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Case Study

Focal Epilepsy in Pregnancy with Underlying Antiepileptic Drug Allergy: A Case Report

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ABSTRACT

Background: The first-line antiepileptic drugs (AED) approved for focal epilepsy are levetiracetam, carbamazepine, phenytoin, and zonisamide. Uncontrolled seizures can be caused by non-adherence, inadequate treatment, drug tolerance, or adverse drug reactions. In a resource-limited setting, a patient can run out of treatment options if having an AED allergy and is pregnant. **Case presentation:** A 24-year-old woman with temporal lobe epilepsy was admitted to the hospital due to a breakthrough seizure. Because of her allergy to carbamazepine, with contraindication of sodium valproate in pregnancy and women of childbearing age, clobazam was added to levetiracetam as her treatment regime for focal epilepsy. The patient has reduced seizure frequency since the commencement of clobazam treatment. **Conclusion:** Clobazam is feasible as an add-on treatment option for focal epilepsy in childbearing-age women with AED allergies. Future studies are needed to establish the safety and dosing adjustment of clobazam in pregnant women.

BACKGROUND

The prevalence of epilepsy in Southeast Asia is between 3.8 to 7.7 per 1000 population, with Singapore being the lowest and Laos being the highest [1]. Unfortunately, the epidemiology data of epilepsy patients in Malaysia is still unavailable. Focal epilepsy, as described by the International League Against Epilepsy (ILAE), is unifocal, multifocal disorder or seizures involving one hemisphere. This type of epilepsy represents most cases of epilepsy in adults and children. A structural brain abnormality, especially hippocampal sclerosis, also known as mesial temporal sclerosis, is the most common pathological finding in patients with focal epilepsy [2].

The approved antiepileptic drugs (AED) for focal epilepsy with Level A evidence are levetiracetam, controlled-release carbamazepine, phenytoin, and zonisamide [3]. The causes of uncontrolled seizures can be non-adherence, inadequate AED doses, adverse drug reactions or drug-drug interactions. The 6-month seizure-free rate with pharmacological treatment is 73 to 84% [3]. However, the remission rate of refractory epilepsy, as shown by a retrospective cohort study, was only 14% [4]. Beside adherence, hypersensitivity reaction to AED, especially severe cutaneous adverse drug reactions (SCARs), is a major concern in epilepsy treatment. Aromatic AED, for example, carbamazepine, lamotrigine and phenytoin, showed the highest risk of causing SCARs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrosis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) [5].

In Malaysia, HLA-B*1502 was significantly associated with carbamazepine-induced SJS/TEN, especially among the Malay ethnicity group (75%, $p < 0.01$) [6]. Unfortunately, the cost of HLA-B*1502 screening with conventional real-time PCR was estimated to be approximately MYR 300 (≈ USD 75) per patient [7]. Therefore, the genetic test is not readily available in the majority of Malaysian hospitals, especially in district hospitals. Other alternatives were preferred for patients who reported AED allergy. We report a case of a pregnant woman who presented with temporal lobe epilepsy, having multiple

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AED intolerance and allergies in a resource-limited district hospital.

Ethical Approval and Consent

Ethical approval was granted from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-22-00369-KUI). Informed consent and publication consent were obtained from the patient.

CASE PRESENTATION

A 24-year-old woman with underlying temporal lobe epilepsy presented to the emergency department of a district hospital following a fall. Her vital signs were stable, with SpO_2 97% under room air. She has had thirteen admissions for breakthrough seizures in the past three years since her diagnosis, with the last being three months ago. Her electroencephalogram (EEG) during the first diagnosis showed epileptiform discharges at the left anterior temporal region. Her MRI brain showed right mesial temporal sclerosis and encephalomalacia changes in the right posterior parietal lobe. She had received multiple AED regimens before this admission but to no avail due to intolerable adverse effects and allergic reactions. However, HLA-B*1502 was not detected in her genotyping test. The patient claimed to be compliant with levetiracetam 1g BD, using the mobile phone alarm as a reminder tool. Despite good adherence, the patient's seizure frequency was at least twice a week, with recorded videos as evidence. Therefore, clobazam 5mg BD was initiated. She was discharged three days later, with no new seizure episode reported.

About two months later, the patient had an unplanned pregnancy (week 9 of gestation). Even though multiple counselling was given previously, she discontinued contraception on her own and became pregnant. Clobazam was withheld due to its limited data on focal epilepsy in pregnancy. However, because her seizures were poorly controlled, clobazam was restarted at week 12 of gestation. Her detailed foetal scan at week 20 of gestation was normal. The patient's medication history since diagnosis was as presented in Table I. After two months of being fit-free, the patient was admitted

Table I. Summary of the patient's medication history and hospital admissions

Month/Year	Antiepileptic Drugs Regimen	No. of Admissions	Reasons for Regimen Change
Jul 2019	VPA 200mg BD	Newly diagnosed	Poor response (13 times seizures at home)
Sep 2019	LEV 500mg BD CBZ 200mg BD	Clinic appointment	
Nov 2019	LEV 750mg BD CBZ 200mg BD	Clinic appointment	
Dec 2019	LEV 1g BD	First admission	Itchiness over the whole body due to CBZ
Jan - Jun 2022	None	Defaulted	
Jul 2020	LEV 500mg BD	Second admission	Restarted AED
	LEV 1g BD	Third admission	
Dec 2020	LEV 1g BD LTG 50mg BD	Seventh admission	
May 2021	LEV 1.5g BD LTG 100mg BD	11th admission	
Jun 2021	LEV 1.5g BD	12th admission	Could not tolerate LTG (itchiness)
Nov 2021	LEV 1g BD CLB 5mg BD	14th admission	Could not tolerate 1.5g BD LEV (tremor), add CLB
Jan 2022	LEV 1g BD CLB 5mg BD	Clinic appointment	Positive urine pregnancy test
Mar 2022	LEV 1g BD ZNS 100mg ON	Clinic appointment	Limited data on CLB in focal epilepsy in pregnancy
Mar 2022	LEV 1g BD	15th admission	Could not tolerate ZNS (insomnia)
Mar 2022	LEV 1.25g BD CLB 5mg BD	16th admission	Tolerating current regimen although having slight dizziness on CLB
Jun 2022	LEV 1.5g BD CLB 10mg BD TPM 25mg BD	17th admission	Developed generalized seizure, add TPM
Aug 2022	LEV 1.5g BD CLB 15mg BD TPM 25mg BD	20th admission	Delivery

AED: antiepileptic drugs; CBZ: carbamazepine; CLB: clobazam; LEV: levetiracetam; LTG: lamotrigine; TPM: topiramate; VPA: sodium valproate; ZNS: zonisamide.
Note: Only admissions due to breakthrough seizures are counted and presented.

again with a generalized tonic-clonic seizure. Topiramate 25mg BD was added to her AED regimen. She had only one seizure episode per month until her delivery via a lower segment Caesarean section (LSCS) at 36 weeks of gestation due to preterm labour with a history of recent uncontrolled epilepsy. The newborn weighed 2.37kg at birth and with no major congenital malformation. The baby girl's 1-minute Apgar score was only 5, most probably due to the general anaesthesia used during the emergency LSCS operation. Nevertheless, her Apgar score at 5 minutes of life was normal at a score of 10.

DISCUSSION

Among the first-line AED for focal epilepsy, the patient can only tolerate levetiracetam. Phenytoin was not given due to the concern of inducing similar allergic reactions associated with carbamazepine. With levetiracetam monotherapy, the patient had more than ten hospital admissions in the past three years. Sodium valproate was not restarted because the patient is a childbearing-age woman and refused to use contraception. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) has issued advice on the contraindication of using sodium valproate in pregnancy and women of childbearing age. Otherwise, sodium valproate can be an effective adjunctive treatment in focal epilepsy [8]. For levetiracetam, exposure during pregnancy does not associate with an increased risk of delayed cognitive development [9]. Yet, a study reported reduced levetiracetam concentration during pregnancy because of increased clearance [10]. The established dose increment during pregnancy for levetiracetam was not available.

Clobazam was listed by the ILAE as a treatment option for children with partial seizures based on the results of a Canadian randomized controlled trial [3,11]. Clobazam, as an add-on therapy, recorded a 50% or more reduction in seizure frequency and approximately 15% seizure freedom. Nevertheless, limited data were available regarding the adverse effects and tolerance of clobazam in adults. The adverse effects reported in the literature were mood or behavioural changes, drowsiness and dizziness [12]. Similarly, data on the efficacy and safety of clobazam use in pregnancy was lacking. Pregnant women with epilepsy exposed to clobazam monotherapy were associated with an increased risk of major congenital malformation, but the results were not statistically significant. Besides, the clobazam dose and its use during the pregnancy trimester were also not reported [13]. Our patient had fewer breakthrough seizures after taking clobazam and tolerated it well. Therefore, clobazam appeared to be the only feasible option for this patient, although it is an off-label use. We used the recommended dose (15mg BD), as reported in the literature (10-40mg/day) [12].

HLA-B*1502 screening is proven to be cost-effective in many countries. However, in resource-limited settings, the AED-induced hypersensitivity reactions can only be identified clinically. A local study has shown that some patients developed rashes, even without the HLA-B*1502 allele [14]. For this patient, it is better not to restart lamotrigine or carbamazepine, although she has a negative result for HLA-B*1502. Apart from medical treatment, surgical therapy and brain stimulation are the available options for this patient.

CONCLUSION

In conclusion, we have shown that in a resource-limited institution, adjunctive treatment, such as clobazam, can be effective in focal epilepsy when no other treatment options are available, especially in pregnant patients with AED allergy. Yet, more evidence is needed regarding the efficacy and safety of clobazam to conclude the dosing regimen in pregnancy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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