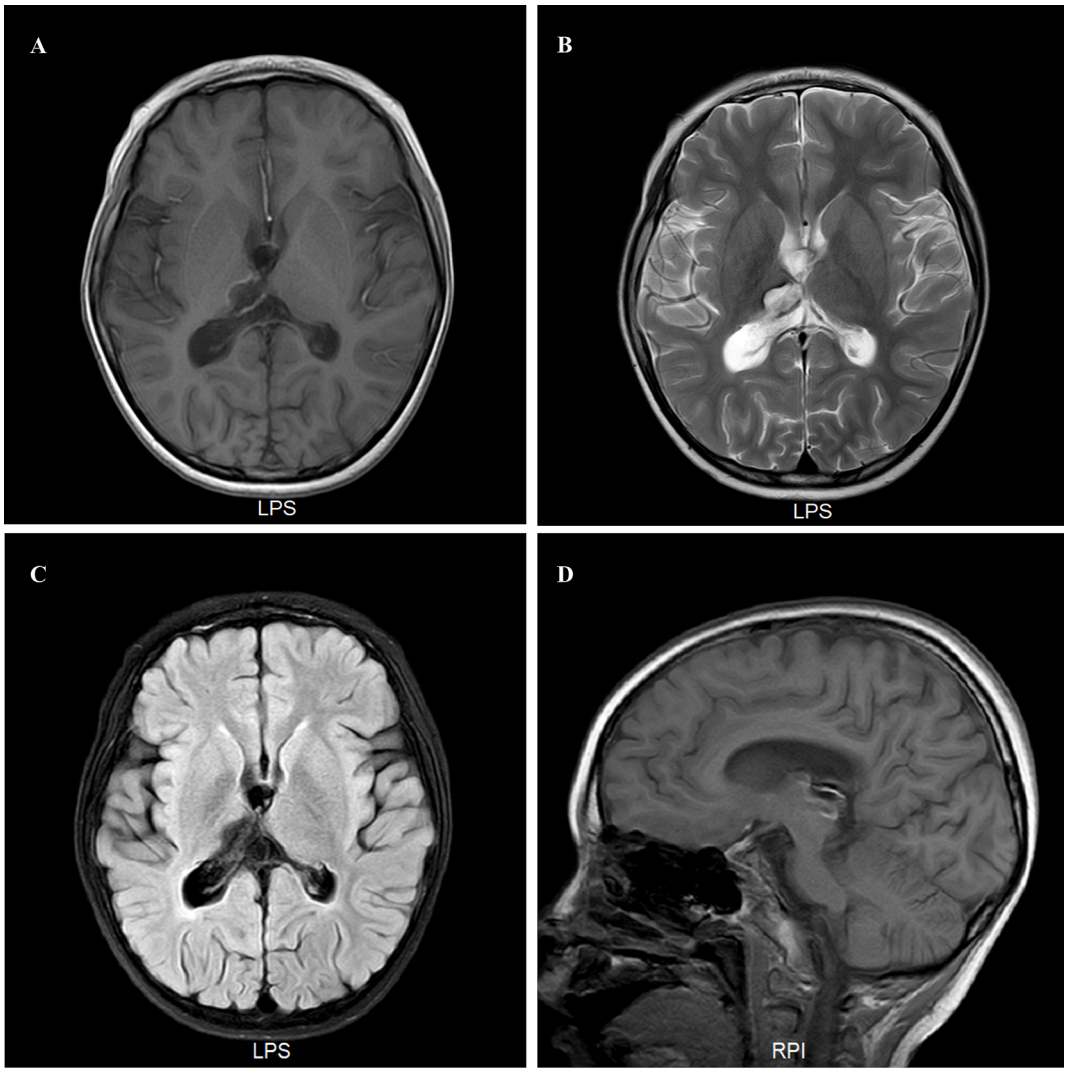

Fig. 1. Brain MRI of the patient in March 2020. MRI [(A, D) T1, (B) T2, (C) FLAIR] demonstrated cerebral softening lesions in the right thalamus and posterior and splenium of the corpus callosum.

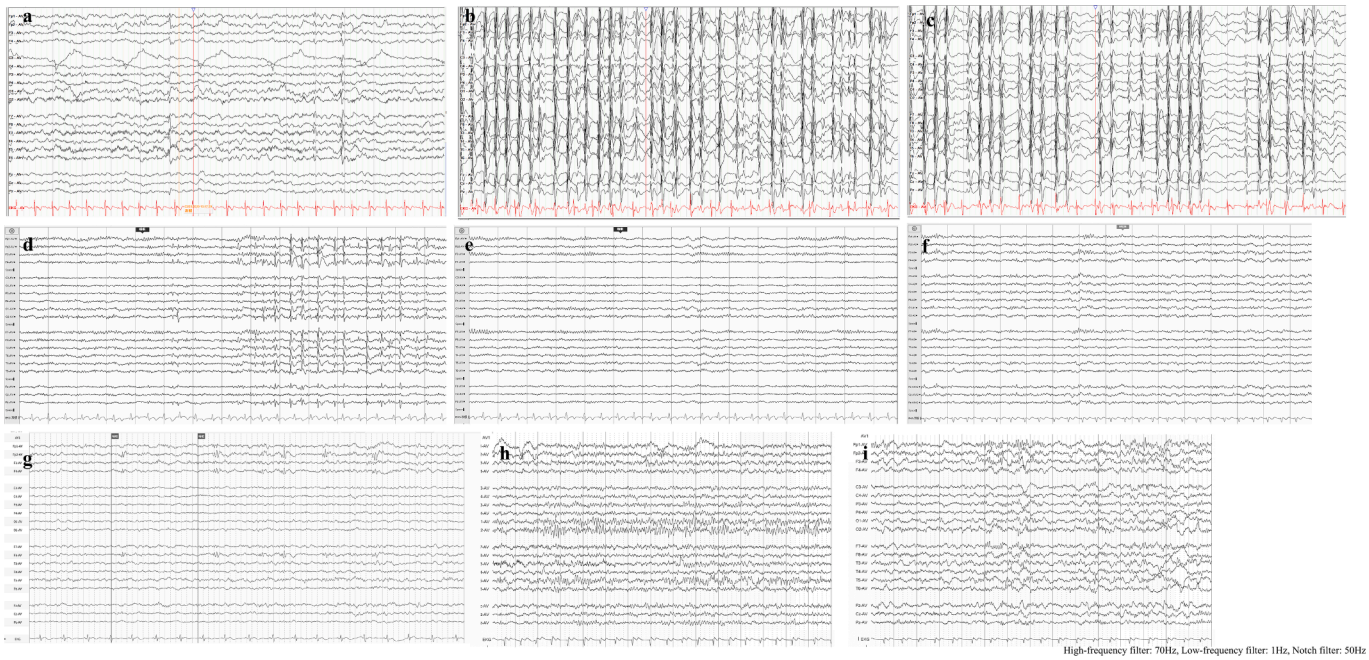

Fig. 2. Electroencephalogram (EEG) of the patient. (a–c) EEG tracing in March 2020. Epileptiform discharges were observed in the right parieto-occipital and right central temporal regions during wakefulness with almost continuous widespread spike-waves occupying approximately 80 % of the NREM sleep recording. (d and e) EEG tracing in November 2020 (one week after the completion of combined treatment). A significant reduction in sleep discharges, with epileptiform discharges observed in the right frontal region. (f) EEG tracing in February 2021. No signs of ESES were observed. (g) EEG tracing in January 2023. No signs of ESES were observed, with a small amount of epileptiform discharges observed in the right frontal region. (h and i) EEG tracing in February 2024. No epileptiform discharges and no signs of ESES were observed.

was able to engage in typical verbal communication and social interactions; however, certain limitations remained. Response times were slower compared to peers, language organization skills were less developed, and attention span was reduced. The Raven's test score was 78, and the SNAP-IV summary score for attention deficit was 1.89. The treatment regimen, and changes in seizure frequency, SWI and cognitive function are shown in Fig. 3.

3. Discussion

ESES presents a distinct electrographic pattern characterized by epileptiform discharges that prominently activate and persist during NREM sleep [3]. Previously, an SWI ≥ 85 % was considered diagnostic for ESES, however, this criterion is seen as overly restrictive. Studies revealed no linear correlation between SWI value and the severity of

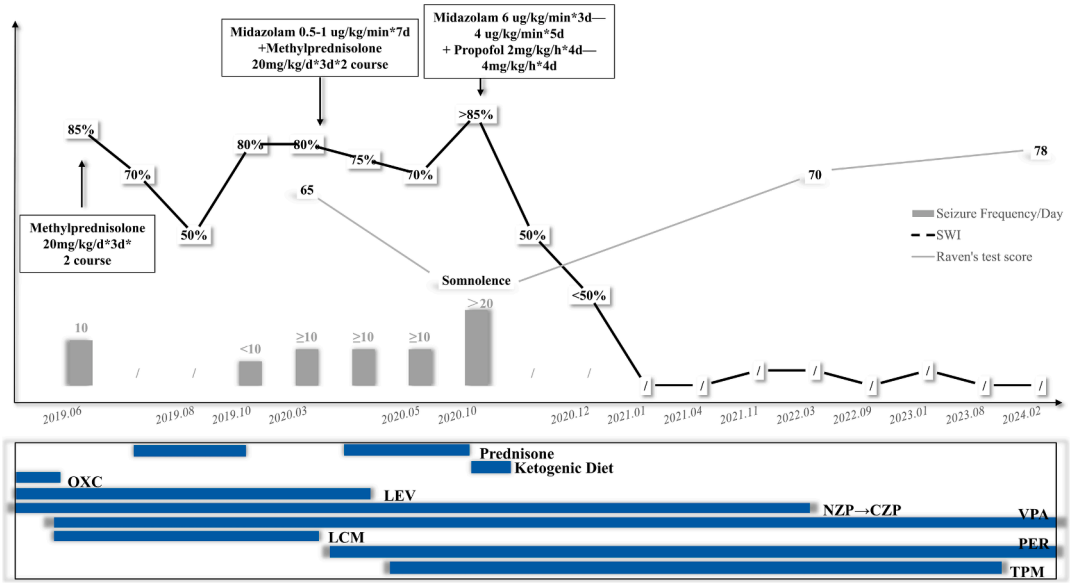

Fig. 3. The treatment regimen, and changes in seizure frequency, spike-wave index (SWI) and cognitive function. Note: The height of the gray bars represents the frequency of seizures at various time points; The black dashed line shows the SWI over time; The gray dashed line reflects changes in cognitive function, assessed by the Raven's test score; The blue bars below the graph indicate the duration of various medications used over the treatment period; OXC: Oxcarbazepine; LEV: Levetiracetam; LCM: Lacosamide; NZP: Nitrazepam; CZP: Clonazepam; VPA: Valproic Acid; PER: Perampanel; TPM: Topiramate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ESES, leaving the diagnostic cut-off still a matter of controversy. A majority of previous studies define ESES as activity occurring during 50 %–85 % of NREM sleep [4], associating it with neuropsychological impairment, which is considered the hallmark of ESES.

ESES exhibits heterogeneity in etiology, encompassing structural, genetic, metabolic, vascular, and cryptogenic factors. Structural injuries, especially thalamic, are implicated in ESES development [5], with the cortico-thalamic circuitry involved in pathogenesis. Our patient's history of cerebral hemorrhage in the right thalamus supports this finding. Additionally, the refractory nature of ESES in this case could potentially be linked to the thalamic lesion. Genetic etiologies have also been implicated in ESES, with various genetic alterations identified over the years, including variations in *GRIN2A*, *KCNA2*, *KCNB1*, *KCNQ2* and so on. Inflammation may also play a role [6], as evidenced by the favorable responses of ESES patients to steroids and intravenous immunoglobulin (IVIG). However, the pathogenesis of ESES remains incompletely understood.

Despite the age-dependent long-term favorable outcome of seizures and electrographic features, the prognosis of ESES is not as favorable due to the potential persistence of behavioral and cognitive impairments into adulthood [7]. Research indicates that only 10–40 % of patients experience normalization of their neurocognitive status after electrographic resolution, with unfavorable outcomes associated with early onset and long duration of ESES [8]. Studies have shown that epileptic activity can disrupt thalamocortical oscillation circuits and inhibit thalamic sleep spindles, thereby contributing to cognitive deficits in ESES [9]. Therefore, prompt initiation of effective treatment strategies is necessary to prevent long-term sequelae.

The aim of treating ESES is to prevent neuropsychological impairment, not only for seizure control. However, the treatment of ESES remains controversial due to a lack of consensus and large randomized controlled trials. Benzodiazepines (BDZs) and corticosteroids are the most recommended treatments, with a remission rate of 40–80 % reported in many studies. Research indicates that corticosteroids are particularly effective in improving cognitive outcomes in patients with ESES compared to BDZs and other ASMs, especially in short-term follow-ups [10]. However, the recurrence rate with both steroids and BDZs remains high, ranging from 60 % to 80 % [11], and a significant proportion of ESES patients remain refractory or prone to relapse. Refractory ESES, characterized by continuous spike-wave discharges during NREM sleep despite treatment with steroids, BDZs, and other ASMs, can be deemed as a form of "subclinical electrical status epilepticus". Our patient endured refractory ESES for over six months, with a nearly 85 % slow wave index, leading to progressive cognitive impairment. Despite receiving high-dose methylprednisolone pulses twice, intravenous MDZ infusion, ketogenic diet, and multiple ASMs with reported efficacy in ESES, the patient's condition persisted. Given the potential irreversible neuropsychological deterioration associated with prolonged ESES and its correlation with duration, a more "aggressive" therapeutic approach became necessary.

We report a case successfully treated with intravenous midazolam and propofol. Midazolam, a BDZ, allosterically potentiates $GABA_A$ receptors and is considered the first-line drug for acute repetitive seizures and status epilepticus. A *meta*-analysis suggests that midazolam is being considered as a replacement for diazepam due to its faster absorption and higher product stability [12]. Consistent with other BDZ, a retrospective study found that 80 % of ESES patients responded to midazolam infusion [13]. Responders not only experienced a remission of SWI by 50 % or more but also showed improvement in clinical symptoms and behavior.

Propofol (PRO), an intravenous anesthetic, primarily potentiates the activity of GABAa receptors, resulting in a reduction in neuronal excitability. It has been widely considered for managing refractory status epilepticus (RSE), which refers to status epilepticus (SE) unresponsive to BDZs and other ASMs, with minimal accumulation propensity and short distribution half-lives [14]. PRO's ability to suppress spike-wave patterns and eliminate seizure-like phenomena of epileptic origin positions it as an effective agent for seizure management and sedation in epileptic patients. Cureus et al. demonstrated successful PRO use in ICU settings to control severe seizure activity, stabilizing neuronal firing patterns effectively [15]. Additionally, beyond its antiepileptic effects, PRO exhibits neuroprotective properties, including anti-inflammatory, antioxidant, and anti-apoptotic effects [16], potentially mitigating long-term neurocognitive deficits caused by ESES.

Recent studies advocate for early initiation of intravenous anesthesia after first-line treatment failure, resulting in shorter SE duration and ICU stay without increased adverse events [17]. PRO carries risks such as respiratory depression, hypotension, and PRO infusion syndrome, which necessitate rigorous monitoring throughout treatment, especially in pediatric patients. Studies consistently indicate that with appropriate management, the benefits of PRO in controlling severe epileptic activity outweigh its risks. A retrospective study comparing PRO and MDZ in RSE found no significant difference in mechanical ventilation duration, hemodynamic compromise, or mortality, suggesting a low incidence of treatment-related adverse events [18]. Treatment-related complications are linked to prolonged duration and dosage of PRO administration. MDZ has been shown to synergize hypnotically with PRO as a premedicant or coinductant during induction by enhance GABAergic inhibition through different binding sites. A double-blind, randomized controlled prospective study found that patients who received MDZ premedication were able to reduce the required dosage of PRO [19], theoretically inducing lower risk of adverse events, and had better outcome compared with PRO alone [20], suggesting that reducing PRO dosage while ensuring efficacy may be feasible. Our patient was closely supervised and mechanically ventilated in an intensive care unit, with MDZ administered concomitantly with PRO. Ultimately, the epileptiform discharges remitted without recurrence during follow-up after the combined treatment. These findings suggest the feasibility of combining PRO with MDZ in treating ESES, providing a potential therapeutic avenue for refractory cases. The long-term effects of propofol on neurodevelopment remain controversial, as early, repeated exposure may increase the risk of cognitive or behavioral impairments [21]. Its use in refractory ESES requires careful evaluation, weighing risks and benefits individually with vigilant monitoring.

4. Conclusion

This study presents a case of refractory ESES successfully managed with a combination of propofol and midazolam, showing resolution of ESES and improvement in neuropsychological function, which should be further confirmed in larger cohorts of ESES patients.

Ethical statement

Ethical review was waived for this study due to its case report nature, and informed consent was obtained from the parents.

CRediT authorship contribution statement

Xiaorui Liu: Writing – original draft, Data curation. **Tiejia Jiang:** Validation, Data curation. **Lu Xu:** Investigation. **Weiran Zhang:** Data curation. **Feng Gao:** Writing – review & editing, Supervision, Resources, Project administration.

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Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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