

Defek Septum Ventrikel Dan Riwayat Pengobatan Epilepsi Pada Ibu: Sebuah Laporan Kasus

Ventricular Septal Defect and Maternal History of Epilepsy Medication: A Case Report

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Abstrak

Kehamilan dengan epilepsi dapat menimbulkan risiko yang besar bagi ibu dan anak. Telah diketahui bahwa penggunaan obat antiepilepsi (OAE) selama kehamilan dapat meningkatkan risiko malformasi jantung. Jurnal ini melaporkan kasus bayi laki-laki, usia 19 hari, datang dengan keluhan sesak napas disertai bibir kebiruan. Riwayat ibu pasien berusia 21 tahun, mempunyai 1 anak, tidak mempunyai hipertensi maupun diabetes, namun mempunyai riwayat epilepsi dan telah mengonsumsi obat epilepsi secara teratur sejak sebelum hamil. Pemeriksaan fisik menunjukkan bibir sianosis, retraksi dinding dada, serta bunyi rhonki kasar dan murmur. Presentasi klinis pasien terkait dengan penyakit jantung kongenital, sehingga dilakukan perawatan lebih lanjut di ruang NICU. Ekokardiografi bedside menunjukkan adanya foramen ovale paten dan defek septum ventrikel perimembran. Efek teratogenik OAE diduga menjadi salah satu faktor penyebab penyakit jantung kongenital. Defek septum ventrikel merupakan malformasi jantung tersering yang ditemukan pada studi berbasis populasi. Penelitian lebih lanjut diperlukan mengenai dampak jangka panjang paparan OAE saat hamil, baik terkait jenis OAE (lama atau baru) maupun durasi konsumsi OAE. Edukasi terhadap calon ibu mengenai faktor risiko ini sangat penting, terutama untuk menghindari resiko terjadinya penyakit jantung kongenital pada keturunannya.

Kata Kunci: defek septum ventrikel, epilepsi, malformasi jantung

Abstract

Pregnancy with epilepsy can cause major risks for both the mother and the offspring. It is known that the use of antiepileptic drugs (AEDs) during pregnancy can increase the risk of cardiac malformations. This journal reports a 19-day-old male infant who came with complaints of shortness of breath and a blue lip 2 days before admission. The patient's mother was 21 years old, had 1 child, no hypertension or diabetes, but had a history of epilepsy and had taken epilepsy medication regularly since before pregnancy. Physical examination revealed cyanotic lips, chest wall retraction, coarse crackles, and murmurs. The patient's clinical presentation was associated with congenital heart disease, so he was further observed in the NICU. A perimembranous ventricular septal defect and a patent foramen ovale were found on bedside echocardiography. The teratogenic effect of AED is thought to be one of the major causative factors of congenital heart disease. A ventricular septal defect is the most common cardiac malformation found in population-based studies. The long-term effects of AED exposure during pregnancy require further investigation, both in terms of the type of AED (old or new) and the duration of AED consumption. It is important to educate mothers-to-be about this risk factor, especially to avoid the risk of congenital heart disease in their offspring.

Keywords: cardiac malformation, epilepsy, ventricular septal defect.



Pregnancy in women with epilepsy may pose a greater risk to both mother and child. Epilepsy is one of the most common neurological disorders that usually requires ongoing treatment during pregnancy. Women with epilepsy are often considered high risk in pregnancy due to increased obstetric and fetal risks as well as maternal mortality rates that are up to 10 times higher in women with epilepsy than the general population (Edey *et al.*, 2014; Li & Meador, 2022).

Congenital heart disease (CHD) is the most common congenital malformation (CM) in newborns. It remains the leading cause of perinatal and infant mortality. However, there is limited information about the risk factors that may adversely affect fetal heart development. This lack of information is a major obstacle in the prevention of CHD (Chou *et al.*, 2016). It is commonly acknowledged that the use of antiepileptic drugs (AED) during pregnancy increases the risk of CM. Antenatal anti-epileptic drug exposure is linked to some CM, including CHD. It is estimated that 0.3 to 0.5% of all children are born to a mother who has epilepsy. Nonetheless, there are some fetal and obstetric complications associated with women with epilepsy. Clinicians and women with epilepsy must be aware of this when planning and managing pregnancy (Li & Meador, 2022; Verrotti *et al.*, 2015).

Epidemiological data on the prevalence of CMs vary greatly depending on the time of the examination, the methods of ascertainment, and various other factors. An isolated ventricular septal defect (VSD) is the most common CM found in both population-based studies and hospital-based samples. Women with this condition should control their disease as much as possible before conception to minimize the risk of CHD in their children. For pregnant women who are at high risk, prenatal screening should be performed more frequently, especially fetal echocardiography examination (Algahtani *et al.*, 2019; Verrotti *et al.*, 2015).

This interesting case report highlights its importance in educating couples, especially mothers-to-be, about the risks that may predispose their offspring to CHD. This knowledge is especially important for women who have a history of epilepsy, either still on treatment or have completed treatment. The lack of information regarding the link between maternal epilepsy and CHD incidence, especially VSD, makes this case report interesting to discuss. It is aimed that readers (especially clinicians) can provide this information to the community in daily medical practice.

Case Report

A male infant, 19 days old was admitted to the ED with a complaint of shortness of breath that occurred 2 days before admission. Initially, the patient complained of a croaking cough but was not treated immediately. Then, the cough was accompanied by shortness of breath that occurred 1 day before admission. The shortness of breath become worsened, so the patient was brought to the hospital. The patient's lips also looked bluish since the onset of tightness. No complaints of fever and cold. The patient was also exposed to cigarette smoke from the patient's father (an active smoker). The patient's mother had a history of epilepsy since before pregnancy. She

used to take valproic acid regularly since before pregnancy, but now she rarely seeks medical attention because no seizures have been reported.

On physical examination, the patient appeared moderately ill with compos mentis consciousness. Vital signs were HR of 174 beats/minute, RR of 66 times/minute, temperature 36.7°C, and Spo2 90% (free air). On physical examination, blushing is the most obvious sign, but there are no limbs edema. There were chest wall retraction and vesicular breath sounds with coarse rales. The S1 and S2 heart sounds were normal, but murmurs were heard.

Early supporting examination were carried out which included complete blood counts and a chest X-ray. Laboratory examination revealed leukocytosis (WBC = 18.44 x 10³/mm³), with other results within normal (Table 1). Chest X-ray revealed a suggestion of pneumonia (Figure 1A). The patient was admitted to the NICU for observation. The patient was consulted to the cardiologist and echocardiography was planned. Bedside echocardiography examination was performed and the results revealed a 0.2 cm ventricular septal defect perimembranous outlet (VSD PMO) left to right shunt and a 0.4 cm patent foramen ovale (PFO) (Figure 1B).

Based on the anamnesis, physical examination, and supporting investigations, the patient has been diagnosed with bronchopneumonia with VSD PMO and PFO. The patient was treated in the NICU and given nasal cannula oxygen 2 lpm, ampicillin 2x200 mg intravenous (IV), gentamicin 1x15 IV, nebulization of NaCl 0.9% 2cc every 6 hours, drink via nasogastric tube (NGT; 8 ml every 2 hours), and 2x1 puffers (combination of digitalis, loop diuretic, and ACE-inhibitor). The patient was observed regularly for vital signs, general condition, and oxygen saturation.

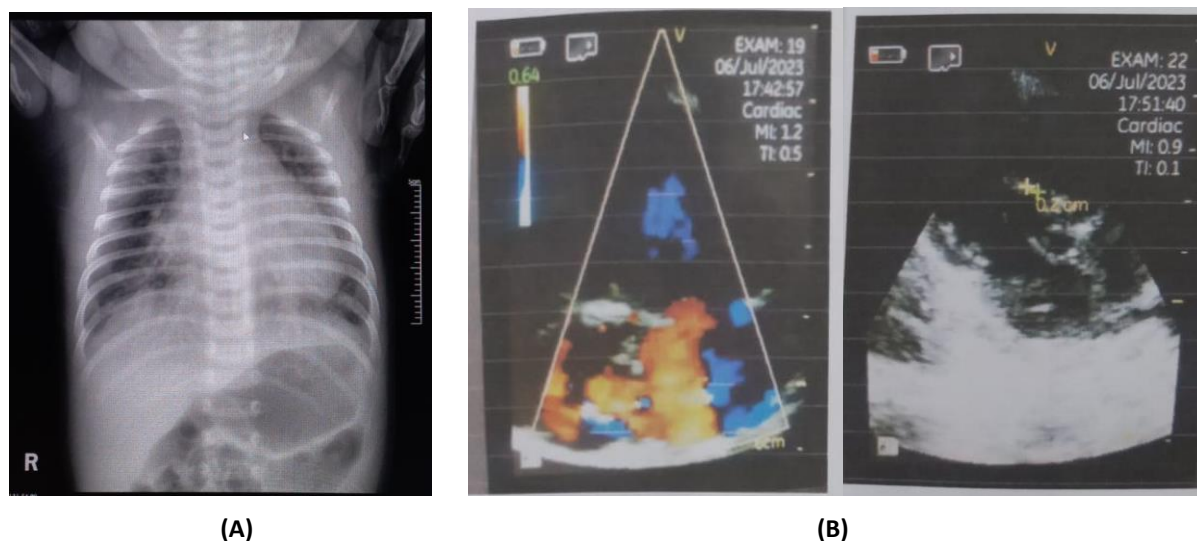
Discussion

Children of women with epilepsy have a higher risk of congenital malformations compared to children of women without epilepsy. The incidence of major congenital malformations seems linked to early (first trimester) AED exposure, polytherapy versus monotherapy of AED, dose and type of AED, low serum folate concentration, and low maternal education level (Li & Meador, 2022). Women with epilepsy who had a child with malformation had a higher risk of having the next child with malformation than women with epilepsy who had no malformation in their first child (16.8%:9.8%). This indicates a potential genetic link to teratogenic risk (Campbell *et al.*, 2013; Vajda *et al.*, 2013).

One of the main causative factors is the teratogenic effects of AED, although other factors such as genetic factors may contribute as well. The most common malformation in children of women with epilepsy is CHD (highest to lowest sequence: atrial or ventricular septal defect, tetralogy of Fallot, patent ductus arteriosus). However, an isolated VSD is the most common CM found in both population-based studies and hospital-based samples. A 2016 Cochrane Review conducted a meta-analysis of AED monotherapy. Data showed that the prevalence of malformation was 1.47% for gabapentin, 1.77% for levetiracetam, 2.39% for oxcarbazepine, 4.28% for topiramate, 4.93% for carbamazepine, 6.26% for phenytoin,

Tabel 1. Laboratory result.

Parameter	Result	Reference range	Unit
WBC	18.44	4.8-17.5	10 ³ /mm ³
HGB	12.6	11.0-18.0	g/dl
PLT	520	150-450	10 ³ /mm ³
Hematocrit	37.1	31.0-52.0	%
MCV	93.5	86-110	fL
MCH	31.7	26.0-38.0	pg
MCHC	34	31.0-37.0	gr/dl
Lymphocyte%	47.1	20-50	%
Neutrophil%	61.4	20-50	%
Monocyte%	15.1	0-14	%
Eosinophil%	1.5	0-6	%
RDW-SD	51.1	37-54	fL

**Figure 1. (A)** Chest X-ray result and **(B)** Bedside echocardiography revealed 0.2 cm VSD PMO L-R shunt and 0.4 cm PFO.

7.10% for phenobarbital, 8.49% for primidone, and 10.93% for valproate. It is commonly acknowledged that antenatal AED exposure raises the risk of CM by two to three times, with the risk increasing with polytherapy and greater dosages (Li & Meador, 2022; Weston et al., 2016).

Family planning and pregnancy planning should be discussed with all women of childbearing age with epilepsy who are prescribed AEDs. Guidance should be carefully communicated to cover potential risks, but without causing unnecessary worry. This program aims to provide information before pregnancy. This is because the incidence of unplanned pregnancies was reported to be more than 50%. Discussions should include the possibility of adjusting AED management from polytherapy to monotherapy or changing the dose to lower in monotherapy (if possible), as well as possible adverse effects on the fetus due to the AED prescribed to the patient. Patients should be informed that regular monitoring of AED medication levels during pregnancy should be considered as the dose may need to be increased or decreased (Li & Meador, 2022).

Periconceptual folate is very important for women with epilepsy who are taking AEDs. This is because some AEDs, especially cytochrome P450-inducing enzymes, are known to deplete serum folate levels. Folic acid supplementation in early pregnancy has been shown to have a preventive effect on the incidence of major CM (Reynolds, 2020). However, the low prevalence of preconception folic acid supplementation (47.6%) in women with epilepsy of childbearing age currently suggests

the need for further education, especially in low-moderate socioeconomic societies (Herzog et al., 2017; Li & Meador, 2022).

Epilepsy management planning during pregnancy should be conducted for women with epilepsy. The mother-to-be should be educated and discuss with her physician (obstetrics and neurology) about the importance of several issues. These may include initiation of folic acid supplementation if the patient isn't already taking it, more frequent monitoring of anti-seizure drug concentrations during pregnancy, and possible adjustment of AED doses during pregnancy compared to the pre-pregnancy (Li & Meador, 2022; Sveberg et al., 2015).

According to a 2019 International League Against Epilepsy Task Force report on women and pregnancy, the most significant decrease in serum concentration is seen with lamotrigine, levetiracetam, and oxcarbazepine (a decrease ranging from 40% to 70%). Serum levels of phenobarbital, phenytoin, topiramate, and zonisamide are reduced moderately (between 30% and 60%). In contrast, carbamazepine and valproate have relatively small changes in serum concentration, which typically decrease from 10% to 20%. Studies have shown that when AED levels fall by more than 35% below the target level, the risk of seizures worsens. It is critical to establish a preconception antiseizure medication level while seizures are effectively controlled (Li & Meador, 2022; Reisinger et al., 2013; Tomson et al., 2019).

In this case report, the patient presented with complaints of cough and shortness of breath, which was initially suspected as

pneumonia. However, the suspicion that led to CHD was the patient's bluish lips and the mother's history of epilepsy. The patient's mother also explained that she didn't regularly take AED and control her epilepsy condition. The patient's family has a low socioeconomic background, and there is a suspicion that when she got pregnant, she didn't routinely perform antenatal care for her fetus and control her epilepsy treatment. Women with epilepsy face unique challenges, particularly during pregnancy. Epilepsy management in women of childbearing age necessitates careful counseling and planning (Lacey *et al.*, 2018; Laganà *et al.*, 2016). As a result, education and discussion about these risk factors are critical for clinicians and women with epilepsy. This aims to prevent the occurrence of CHD, which has a poor prognosis for the offspring. To provide the best possible care, practitioners who care for women with epilepsy should stay current on the latest guidelines and recommendations (Li & Meador, 2022).

Conclusion

Maternal chronic diseases, such as epilepsy, may predispose mothers to have children with CHD. Women with this condition should control, especially for AED medication, as much as possible before conception to reduce the risk of CHD in their children and more studies on AED safety are also required. More frequent prenatal screening (with fetal echocardiography) may be necessary for pregnant women who are at high risk. Early diagnosis of CHD allows for better planning and care during pregnancy, delivery, and the postnatal period.

Conflict of interest

The authors declare no conflict of interest.

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