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Increasing serum HMGB1 as a potential biomarker of treatment-resistant epilepsy in children: A case series and literature review

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ABSTRACT: Epilepsy still causes the most burden compared to any other neurological diseases in children. Recent studies point to a connection between inflammation and epilepsy, particularly in epileptogenic epilepsy development, and the long-term effects of seizures. This pilot study describes the increasing serum High Mobility Group Box 1 (HMGB1) in two children with treatment-resistant epilepsy and how this marker could be considered a promising biomarker for treatment-resistant epilepsy in children. **Case 1**: A four-year-eight-month-old boy was presented with treatment-resistant epilepsy, communicating hydrocephalus on the ventriculoperitoneal shunt, cerebral palsy and global developmental delay. The seizure form was involuntary jerky head twisting and body shivering three times a day. Despite three antiepileptic medications (valproic acid, phenobarbital, and levetiracetam) given in maximal dose, the seizures were not well-controlled, three up to four times per week. The serum HMGB1 level was 5.93 ng/ml. **Case 2**: A four-year-three-month-old boy was presented with treatment-resistant epilepsy, cerebral palsy, global developmental delay, and sensorineural hearing loss. His first seizure started as status epilepticus. Symptoms progressed to generalized tonic seizures, with eyes bulging upward, occurring more than five times a day. The patient still suffers seizures daily for one minute despite the maximal dosage of valproic acid and levetiracetam therapy. The serum HMGB1 level was 5.342 ng/ml. Serum HMGB1 could be considered a potential biomarker for treatment-resistant epilepsy in children. Further diagnostic studies with adequate sample sizes are needed to support the proposed aetiology for developing targeted treatment options.

Keywords: HMGB1; Treatment-resistant epilepsy; Potential biomarker; Neuroinflammation

1.0 INTRODUCTION

Epilepsy still causes the most burden compared to any other neurological diseases in children. The more frequent and severe the epileptic seizures experienced will result in brain damage and permanent neurobehavioral and neuropsychiatric disorders (Yang et al., 2017). Epilepsy places a considerable burden not only on the affected individual but also on the family and society (Kan et al., 2019; Paudel et al., 2018). Despite the availability of more than 20 anti-seizure medications (ASM) nowadays, around one-third of epilepsies are treatment-resistant (Kan et al., 2019). The variability of seizures and epilepsies, the combination of comorbidities, and the broad spectrum of effectiveness, safety, and tolerance associated with ASM make managing these individuals challenging.

Recent studies point to a connection between inflammation and epilepsy, particularly in epileptogenic epilepsy development, and the long-term effects of seizures (Kan et al., 2019; Paudel et al., 2018). HMGB1 is an intriguing protein recognized as a danger signal or a damage-associated molecular pattern (DAMP), actively participating in sterile inflammation (Paudel et al., 2018). Within the central nervous system (CNS), HMGB1 will be passively released by necrotic cells and actively released by neurons and glia upon inflammasome activation (Ravizza & Vezzani, 2018). In the pathophysiology of seizures and epilepsy, neuroinflammatory processes were found to play a role, and HMGB1 has been reported to behave similarly to an inflammatory cytokine in response to epileptogenic insults (Kamaşak et al., 2020; Vieri et al., 2021). Monoclonal antibodies to HMGB1 emerged as new treatment targets for epileptogenesis, but much remains to be explored before testing in patients (Fu et al., 2017).

This paper reported two cases of drug-resistant epilepsy with increasing serum HMGB1 markers. We also describe how this marker can be a potential biomarker for epilepsy in children and contribute to epileptogenesis.

2.0 METHODOLOGY

The whole blood samples from the peripheral vein (2 mL) were taken from the treatment-resistant epilepsy patients that met the International League Against Epilepsy (ILAE) criteria based on the failure of adequate trials of two tolerated, appropriately selected and used anti-seizure medications to achieve sustained seizure freedom, with informed consent conducted before (Kwan et al., 2010). The samples were stored at room temperature for two hours or at 2-8^{o}C overnight. The whole blood was centrifugated at 1000 x g for 20 minutes to collect the supernatant and stored at -80^{o}C until use. HMGB1 concentrations were measured using a commercially available ELISA (enzyme-linked immunosorbent assay) kit according to the manufacturer's instructions (ABclonal Technology Co. Ltd). Detailed standards and quality control for ELISA methods are available in supplementary information. The reference value of serum HMGB1 levels in the normal pediatric population and treatment-responsive epilepsy is 0.239 – 0.721 ng/ml and 0.267 – 0.859 ng/ml respectively. The reference value (cut-off) of increasing serum HMGB1 concentration was <0.772 ng/ml, according to the research by Kamaşak et al. (2020).

2.1 Case 1

A four-year-and-eight-month-old boy was presented to the clinic with treatment-resistant epilepsy, communicating hydrocephalus with a ventriculoperitoneal (VP) shunt, cerebral palsy and global developmental delay. He suffered from seizures since he was one year old in the form of involuntary jerky head twisting and body shivering, which occured three times a day during activities with a varied duration between 1 – 5 minutes. Despite three kinds of antiepileptic medications (valproic acid, phenobarbital, and levetiracetam) given in maximal dose, the seizures were not well controlled, up to 3 – 4 times per week.

He was the first child of non-related healthy parents. The patient was born prematurely at 34 weeks gestation to a mother with partial hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores (a standardized assessment for infants after delivery) were 4 and 6 at the 1st and 5th minutes, respectively, and birth weight was 1558 grams. He was hospitalized in the neonatal intensive care unit (NICU) ward for up to four months with a history of early-onset sepsis, hyaline membrane disease, anaemia of prematurity, neonatal jaundice, necrotizing enterocolitis grade II, and obstructive hydrocephalus. The VP shunt surgery was conducted when he was three years and six months old. On anthropometric measurement, his nutritional status was moderate acute malnutrition and microcephaly based on the World Health Organization (WHO) child growth standards. On physical examination, leucoplakia was observed in the left eye and brachiocephalic head. On neurological examination, the extremities were spastic, especially on the right side, with increased tone, limited movement, and Chaddock pathological reflex was positive.

The electroencephalogram (EEG) at four years old showed diffuse epileptogenicity with a hypsarrhythmia pattern suggesting West Syndrome. The head Computed Tomography (CT) that was conducted before VP shunt surgery showed obstructive hydrocephalus with possible obstruction at the level of the foramen of Luschka and Magendie with encephalomalacia of both hemispheres, especially the left temporo-occipital (**Figure 1**).

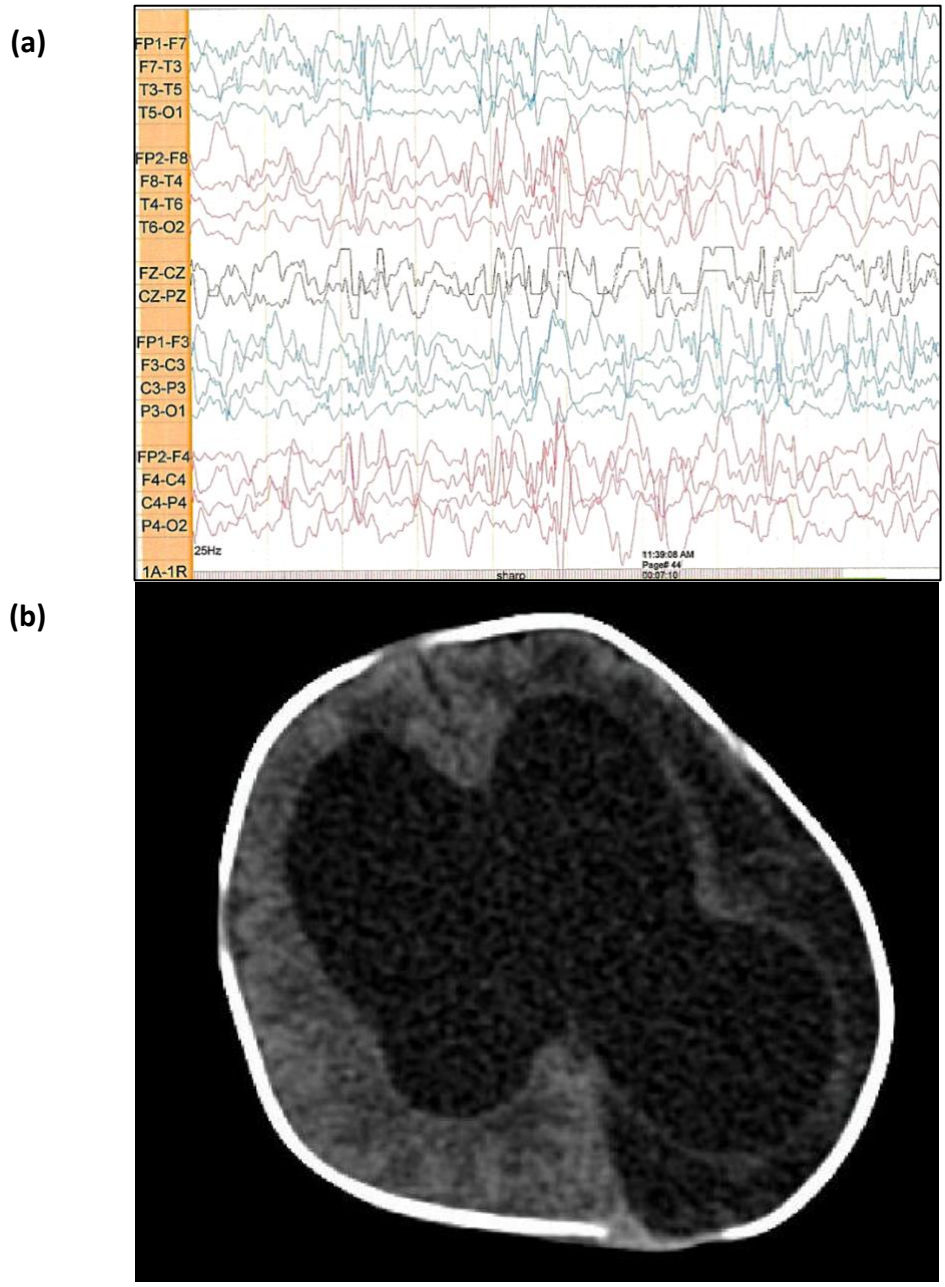

Figure 1: (a) The electroencephalogram (EEG) showed diffuse epileptogenicity with hypsarrhythmia; **(b)** brain CT scan showed ventriculomegaly, and encephalomalacia of both hemispheres, especially in the left parietooccipital.

2.2 Case 2

A four-year-three-month-old boy was presented to the clinic with treatment-resistant epilepsy, cerebral palsy, global developmental delay, and sensorineural hearing loss. At two months old, the patient experienced his first seizure in the form of an epileptic spasm, which occurred more than five times a day. The symptoms progressed to generalized tonic seizures, with eyes bulging upward. The patient still suffers seizures daily for one minute despite the maximal dosage of valproic acid and levetiracetam therapy.

The patient was the second child of non-related healthy parents, and he has an older brother with normal development. The patient was born at 39 weeks of gestation spontaneously without any complication, with a birth weight of 2800 grams, length of 48 cm, and head circumference of 32 cm. There was no history of hospitalization in the neonatal period. At the time of the presentation, he was still unable to sit and could not grab toys. The patient could roll around from a supine to a prone position. He was able to coo but was unable to bubble.

On anthropometric measurement, his nutritional status was moderate acute malnutrition and microcephaly based on WHO child growth standards. There was hypotrophy of the extremities on general examination. There was also increased tone, limited movement, and increased physiological reflexes upon neurological examination. The extremities were spastic bilaterally. EEG result at three years and ten months old showed diffuse epileptogenicity, which supported the clinical seizure. **Figure 2** shows the head CT scan with cerebral atrophy, microcephaly, and a left arachnoid cyst on the middle cranial fossa.

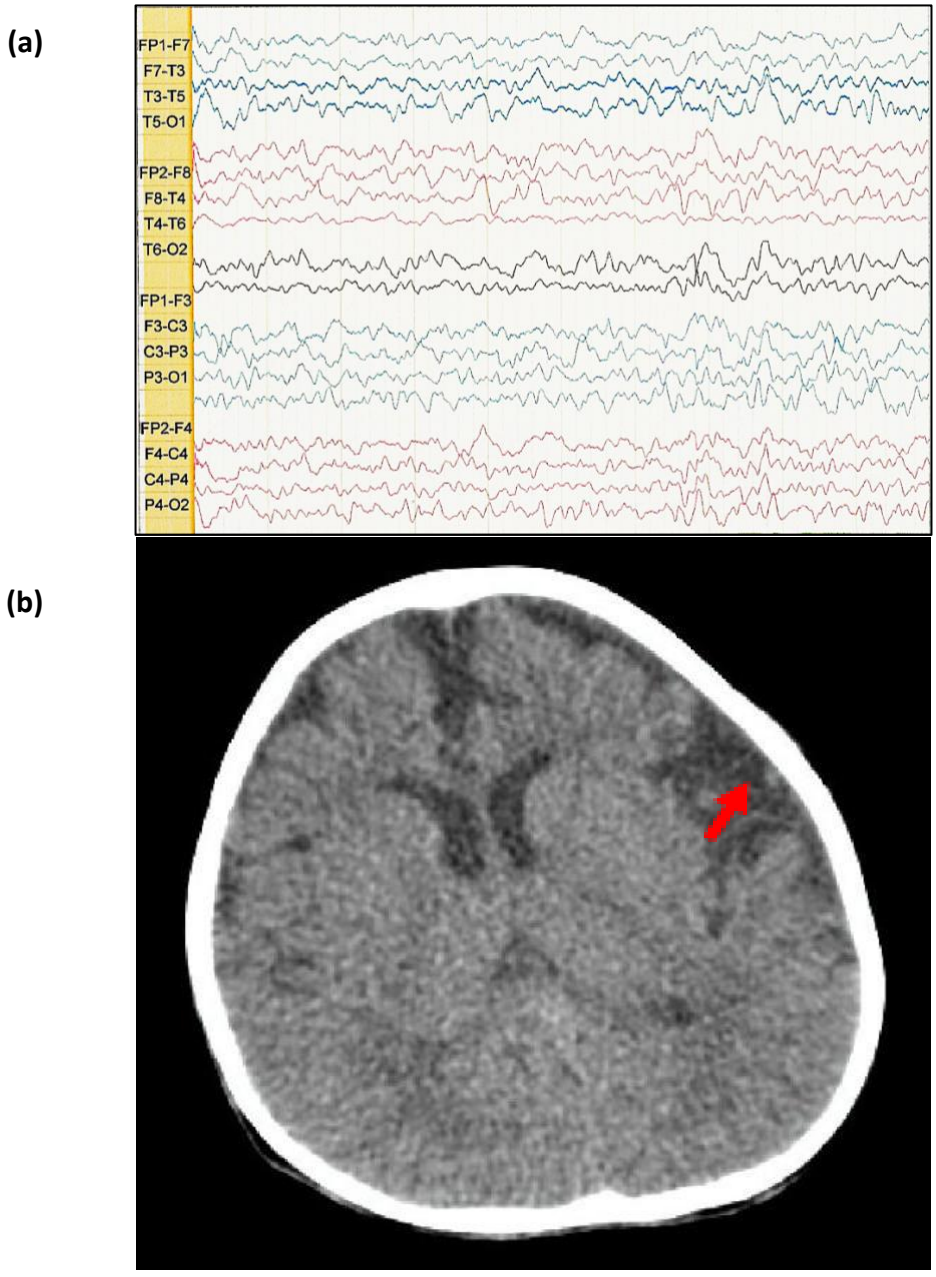

Figure 2: (a) EEG showed abnormal with diffuse slowing; **(b)** brain CT scan showed cerebral atrophy, microcephaly and left arachnoid cyst on the middle cranial fossa (red arrow).

4.0 DISCUSSION

The two patients reported here have received ASM in maximal dose, but the seizures were not well-controlled. Regarding medication, clinical studies demonstrate that patients who do not react to two ASM have a small probability of controlling their seizures with any more ASM that are delivered (Siddiqui et al., 2003). The first response to medication, the underlying aetiology, and a patient's history of seizure frequency are some characteristics that outcome studies in epilepsy have consistently shown to predict treatment-resistant epilepsy (Mohanraj & Brodie, 2013). Even though these factors help predict refractoriness in epilepsy, none of these factors explains the underlying mechanism of pharmacoresistant (Siddiqui et al., 2003). Some hypotheses about ASM resistance were postulated but did not thoroughly explain the neurobiological basis of this phenomenon (Tang et al., 2017). Consequently, a thorough understanding of the molecular processes behind seizures is required, as it is the development of treatments that employ particular strategies (Di Maio, 2014).

Recent studies point to a connection between inflammation and epilepsy, particularly in epileptogenic epilepsy development, and the long-term effects of seizures. Neuroinflammation contributes to the pathogenesis of drug-resistant epilepsy (Ravizza & Vezzani, 2018). HMGB1 is one of the significant DAMPs for mechanisms in developing seizures and neuroinflammation (Kamaşak et al., 2020).

The two patients with treatment-resistant epilepsy presented in this case report showed increased expression of HMGB1 serum levels. Studies on serum HMGB1 levels in pediatric patients with epilepsy are still very limited. Kamaşak et al. (2020) showed a possible correlation between HMGB1 levels and the severity of epilepsy in children. This study demonstrates that the serum level of HMGB1 is higher in cases of drug-refractory epilepsy. Another study by Zhu et al. (2018) showed that serum concentrations of HMGB1 were significantly higher in the epilepsy group within 24 hours of a seizure episode than in the control group. HMGB1 was a significant predictor of epilepsy prognosis (Zhu et al., 2018). Furthermore, a case-control study in adult patients discovered a correlation between serum HMGB1 and the risk of epilepsy. According to the study, increasing HMGB1 and TLR4 serum levels were correlated with increased risk and severity of epilepsy, and their level was higher in patients resistant to ASM (Kan et al., 2019). A summary of clinical studies on HMGB1- related epilepsy was presented in **Table 1**.

HMGB1 is released into the extracellular space through active and passive mechanisms. HMGB1 can be secreted passively by necrotic or injured cells. Several stimuli that cause cell damage, including physical factors such as ischemia, hypoxia, nonpenetrating trauma, toxaemia, and sterile tissue damage, provoke the passive release of HMGB1. Epileptogenic brain injury and seizures induce HMGB1 translocation from the nucleus to the cytoplasm in neurons and glial cells in brain regions, such as the hippocampus, amygdala, and neocortex, involved in seizure formation and propagation. Extranuclear HMGB1 is released passively by dying cells or actively released by neurons and glia upon inflammasome activation.

HMGB1 disulfide activates TLR4, mediating glia's pro-inflammatory activity and increasing neuronal excitability. HMGB1 can bind to various receptors, including the receptor for advanced glycation end products (RAGE), toll-like receptor 4 (TLR4), and TLR2, to activate intracellular nuclear factor kappa B (NF-kB), interleukin-1 beta (IL-1β), and other pro-inflammatory cytokines (Walker & Sills, 2012; Yang et al., 2017; Zhu et al., 2018). HMGB1 has been suggested to exert a proepileptic effect via the TLR4/NF-kβ signalling (Ravizza & Vezzani, 2018). HMGB1, when released from glia and nerve cells in the central nervous system, activates its primary receptors (TLR4 and RAGE). Activating the HMGB1-TLR4 signalling axis leads to phosphorylation of the NF-kβ subunit and potentiation of NMDA-mediated Ca^{2+} influx into neurons. The NMDA receptor activation could potentiate unstable neuronal activity, leading to neuronal hyperexcitation. Several studies in experimental animal models and brain specimens have shown that HMGB1 contributes to the occurrence and persistence of seizures (Huang et al., 2015). The increasing of HMGB1 concentration after seizure onset leads to susceptibility to recurrent seizures, especially for the treatment-resistant epilepsy patient (Dai et al., 2021). Animal studies related to HMGB1 and epilepsy were summarized in **Table 2**.

HMGB1 has been indicated as a potential therapeutic agent in epilepsy and a noninvasive biomarker that can identify patients at high risk of epilepsy (Shi et al., 2018). Several strategies for HMGB1 inhibition have been explored, such as HMGB1 antagonists that are capable of interacting with the RAGE receptor, HMGB1 small molecule inhibitors, anti-HMGB1 antibodies (Abs), HMGB1 protein and peptide inhibitors, and HMGB1 oligonucleotide-based inhibitor (Musumeci et al., 2014). Therapeutic strategies targeting HMGB1 with specific antagonists have the potential to minimize epileptic

seizures characterized by excessive HMGB1 release. An experiment used an injection of anti-HMGB1 monoclonal Abs in epileptic mice, and the result decreased epileptic seizures effectively, decreasing the duration, frequency, and severity of the seizures (Dai et al., 2021; Zhao et al., 2017).

Table 1: Summary of clinical studies about HMGB1 related to epilepsy

Study design & participants	Participants characteristic	HMGB1 levels	Relationship between HMGB1 levels and seizure characteristics	Relationship between HMGB1 levels and outcome
A case-control study in China; 105 epilepsy patients and 100 healthy controls (HCs) (Kan et al., 2019)	• The mean age of epilepsy patients vs HCs = 29.65±10.82 vs 29.83±10.51 • Seizure characteristics: 51.4% of epilepsy patients had >5 min average seizure; 27.6% had >3 times seizures per month; 41% had intractable seizures	Expressions of HMGB1 in epilepsy patients vs HCs = 6.3, 4.4–7.8 ng/mL vs 1.9, 2.4–3.3 ng/mL; **(*p*<0.001)**	HMGB1 levels were higher in: • Patients with seizure duration >5 minutes average than those ≤5 minutes **(*p*=0.001)** • Patients with seizure frequency >3 times per month than those ≤3 times per month **(*p*=0.001)** No significant statistical analysis on disease course and type of seizure	HMGB1 expression in patients with intractable epilepsy was significantly higher than that in patients with drug-responsive epilepsy **(*p*=0.002)**
A case-control study in China; 180 new-onset epilepsy children and 40 HCs aged 1 month to 13 years old (Zhu et al., 2018)	• Epilepsy patients divided into generalized tonic-clonic (GTC) (37%), focal seizures (n = 51%), and epileptic spasms (ES) (n=12%) • Mean age of epilepsy patients vs HCs = 30.50 ± 34.55 months vs GTC 33.52± 33.04; focal 23.59± 25.40; ES 9.95 ± 8.35 months	Expressions of HMGB1 were higher in patients with all types of epilepsy (>15 ng/mL) than in HCs (7.5 ng/mL); **(*p*<0.05)**	HMGB levels were higher in the epileptic spasm group than in other epilepsy groups **(*p*<0.05)**	HMGB1 was a significant predictor of epilepsy prognosis **(*p*<0.001)**
A case-control study in Turkey; 57 children aged 4-17 years were divided into 3 groups (Kamaşak et al., 2020)	• There were 3 groups of participants: 28 children with severe epilepsy, 29 with mild epilepsy, 27 HCs • Mean age of severe epilepsy vs mild epilepsy vs HCs=10.11 ± 4.16 vs 11.48 ± 3.23 vs 11.07 ± 3.47	Expression of HMGB1 in severe epilepsy vs mild epilepsy vs HCs= 1.05± 0.37 vs 0.85± 0.26 vs 0.7 ± 0.2 ng/mL	HMGB1 levels were higher in: • Patients with severe epilepsy than mild epilepsy and HCs **(*p*=0.001)** • Patients with severe epilepsy than HCs **(*p*=0.0001)** • Patients with severe epilepsy than mild epilepsy **(p=0.029)** • Patients with mild epilepsy than HCs **(*p*=0.027)**	HMGB1 expression in patients with drug-refractory epilepsy **(*p*=0.001)**

Table 2: Summary of animal studies about HMGB1 related to epilepsy

Study designs, participants, and methods	Relationship between HMGB1 levels and seizure characteristics in animals	The role of anti-HMGB1 mAb in seizure
Experimental study: Mice weighing 18 to 23 grams (Fu et al., 2017)	• During an acute status epilepticus, HMGB1 promoted blood-brain barrier (BBB) breakdown **($p<0.05$)** • The amount of HMGB1 in the cerebrum reduced due to translocation under an acute epileptic state **($p<0.05$)**	• The anti-HMGB1 mAb reduced the BBB breakdown, decreased the translocation of HMGB1, and decreased the HMGB1 level in plasma **($p<0.05$)**
Experimental study: The C57BL/6 mice and C57BL/10ScNJ mice, 2–4 months old (Zhao et al., 2017)		• In the rapid hippocampal kindling model, the anti-HMGB1 decreased the severity of seizure **($p<0.01$)** • Anti-HMGB1 mAb decreased MES- and PTZ-induced seizures, as well as the translocation of endogenous HMGB1 **($p<0.01$)** • Anti-HMGB1 mAb alleviates the severity of kindling-induced seizures and kainic acid (KA)-induced chronic epilepsy **($p<0.05$)**

5.0 CONCLUSIONS

The discovery of correlations between inflammation, the immune system, and epilepsy raises significant new hope in the search for new epilepsy treatments and as a first step to establishing the precise role of inflammatory or immune markers in epilepsy. Identifying the molecular basis of epilepsy can provide additional information regarding the pathophysiology, prognosis, treatment options, personalized medicine precision, and opportunities for future targeted therapies. This molecular identification is essential for specific interventions whose ultimate goal is to improve prognosis and reduce the burden on families. Serum HMGB1 might be a potential biomarker for treatment-resistant epilepsy in children. Further diagnostic studies with adequate sample size are needed to support this aetiology for developing targeted treatment options.

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Author contributions:
APN, ESH, AT wrote, designed the study, and edited the manuscript. KI supervised and reviewed the manuscript. APN, VWW wrote the manuscript and collected and analyzed the clinical data. All the authors read and approved the final manuscript.

Conflicts of interest:
The authors declare no conflict of interest.

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