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Laporan Kasus

6-MONTH-OLD INFANT WITH LISSENCEPHALY TYPE I ASSOCIATED WITH MILLER DIEKER SYNDROME: A CASE REPORT

BAYI 6 BULAN DENGAN LISSENCEPHALY TIPE I YANG BERKAITAN DENGAN SINDROM MILLER DIEKER: LAPORAN KASUS

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A B S T R A K

Malformasi sistem saraf pusat (SSP) terjadi pada 14/10.000 kelahiran. *Lissencephaly* adalah spektrum *Congenital Brain Malformation* (CBM) yang langka yang disebabkan oleh faktor genetik & non-genetik. *Lissencephaly* terdiri dari tipe I & tipe II yang diakibatkan oleh migrasi neuron yang terganggu selama perkembangan otak serta terkait dengan *Miller-Dieker syndrome (MDs), Fukuyama Congenital Muscular Dystrophy (FCMD), Muscle-Eye-Brain Disease (MEBD)* dan *Walker-Warburg syndrome (WWs). Lissencephaly* tipe I berkaitan dengan MDs, sedangkan tipe II berkaitan dengan FCMD, MEBD, WWs. Seorang bayi berusia 6 bulan datang ke unit gawat darurat Rumah Sakit Royal Prima Medan dengan kejang berulang sejak 5 hari sebelum masuk rumah sakit, yang telah diobservasi sejak usia 1,5 bulan tanpa disertai demam. Pasien menunjukkan dismorfisme wajah, keterlambatan pertumbuhan dan perkembangan, disertai PDA sedang dan ASD kecil (ekokardiografi), dan memiliki hasil pemeriksaan EEG dan CT yang abnormal. Lissencephaly merupakan malformasi perkembangan kortikal yang jarang terjadi. MDs adalah suatu kondisi genetik yang diakibatkan oleh delesi pada kromosom 17p13.3 dengan karakteristik *lissencephaly* tipe I, dismorfisme wajah, serta kelainan neurologis yang berat. MDs adalah kelainan kromosom yang jarang terjadi dan diagnosis akurat berdasarkan temuan klinis saja dapat menjadi tantangan, oleh karena itu penggunaan CT scan kepala sangat penting dalam kasus ini.

A B S T R A C T

Central Nervous System (CNS) malformations occur in 14/10,000 births. Lissencephaly is a rare spectrum of Congenital Brain Malformations (CBM) caused by genetic and non-genetic factors. Lissencephaly consists of type I and type II resulting from disrupted neuronal migration during brain development and is associated with Miller-Dieker syndrome (MDs), Fukuyama Congenital Muscular Dystrophy (FCMD), Muscle-Eye-Brain Disease (MEBD), and Walker-Warburg syndrome (WWs). Type I lissencephaly is associated with MDs, while type II is associated with FCMD, MEBD, and WWs. A 6-month-old infant presented to the emergency department of Royal Prima Medan Hospital with recurrent seizures since 5 days prior to admission, which had been observed since the age of 1.5 months without fever. The patient exhibits facial dysmorphism, growth and developmental delay, with moderate PDA and small ASD (echocardiography), and abnormal EEG and CT findings. Lissencephaly is a rare cortical developmental malformation. MDs is a genetic condition caused by a deletion on chromosome 17p13.3 with characteristics of type I lissencephaly, facial dysmorphism, and severe neurological abnormalities. MDs is a rare chromosomal anomaly and accurately diagnosing based on clinical findings alone can be challenging, thus use of Head CT scan is essential in this case.

INTRODUCTION

The occurrence of central nervous system (CNS) malformations is reported in 14 out of 10,000 births. Nevertheless, the true incidence is believed to be much higher, approximately 1 in 100 births, considering late-manifesting CNS anomalies. The pathogenesis of CNS malformations involves abnormalities in various developmental processes, including abnormal neurulation, telencephalic division, neuronal proliferation, migration, and cortical organization.[1] Lissencephaly, pachygyria, periventricular nodular heterotopias and Subcortical Band Heterotopia (SBH) are examples of neuronal migration disorders. These rare brain malformations occur due to disrupted neuronal migration during embryonic development.[2,3]

Lissencephaly is a spectrum of severe and rare Congenital Brain Malformation (CBM) caused by genetic & non-genetic factors.[1,4,5] It consists of type I (classic) & type II cobblestone.[5–7] It is associated with Miller-Dieker syndrome (MDs), Fukuyama congenital muscular dystrophy (FCMD), Muscle-Eye-Brain Disease (MEBD) and Walker-Warburg syndrome (WWs).[6,8] Lissencephaly type I is linked to MDs, while type II is associated with FECMD, MEBD, WWs.[6]

The presence of lissencephaly signifies a rare occurrence, its comorbidities are serious, and significantly affect neurodevelopment, resulting in disability and a compromised quality of life, as well as impacting the overall prognosis. While diagnosing this condition based solely on clinical findings can be challenging, the use of neuroimaging (CT or MRI scans) and genetic studies (chromosome analysis tests) is indispensable in ensuring an accurate assessment. The significance of genetic and neuroimaging studies lies in their ability to ensure accurate diagnoses, predict disease progression, provide genetic counseling, and palliative treatment.[9] The aim of this case report is to demonstrate the challenges in finding and diagnosing the cause of recurrent seizures in patients and the importance of using neuroimaging assessment in the diagnosis of lissencephaly and MDs with clinical presentation of recurrent seizures

CASE REPORT

A 6-month-old infant presented to the emergency department of Royal Prima Hospital Medan with recurrent seizures since 5 days before admission, which had been observed since the age of 1.5 months without preceding fever. She is the second child out of two siblings. She was born per vaginam with a birth weight of 2.2 kg. During pregnancy, the patient's mother only had one antenatal ultrasound examination at 7 months of gestation at the primary health care center (puskesmas), which showed that the baby's weight was low, and the amniotic fluid was sufficient.

The patient was born with a history of cyanosis and respiratory distress and was admitted to the Neonatal Intensive Care Unit (NICU) for 4-5 days. Until the age of 6 months, the patient has not received any immunizations. According to the patient's mother, the first child had normal growth and development.

On physical examination at admission, the patient's weight was 3.5 kg, body length was 50

cm, head circumference of 34.5 cm, RR (40 times/min), HR (140 bpm), Tempt. (36.5 ºC), SpO2 (98%), and has facial dysmorphism, growth and developmental delays. On examination with echocardiography and EEG, she was found to have moderate PDA and small ASD, as well as abnormal EEG results with epileptiform waves in Fp2.

The Non-Contrast Head CT examination revealed Lissencephaly Type I- diffuse agyria subtype with Subcortical Band Heterotopia (SBH) and colpocephaly (figure 1), calvaria thickness of frontal, parietal and occipital bone (figure 2), micrognathia (Mandible measurement) (figure 3) CoPCoP = 6.6 cm and GoGo = 4.67 cm; Left: CoGo = 2.16 cm, GoMn = 3.22 cm, CoMn = 4.47 cm, Gonion angle = 117º; and Right: CoGo = 2.25 cm, GoMn = 3.5 cm, CoMn = 4.85 cm, Gonion angle = 119º)

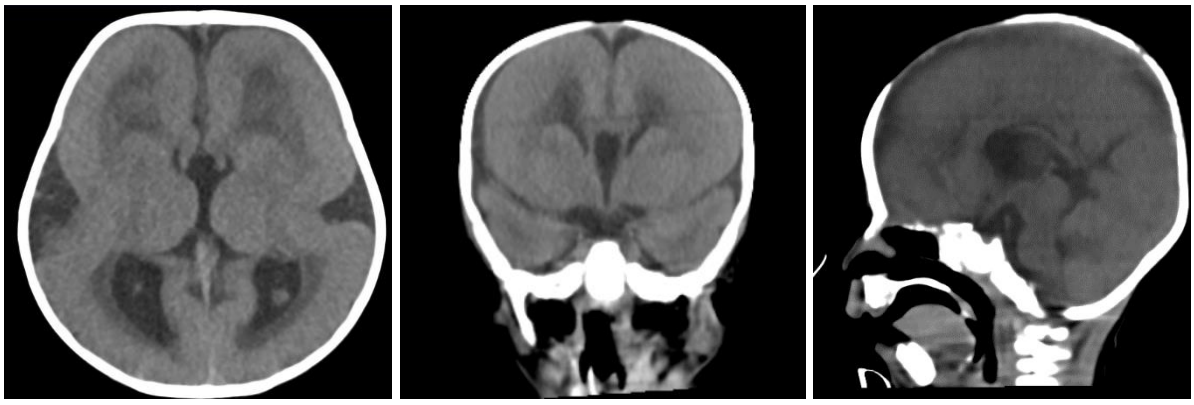


Figure 1. Non-contrast Head CT (axial-coronal-sagittal view)

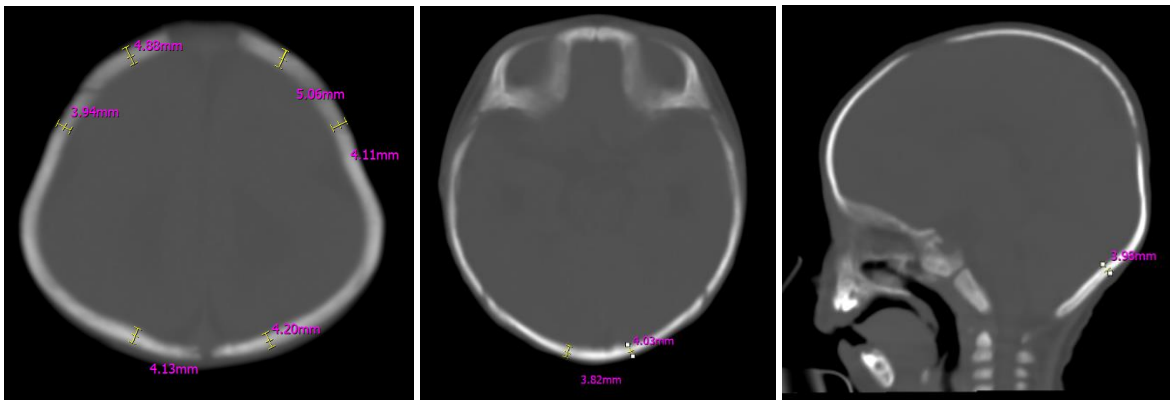
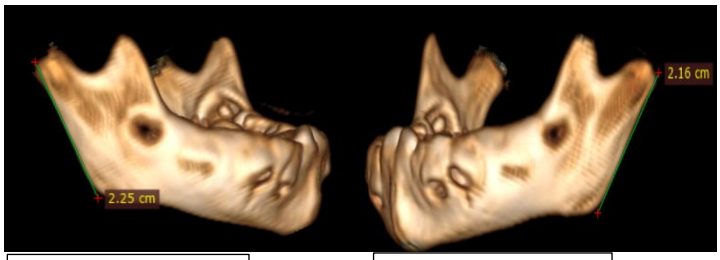


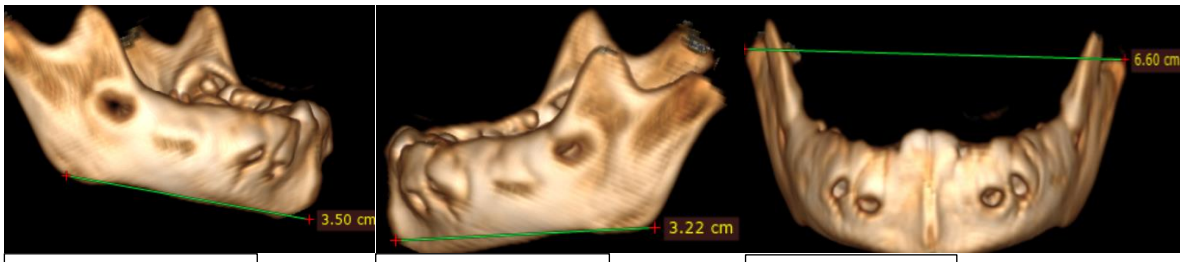
Figure 2. Calvaria thickness (Frontal = 5 mm, Parietal anterior & posterior = 4mm, Occipital = 4 mm)



CoGo (ramus) = condylion superioris and gonion
GoMn (corpus) = Gonion and Menthon
CoPCoP (bicondylar width) = condylion posterioris left and right
CoMn (condylion superioris & menthon)

Right CoGo 2.25cm

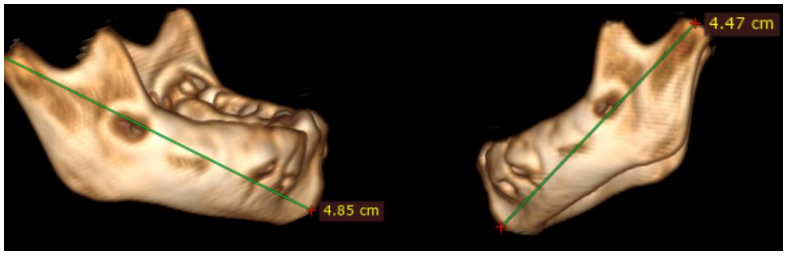
Left CoGo 2.16cm



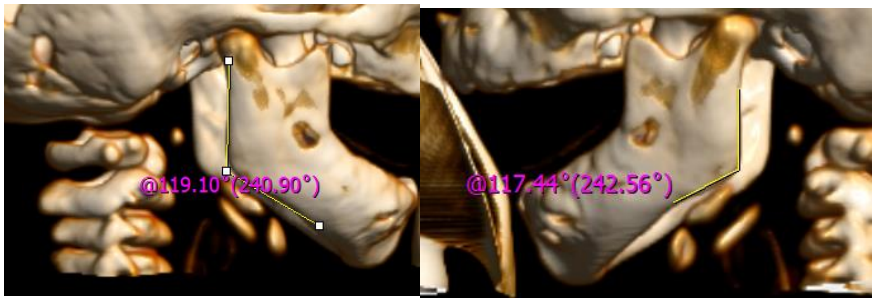
Right GoMn 3.5cm

Left GoMn 3.22cm

CoP CoP 6,6cm



Right CoMn 4.85cm
Left CoMn 4.47cm



Gonion angle
Right 119.10
Left 117.44

Figure 3. Mandible measurement

DISCUSSION

Lissencephaly is a malformation of cortical development (agyria and pachygyria), and together with SBH comprises a spectrum of rare malformations of cortical development.[4,10] Lissencephaly consists of type I and type II and associated with impairment of neuronal migration in the developing brain.[5–7] Type I lissencephaly is a malformation caused by generalised abnormal transmantle migration.[6] There are 8 subtypes of type I lissencephaly, and this patient belongs to the diffuse agyria subtype. Patients with diffuse agyria imaging pattern are characterised by profound intellectual disability, poorly controlled seizures, short survival with a mortality rate of ~50% at 10 years with normal

cerebellum, and higher with cerebellar hypoplasia.[4]

Miller-Dieker syndrome (MDs) is a genetic condition characterized by lissencephaly type I, facial dysmorphism and severe neurologic abnormalities such as intellectual disability and seizures.[6,11,12] Other clinical features of MDS encompass failure to thrive and feeding difficulties. Newborns generally exhibit hypotonic at birth and later develop spasticity.[2] Furthermore, MDs is correlated with microcephaly, micrognathia and cardiovascular defects such as ASD, CHD and conduction abnormality.[6,11] It is a disorder of neuronal migration resulting from deletions on the short arm of chromosome 17 (17p13.3).[13] Patients diagnosed with MDs have a poor prognosis, as mortality usually occurs within the initial 1 to 2 years of life.[2] Only a small number of children who are affected manage to survive beyond their childhood years.[11]

A 6-month-old infant presented to the emergency department with recurrent seizure and typical clinical features of DMs. Clinical examination revealed facial dysmorphisms, growth and developmental delay. The facial dysmorphisms are quite distinctive and consist of microcephaly (< -3 SD) (WHO- z score), a high and prominent forehead, bitemporal pitting, a short nose with anteverted nares (flared nostrils), an abnormal upper lip (thick upper lip), downturned corners of the mouth, micrognathia, microgenia. Additionally, a prominent occiput was observed. The Echocardiography assessment reveals the presence of moderate PDA and small ASD, while the EEG indicates an abnormal result characterized by epileptiform waves in Fp2.

Due to recurrent seizures with abnormal results on physical examination as well as echocardiography and EEG results, the patient underwent a non-contrast head CT scan examination to look for possible brain abnormalities causing seizures. The Non-contrast Head CT scan shows a figure-8 appearance with absence of sulci and gyry, a thickened cortex with smooth surface of bilateral cerebral hemispheres and a grey matter band parallel to the cortex (lissencephaly type I - diffuse agyria subtype with SBH). Ratio of posterior horn to anterior horn of lateral ventricle ≥3 (colpocephaly) was also seen. Based on the results of measuring patient's mandible, it was found that the patient has micrognathia.

MDS is an untreatable condition with no known prenatal treatment or interventions options. Currently, there are no specific treatments available and postnatal management of MDS patients primarily involves the use of antiepileptics for seizure control and providing supportive care.[2] But despite the wide use of anti-seizure drugs in the treatment of seizures, they often prove ineffective in achieving seizure control, leading to a significant burden for both patients and caregivers. A recent study focused on perampanel (PER) as a potential alternative therapy for drug-resistant seizures in lissencephaly patients, including those with Miller-Dieker syndrome. Out of the five patients involved in the study, four experienced a notable reduction of at least 50% in their seizure. The study concluded that perampanel (PER) serves as an effective adjunctive anti-seizure

medication for individuals with lissencephaly. However, the precise mechanism underlying the effectiveness of PER for lissencephaly-associated epilepsy remains unknown, emphasizing the need for further research.[3]

CONCLUSSION

MDs is a rare chromosomal anomaly and accurately diagnosing based on clinical findings alone can be challenging, thus use of Head CT scan is essential in this case.

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