

Case Report

Successful treatment of drug-resistant status epilepticus in an adult patient with Mowat-Wilson syndrome: A case report



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ABSTRACT

Mowat-Wilson syndrome (MWS) is a rare genetic disorder characterized by intellectual disability, distinctive facial features, epilepsy, and multiple anomalies caused by heterozygous loss-of-function mutations in the zinc finger E-box-binding homeobox-2 gene (*ZEB2*). Treatment choice is very important as patients with MWS because patients sometimes develop drug-resistant epilepsy. Here, we report the case of a 45-year-old male patient with MWS who developed drug-resistant status epilepticus after a 26-years seizure-free period while taking multiple anti-seizure medications. He showed a characteristic magnetic resonance imaging finding with a focal lesion in his left thalamic pulvinar nucleus, a finding not previously reported in status epilepticus with MWS. We succeeded in controlling seizures in the patient after trying multiple new antiseizure drug combinations. These findings indicate that patients with MWS may develop drug-resistant status epilepticus with age, even after a long-term seizure-free period, which can be managed with anti-seizure medication. Therefore, careful monitoring of seizures is important for the treatment of people with MWS, even in patients who have not experienced seizures for a long time.

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1. Introduction

Mowat-Wilson syndrome (MWS) is a congenital anomaly characterized by distinct facial features including a broad nasal bridge, triangular jaw, large uplifted earlobes, moderate-to-severe intellectual deficiency, epilepsy, and variable congenital malformations [1]. It is caused by heterozygous chromosomal deletions at 2q22 or intragenic loss-of-function mutations in the Zinc finger E-box-binding homeobox-2 gene (*ZEB2*) [2]. Nearly a quarter of affected patients with epilepsy are drug-resistant to anti-seizure drugs [3]. Here, we describe an adult male patient with MWS presenting with drug-resistant status epilepticus in a specific left thalamic pulvinar nucleus region after a long-term seizure-free period. His seizures were successfully controlled with new combinations of anti-seizure drugs.

2. Case report

A forty-five-year-old man was referred to our hospital for treatment of his focal bilateral tonic-clonic seizures, which began with motor signs in his left hand. The patient was reported previously as patient 4 in a study in 2001 [2] but described and detailed in this report as the first child of non-consanguineous parents from a family with no history of neurological or developmental disorders, nor congenital malformations. The patient had facial dysmorphisms, microcephaly, megacolon, and right cryptorchidism without congenital heart disease. He also had severe intellectual disability, could not walk independently, and required assistance with dressing, eating, and other everyday activities. Further, he could not communicate verbally due to absence of speech. At eleven months of age, he developed recurrent left-sided hemiconvulsive focal motor seizures. Throughout his childhood, he required administration, adjustment, and combination of antiseizure drugs. Daily treatment with phenobarbital began at 26 months of age, and valproic acid and acetazolamide were incorporated when he was 6 years old. Clonazepam was initiated at 8 years of age and etho-

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suximide was initiated at 17 years of age. Multiple antiseizure medication kept the patient seizure-free since he was 19 years old. At 28 years old, a *ZEB2* mutation (c. 2083C>T, p. R695X) was detected [2]. His antiseizure drug regimen included phenobarbital, valproic acid, acetazolamide, clonazepam, and ethosuximide, and his epilepsy had been under control for 26 years. He presented at our hospital with focal to bilateral tonic-clonic seizures that were ongoing for less than 1 h. His seizures initially subsided with intravenous administration of fosphenytoin. On admission, his body temperature was 38.9 °C, while laboratory investigations, including a complete blood count, serum biochemistry, liver and renal function data, and cerebrospinal fluid (CSF) examination showed no abnormalities; the chest computed tomography scan did not detect any pneumonia. Therefore, it was considered that fever due to a viral infection might have triggered the focal to bilateral tonic-clonic seizure. We initially tried to perform electroencephalography (EEG) as soon as possible, but he was unable to cooperate for the procedure. We were eventually able to obtain two EEGs, one on day 14 and another 7 weeks after the first hospitalization (Fig. 1A-1, 1A-2). Brain magnetic resonance imaging (MRI) revealed a focal lesion on the left thalamic pulvinar nucleus, which appeared hyperintense on diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences, but slightly hypointense on apparent diffusion coefficient (ADC) mapping (Fig. 1B-D). Single-photon emission computed tomography showed hyperperfusion of the left temporal and occipital areas.

The clinical course is summarized in Fig. 2. The patient experienced frequent seizures upon admission. Intravenous administration of fosphenytoin temporarily temporarily controlled the drug-resistant status epilepticus, which subsided on the 14th day of hospitalization. However, the patient experienced recurrent and brief focal seizures. Conventional oral antiseizure medication, including phenobarbital and clonazepam, were ineffective and thus discontinued; thereafter, levetiracetam was introduced. Levetiracetam reduced the seizure frequency and intensity, and lacosamide and perampanel were also added to the regimen. While three antiseizure drugs were effective to provide seizure control, the patient had to discontinue polytherapy because he developed liver dysfunction. He had been taking valproic acid since childhood and had no history of liver dysfunction until admission. Therefore, we considered valproic acid to be safer than the other antiseizure medication and administered it and levetiracetam after improvement of liver dysfunction. However, brief seizures (lasting for a few minutes) were observed twice a week. We initiated carbamazepine to treat the partial seizures and they gradually diminished. Then, the patient was discharged twenty weeks after admission and was advised to continue valproic acid, levetiracetam, and carbamazepine. Three days after discharge, the patient was readmitted because of seizure recurrence. Although we increased the carbamazepine dosage in response, his seizures persisted. Next, carbamazepine was replaced with zonisamide and his seizures were well-controlled. He was discharged with a regimen of levetiracetam (3000 mg/day), valproic acid (1200 mg/day), and zonisamide (200 mg/day). One month after the second hospital discharge, he was once again re-admitted for seizures. Although we considered a surgical treatment to control the seizures, we decided to continue the antiseizure drug regimen because of operative risk. Finally, we increased the zonisamide dosage (400 mg/day) and he became seizure-free again. A follow-up MRI performed three weeks after the first admission showed disappearance of abnormal pulvinar signals on DWI and ADC maps and lesion attenuation on FLAIR-MRI imaging (Fig. 1E-G). In the subsequent 9 months of follow-up, the patient did not experience seizures, and no abnormal signals on DWI, ADC maps, or FLAIR were observed (Fig. 1H-J).

3. Discussion

MWS is caused by heterozygous loss-of-function mutations in *ZEB2* which plays an important role in the formation of the hippocampus, neocortex, and corpus callosum during brain development [4]. Corpus callosal anomalies, hippocampal abnormalities, enlargement of the cerebral ventricles, and reduction of white matter thickness have been found on MRIs of patients with MWS, whereas 3.7–44.6% of the patients have normal MRI findings [5]. In our case, these anomalies were not detected on MRI imaging. However, the patient had the characteristic MRI finding of a hyperintense lesion in the left thalamic pulvinar nucleus on both DWI and FLAIR sequences that appeared improved on the follow-up MRI. In patients with status epilepticus, such abnormalities in both DWI and FLAIR have been reported [6]. This is the first case of MWS with similar MRI findings. ADC mapping results are necessary for evaluating the etiology of the abnormalities on DWI. On ADC maps, cytotoxic and vasogenic edema is indicated by hypointense and hyperintense lesions, respectively. Status epilepticus may be characterized by both forms of edema [7]. In our patient, brain MRI revealed hypointense lesions on ADC mapping, suggesting cytotoxic edema in the left thalamic pulvinar nucleus.

Network-level ictal activity involving the thalamus and ipsilateral pulvinar has been found to be associated with status epilepticus-related MRI abnormalities [8]. Signal changes on FLAIR-MRI sequences were observed in corresponding localized regions and presented as hyperintense lesions on DWI [9]. Reportedly, abnormal findings involving the pulvinar nucleus in patients with focal or generalized seizures are suggested to reflect the epileptogenic hyperexcitation of different cortical areas through their connections with the pulvinar [6,10]. In a previous study, all 11 patients showed reversible changes of their pulvinar abnormalities on follow-up MRI, and most patients responded well to antiseizure medication [6]. However, the present patient continued to manifest drug-resistant focal epilepsy even after the pulvinar MRI abnormality improved. Therefore, in the present patient, we speculate that both pulvinar dysfunction and association brain abnormalities due to *ZEB2* haploinsufficiency may be associated with drug-resistant epilepsy. To the best of our knowledge, this is the first reported case of a middle-aged adult with MWS with drug-resistant epilepsy and status epilepticus with a concomitant thalamic lesion involving the ipsilateral pulvinar.

Epilepsy is one of the most common clinical features of MWS, and patients usually develop seizures from one month to eleven years of age [3,5]. Further, 25.9% of patients with MWS with epilepsy ($n = 15/58$, ranging in age from 6 months to 36 years) are resistant to antiseizure medications [3,11], and previous prospective studies have demonstrated that for >35% of patients, their epilepsy was uncontrolled [12,13]. Based on these findings, the ratio of drug resistance in patients with MWS is lower than expected; therefore, it is important to include adult patients in the analysis of drug resistant epilepsy rates in patients with MWS.

In this case, the patient's seizures started at eleven months of age and were managed with multiple anti-seizure medications (phenobarbital, valproic acid, acetazolamide, clonazepam, and ethosuximide). Although the patient remained seizure-free for twenty-six years, he suddenly experienced drug-resistant status epilepticus with high fever. Valproic acid has been reported to be the most effective drug for both focal and atypical absence seizures in patients with MWS [11]. However, there is no established treatment approach for such patients when valproic acid fails to control seizures. We attempted treatment with novel anticonvulsants such as levetiracetam, lacosamide, and perampanel, but these had limited effectiveness, and lacosamide and perampanel were discontinued because of side effect (liver dysfunction). While

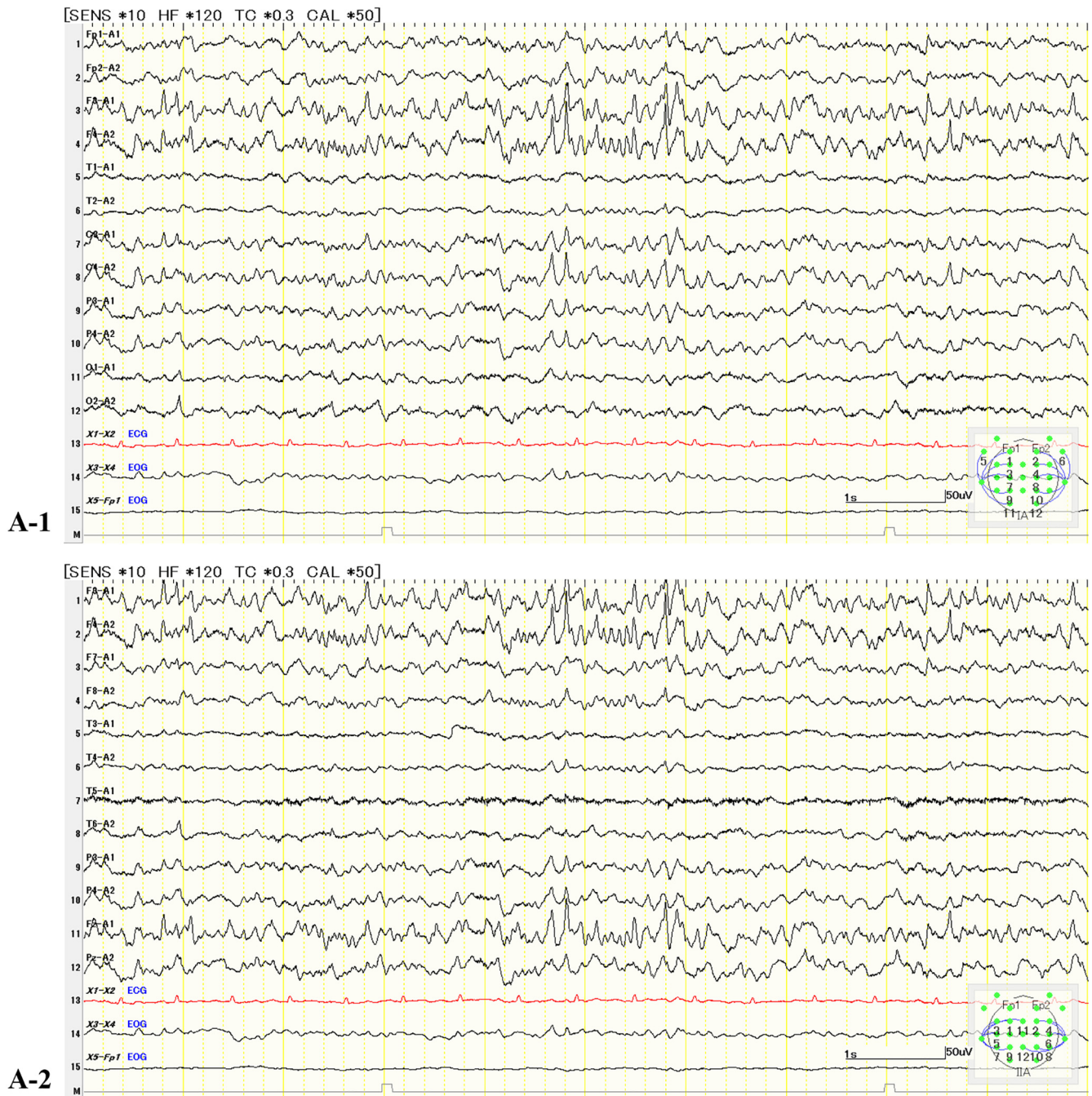


Fig. 1. (A-1, A-2) Electroencephalography (EEG) on the 14th day of hospitalization showing fast spike activity with random spikes from the bilateral frontal areas, and (B-J) changes in brain magnetic resonance imaging (MRI) over time. (B) A high-intensity focal lesion is observed in the left pulvinar nucleus of the thalamus on diffusion-weighted imaging (DWI). (C) The lesion shows slight hypointensity on apparent diffusion coefficient (ADC) maps, and hyperintensity on fluid-attenuated inversion recovery (FLAIR) sequences (D) on the 14th day of hospitalization. Follow-up MRI on the 38th day of hospitalization shows attenuation of abnormal findings on DWI (E), ADC maps (F), and the FLAIR sequence (G). Brain MRI nine months after the first admission shows disappearance of the lesion on DWI (H), ADC maps (I), and on FLAIR sequences (J).

carbamazepine is not recommended for patients with generalized spikes and wave discharges on EEG [14], it could be administered effectively in combination with other antiepileptic drugs, as reported previously [15]. Moreover, a previous study suggested that using carbamazepine, levetiracetam, or valproic acid would lead to good outcomes in patients with status epilepticus [16]. Our patient received carbamazepine for the first time, and since the medication did not cause exacerbation of epilepsy, he was then given carbamazepine in combination with other antiepileptic

drugs (levetiracetam, valproic acid). In this case, unfortunately, brief seizures persisted even though the carbamazepine blood concentration was within therapeutic limits. As zonisamide has been reported to reduce the frequency of seizures in combination with other anti-seizure drugs [17], carbamazepine was replaced by zonisamide.

In Zeb2-deficient mice, cells that ordinarily would become cortical interneurons appear to transform into a subtype of GABAergic striatal interneurons. These results show that Zeb2 is required for

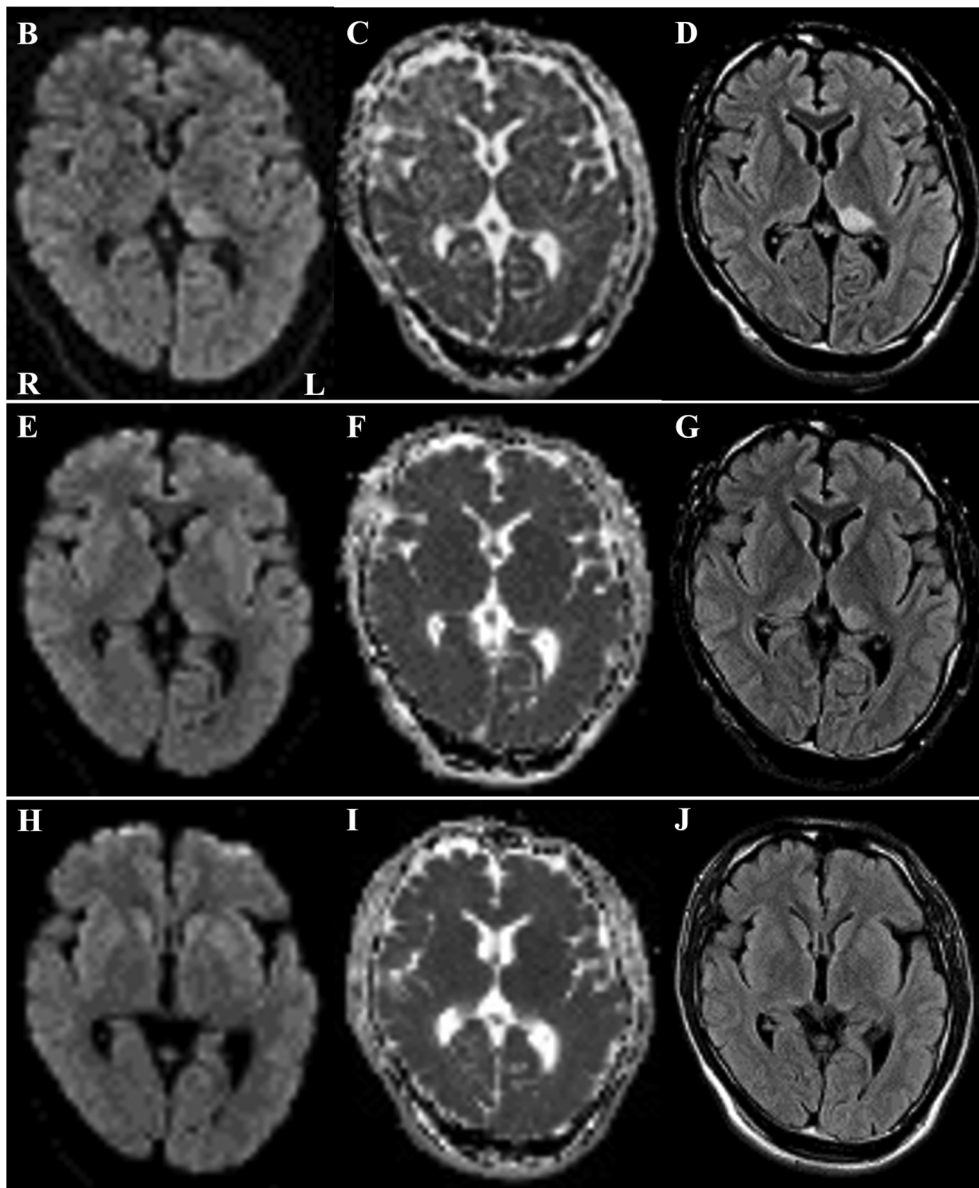


Fig. 1 (continued)

cortical interneuron differentiation and suggest a mechanism for the epilepsy observed in MWS [18]. The age-related electroclinical pattern observed in MWS is also believed to be caused by a genetic form of epilepsy, rather than by anatomical malformations affecting the brain [19]. Furthermore, age-related changes in GABA have been reported, as the GABA concentration decreases in the frontal lobe after 40 years of age [20]. In this case, although his MRI findings did not show obvious anatomical malformations, after a long seizure-free period he suddenly developed drug-resistant status epilepticus. These findings suggest that defective cortical interneurons caused by *ZEB2* mutations led to seizures at 11 months of age which could be controlled by multiple anti-seizure drugs. We speculate the recurrence of his seizures 26 years later was likely due to evolution of epileptogenesis involving GABA neurotransmission, which may have been triggered by high fever. Therefore, adult patients with MWS may persistently be at high risk for drug-resistant status epilepticus, and these patients require careful monitoring. Considering that GABAergic interneurons are affected by *ZEB2* mutations, antiseizure medications such as valproic acid

and zonisamide that target GABAergic pathways could be effective. However, treatment of patients with seizures and MWS remains a challenge.

4. Conclusion

Here, we report the case of a 45-year-old male patient with MWS and physical multiple physical and intellectual disabilities associated with drug-resistant epilepsy and status epilepticus. He manifested drug-resistant seizures after a 26-years seizure-free period while taking multiple antiseizure medications. An associated thalamic lesion identified on the brain MRI regressed, though he continued to experience drug-resistant seizures. Eventual seizure control was attained using a combination of new antiseizure medications. These findings indicate that careful monitoring of focal seizures is important in patients with MWS and epilepsy despite periods of prolonged seizure freedom.

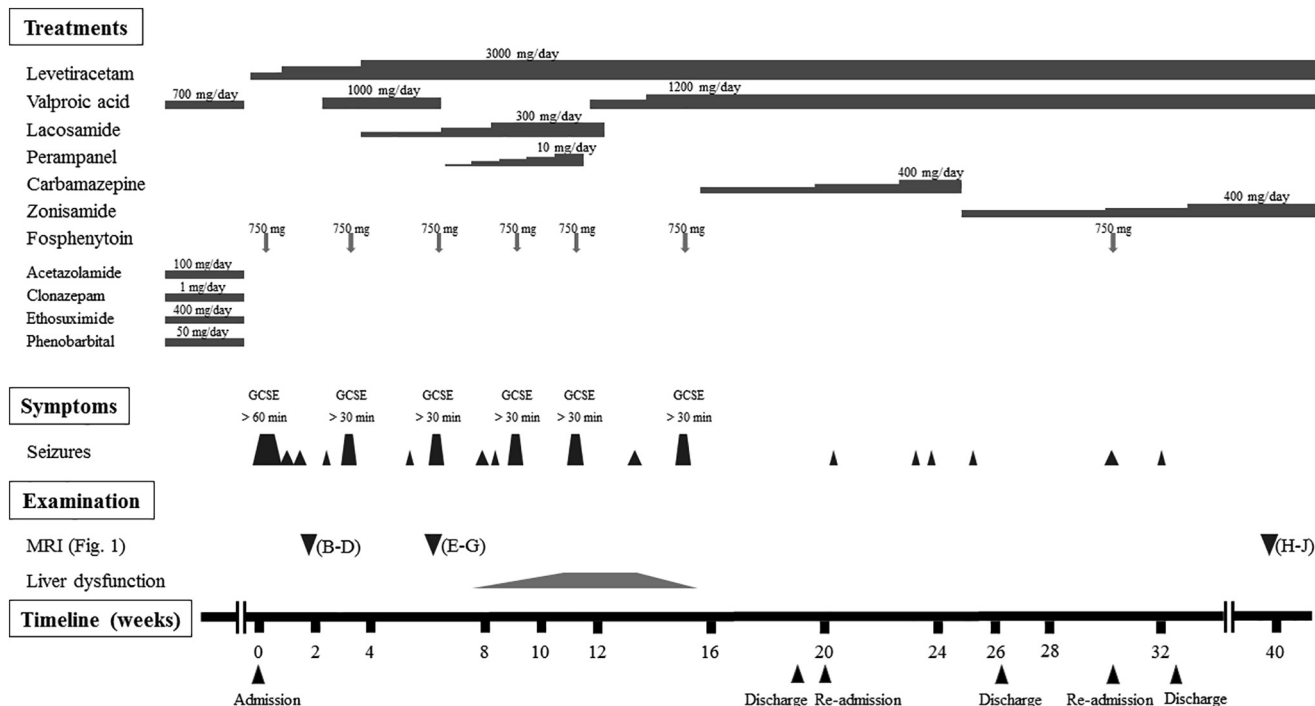


Fig. 2. Summary of the clinical course from first admission to final hospital discharge. Various combinations of multiple therapeutic antiseizure drugs were administered during the clinical course. The recurrent epilepsy was finally controlled with levetiracetam, valproic acid, and zonisamide. GCSE: generalized convulsive status epilepticus.

5. Declarations of interest

None.

Ethical statement

The author ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association for experiments involving humans.

The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations as per shoes recommendations.

The authors include a statement in the manuscript that informed consent was obtained for experimentation with human subjects.

Hereby, I consciously assure that for the manuscript the following is fulfilled:

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