Perinatology
pISSN 2508-4887 • eISSN 2508-4895

Case report
Perinatology Vol. 33, No. 4, December, 2022
https://doi.org/10.14734/PN.2022.33.4.201

A Patient with Tuberous Sclerosis with Hemimegalencephaly Presenting with Intractable Epilepsy in the Early Neonatal Period: A Case Report

Sungbo Shim, MD[1], Jeong Eun Shin, MD, PhD[1], Soo Min Lee, MD[1], Seung Hwan Baek, MD[1], Joon-Sik Park, MD[1], Jung Ho Han, MD[1], Min Soo Park, MD, PhD[1], Hoon-Chul Kang, MD[2], Eun Kyung Park, MD[3], Ho Seon Eun, MD[1]

[1]Division of Neonatology, Department of Pediatrics, Yonsei University College of Medicine, Seoul; [2]Division of Pediatric Neurology, Department of Pediatrics, Yonsei University College of Medicine, Seoul; [3]Department of Pediatric Neurosurgery, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea

Hemimegalencephaly (HME) is a rare disease characterized by partial or complete hypertrophy of one cerebral hemisphere. It is associated with intractable seizures, developmental delay, hemiparesis, and other neurological symptoms. Tuberous sclerosis (TSC) is a neurocutaneous syndrome that affects various organs, including the heart, brain, skin, kidney, and eyes, and is caused by mutations in *TSC1* and *TSC2* genes. Herein, we report the case of a patient with TSC and HME who required early neurosurgical treatment during the neonatal period. A full-term girl was suspected to have TSC prenatally because of left ventriculomegaly and cardiac masses on fetal ultrasonography. HME was confirmed by postnatal neuroimaging studies. Multiple rhabdomyomas and renal cysts were compatible with TSC. Serially performed electroencephalography (EEG) showed intractable electrical seizures in the left hemisphere with secondary generalization, despite rare clinical convulsions. As anti-epileptic drugs did not improve electrical seizures, corpus callosotomy was performed at 39 days of age. Postoperatively, the frequency of secondary generalization of seizures was significantly reduced on EEG. A novel frameshift mutation in c. 1743_1744insCAAGG (p. Thr582GlnfsTer49) in the *TSC1* gene was confirmed using targeted next-generation sequencing.

Key Words: Tuberous sclerosis, Hemimegalencephaly, Epilepsy, mTORpathy

Received: 16 September 2022
Revised: 24 October 2022
Accepted: 26 October 2022

Correspondence to
Ho Seon Eun, MD
Department of Pediatrics, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2060
Fax: +82-2-393-0118
E-mail: hseun@yuhs.ac

Introduction

Hemimegalencephaly (HME) is a rare congenital disease characterized by partial or complete hypertrophy of one cerebral hemisphere.[1] It is associated with intractable seizures, developmental delay, hemiparesis, and other neurological symptoms.[2] Anti-epileptic drugs are not effective in controlling seizures in HME because ictal discharges from the damaged brain rapidly spread to the contralateral side.[3,4]

Tuberous sclerosis (TSC) is an autosomal dominant genetic disease and neurocutaneous syndrome, which is known to result from mutations in *TSC1* (9p34.13) or *TSC2* (16p13.3).[2] This syndrome affects various organs, including the brain, heart, kidney, eye, and skin, and may lead to cortical dysplasia, subependymal nodules and subependymal giant cell astrocytomas, cardiac rhabdomyomas, renal angiomyolipomas, retinal nodular hamarto-

mas, facial angiofibromas, and hypomelanotic macules.[5] The TSC-associated brain lesions can cause seizures, neurodevelopmental delays, and other neurological deficits.[5]

Only a few cases have been reported in association with HME and TSC, and there have been no reports in Korea since a single case of HME and TSC was diagnosed in a 1-month-old infant in 2009.[6] We report the case of a patient diagnosed with HME associated with TSC who was suspected of having TSC prenatally, was further diagnosed with HME after birth, and required aggressive early medical and surgical treatment due to intractable epilepsy.

Case

A 34-year-old mother was transferred to Severance Hospital because of fetal left ventriculomegaly and cardiac masses diagnosed at 35 weeks of gestation (Fig. 1). A female baby was born at a gestational age of 37 weeks and 4 days, at 3.2 kg, by cesarean section, with an Apgar score of 5 at 1 minute and 8 at 5 minutes. At birth, she required positive pressure ventilation due to weak crying and weak activity. She had no visible abnormalities including skin lesions, except for the macrocephaly.

Brain sonography (Fig. 2) and brain magnetic resonance imaging (MRI) (Fig. 3) revealed several tubers in the right hemisphere and HME and band heterotopia in the left hemisphere.

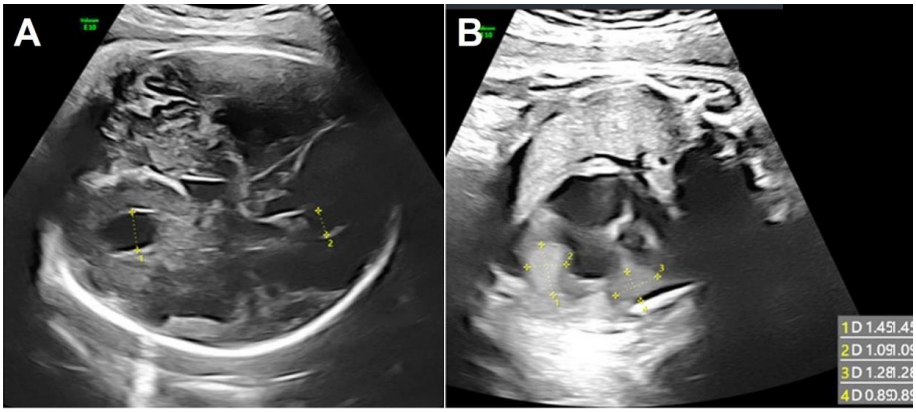

Fig. 1. Prenatal ultrasound at intrauterine period 37 weeks and 0 days. (A) Brain sonography showed left side ventriculomegaly. (B) Echocardiography revealed masses sized 15×11 mm (right ventricle) and 13×9 mm (left ventricle). Written informed consent was obtained for publication of this case report and accompanying images.

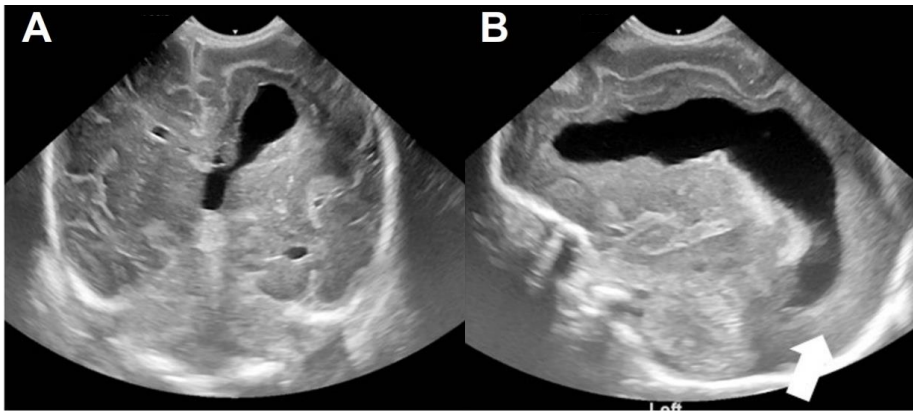

Fig. 2. Brain ultrasound at 1 day after birth (post-conceptual age 37 weeks and 5 days). (A) Coronal view of brain ultrasound showed left sided ventriculomegaly. (B) Sagittal view of brain ultrasound. Ventriculomegaly of the left lateral ventricle and band heterotopia were noted (arrow).

Targeted next-generation sequencing (NGS) of the central nervous system anomaly was used to define disease etiology. We identified a heterozygous frameshift mutation in c. 1743_1744insCAAGG (p. Thr582GlnfsTer49) in the *TSC1* gene, which has not been previously reported.

Serial electroencephalography (EEG) from the day of birth revealed continuous electrical seizures originating from the left hemisphere and secondary generalization to the contralateral side (Fig. 4A), despite her first clinical seizure (clonic movement of the right arm) being noted on the fourth day after birth. The EEG findings did not improve after taking 3 kinds of anti-epileptic drugs (phenobarbital, topiramate, and vigabatrin). Therefore, on the 39th day of her life, corpus callosotomy (functional hemispherectomy) was performed to control the electrical status epilepticus. Postoperative EEG performed at 5 months of age, revealed that subclinical seizures originating from the left side remained, but the duration was decreased from 10 to 15 minutes to 1 to 2 minutes; moreover, secondary generalization was not observed (Fig. 4B). However, the post-operative course was complicated by intraventricular hemorrhage and posthemorrhagic hydrocephalus (Fig. 5). An external ventricular drainage catheter was temporarily inserted and removed after resolution of the hydrocephalus.

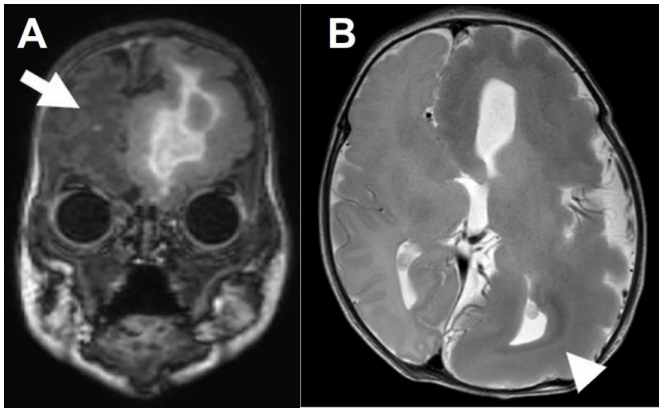

Fig. 3. Brain magnetic resonance imaging at 5 days after birth (post-conceptual age 38 weeks and 0 days). (A) Coronal view of T1-weighted image. The arrow indicates a tuber. (B) Axial view of T2-weighted image. The arrowhead indicates band heterotopia associated with hemimegalencephaly. Midline deviation to the right is also noted.

She had no clinical seizures 3 months after the corpus callosotomy. Clinical seizures recurred in the form of infantile spasms at 4 months of age. EEG findings revealed multifocal spikes (hypsarrhythmia) in the right hemisphere, which was on the contralateral side of the HME. When the patient was discharged from the neonatal intensive care unit at approximately 7 months of age, she was taking 3 anti-epileptic drugs (topiramate, levetiracetam, and vigabatrin) and showed

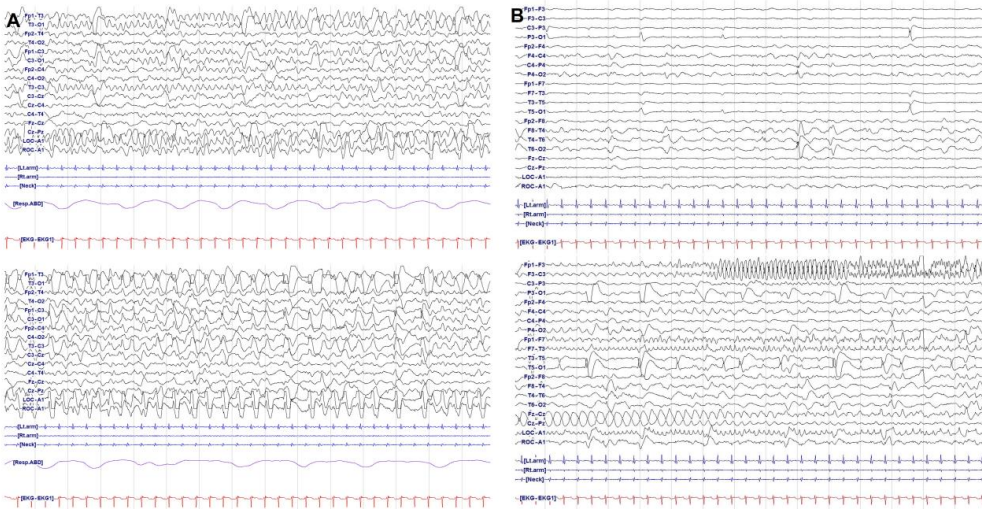

Fig. 4. Comparison of pre-operative and postoperative electroencephalography (EEG). (A) Pre-operative EEG performed at 32 days after birth. There were subclinical seizures with evolving ictal rhythmic discharges from the left occipital (T3-O1) or centro-temporal areas (Fp1-T3, T3-C3). The subclinical seizures spread to the contralateral side. (B) Postoperative EEG performed at 5 months of age. There was inconsistent asymmetric voltage attenuation on the left side of the brain which was the side affected by the hemimegalencephaly. There were subclinical seizures with evolving ictal rhythmic discharges from the left side of brain, but there was no spreading to contralateral side.

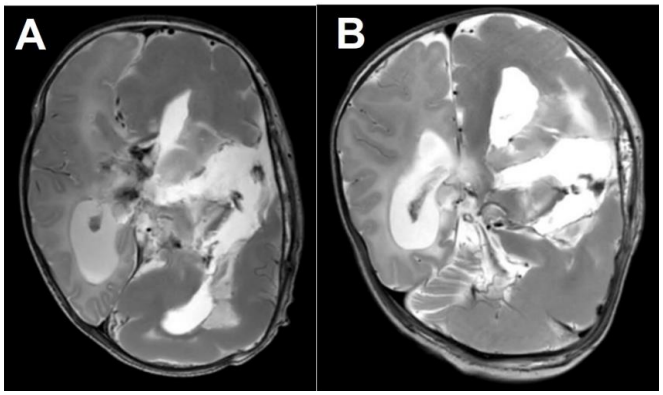

Fig. 5. Postoperative magnetic resonance image performed after corpus callosotomy was performed (post-conceptual age 44 weeks and 0 days, 46 days of age, 6 days after operation). Posthemorrhagic hydrocephalus of the right ventricle was noted. (A) Axial view of T2-weighted image. (B) Coronal view of T2-weighted image.

no clinical seizures.

Prenatal echocardiography revealed multiple cardiac masses (15×11 mm and 13×9 mm). After birth, the size of rhabdomyomas (14×10 mm on the right ventricle [RV] side, 3×4 mm on the ventricular septum, and 11×11 mm on the left ventricle [LV] side) were similar to the antenatal sonography findings, and had not significantly changed for 5 months (11.4×8 mm on RV, 3×4 mm on septum, and 12.9×8 mm on LV) and steadily had no effects on the hemodynamic status (Fig. 6). Multiple tiny renal cysts were found 6 weeks after birth and gradually enlarged to 12 mm in size at the age of 5 months (Fig. 7).

She received enteral nutrition through a nasogastric tube because of feeding difficulties. A gastrostomy was performed at the age of 5 months. She was diagnosed with diabetes insipidus

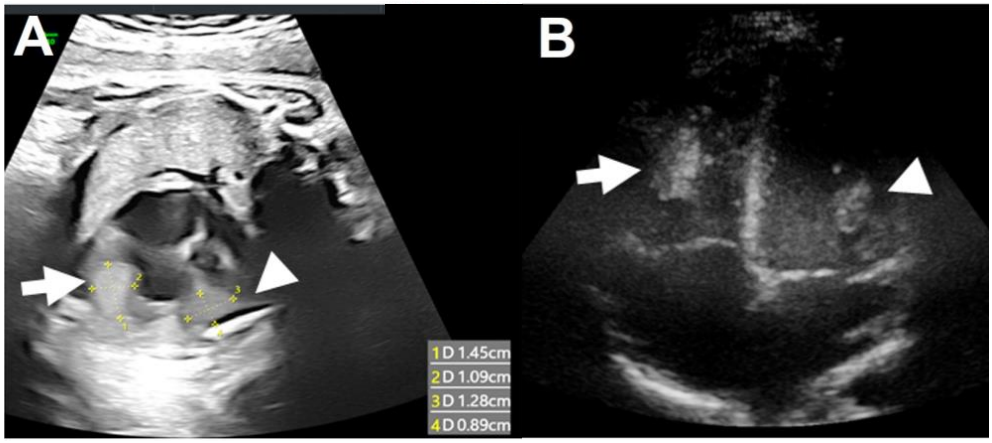

Fig. 6. Echocardiography findings revealed multiple rhabdomyomas without significant change in size. Rhabdomyomas on the right ventricle (RV) are indicated by arrows, and rhabdomyomas on the left ventricle (LV) are indicated by arrowheads. (A) Echocardiography performed on 2 days after birth identified, 3 masses: RV, 15×10 mm; septum, 3×4 mm; and LV, 11×11 mm. (B) Echocardiography performed on 5 months of age identified, 3 masses: RV, 12×8 mm; septum, 3×4 mm; and LV, 13×8 mm.

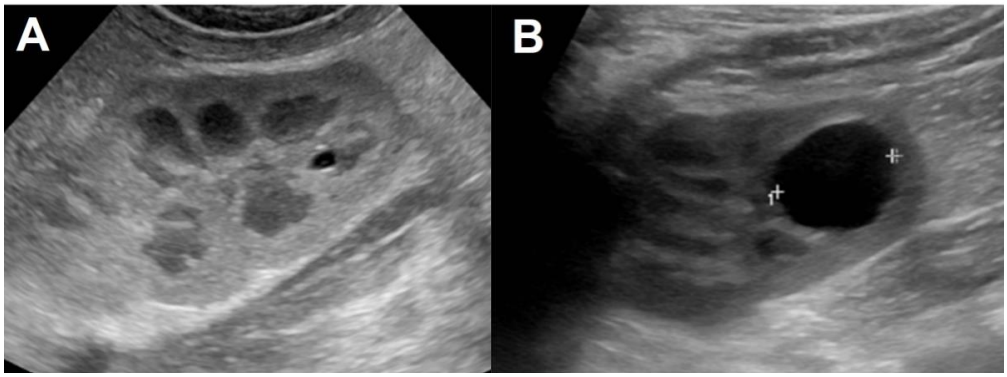

Fig. 7. Kidney ultrasound shows renal cyst. (A) tiny right renal cyst was noted at 6 weeks of age. (B) Further increase in the size of the renal cyst was noted at 5 months of age (d=1.46×1.62 cm).

on the 45th day of life, a week after the corpus callosotomy. Oral desmopressin is needed to balance osmolarity and electrolytes. There were no abnormal findings in the retina, automated auditory brainstem response, or brainstem-evoked response audiometry.

After discharge from the neonatal intensive care unit, she was hospitalized again at the age of 11 months for treatment with high-dose prednisolone (60 mg/day) due to worsening hypsarrhythmia and was successfully treated. In evaluations conducted at 12 months of age, clinical seizures did not recur, rhabdomyomas were stable in size, and the size of the renal cysts decreased with good kidney function. This study was approved by the Severance Hospital Institutional Review Board (approval number: 4-2022-0492).

Discussion

The incidence of TSC is estimated to be 1:6,000 live births globally.[5] Epilepsy occurs in 80% to 90% of patients with TSC over their lifetime, including severe epileptic encephalopathy infantile spasms in 30% to 40%.[7] The diagnosis of TSC in the neonatal period and early start of anti-epileptogenic treatment before the onset of clinical seizures is being emphasized to improve neurodevelopmental outcomes of patients with TSC patients.[8] As cardiac tumors (rhabdomyomas) are the first possible presentation of TSC, all neonates with antenatally detected cardiac tumors need to be thoroughly evaluated for TSC via physical examination, brain MRI, and genetic testing.[5] HME, a hamartomatous malformation affecting one cerebral hemisphere,[9] occurs sporadically or is associated with neurocutaneous syndromes including TSCs.[10] Since first reported by Sims in 1835, HME has been known as one of the most devastating brain malformations accompanying intractable seizures that frequently appear in the neonatal period.[3] The presence of these 2 disorders seems to be associated with a worse clinical course than that of HME or TSC alone.[2]

Our patient showed electric seizures in the left hemisphere, which was the affected side of the HME, and the seizures did not improve despite multiple anti-epileptic drugs. Surgical intervention was needed, and corpus callosotomy was performed on the 39th day of life. In a review of 21 cases from 1961 to 2019, Sidira et al.[2] reported that most patients with HME and TSC were found to have symptoms such as seizures within 1 month of age (range, 0–49 days; median 2 days). The patient reported in Korea had the first clinical seizure on the 26th day of birth and was diagnosed with HME and TSC approximately 36 days after birth.[6] Of the 21 previously reported cases, 10 patients underwent surgery (including anatomical hemispherectomy, corpus callosotomy, and craniotomy), and 8 of whom had surgery before the age of 12 months.[2] From the literature reviews, the earliest surgery case was performed on the 30th day of birth, because of clinical seizures immediately after birth, and repeated status epilepticus on EEG.[11] Postoperative outcomes vary, and most patients maintained a seizure-free period for 2 months to over 5 years.

In our patient, secondary generalization of seizures starting from the left side tended to improve after corpus callosotomy. However, hypsarrhythmia occurred on the right side at approximately 4 months of age. Salamon et al.[12] reported that post-surgical seizure control results are likely to be poorer when corpus callosotomy or hemispherectomy is performed in patients with bilateral cerebral hemispheric abnormalities. In the case of TSC lesions on the contralateral side of the HME, the prognosis for seizure control is expected to be worse.

When the first Korean patient with TSC and HME was reported in 2009, this case was described as an unusual association between 2 rare central nervous system diseases. However, recent studies have shown that both TSC and HME are categorized under the same disease classification of malformations of cortical development.[13] Advances in NGS and single-cell technologies have demonstrated that mutations in the mammalian target of rapamycin (mTOR) pathway are a common cause of brain malformations, including TSC, HME, and focal cortical dysplasia.[7] Abnormal hyperactivation of the mTOR pathway leads to abnormal cell growth and proliferation, which may be a common mechanism underlying TSC and HME. The mTOR inhibitor has recently been used in patients with TSC-associated subependymal giant cell astrocytoma since its approval in 2010. Regarding HME cases, a reduction in seizure frequency after using an mTOR inhibitor in 3-month-aged HME patients was reported in 2019.[10] As clinical studies of mTOR inhibitors for patients with HME are just emerging, anti-epileptogenic medication might become an early treatment of

choice for mTORpathies, including TSC and HME.

Hemispherectomy is advocated as the most appropriate treatment modality for HME cases with refractory epilepsy and cognitive deterioration after trials with anti-epileptic medications.[14] However, brain surgery is associated with high mortality and morbidity, especially in early infancy.[3] In our case, the patient underwent corpus callosotomy at age of 39 days for electrical intractable seizures, and postoperative hemorrhage occurred. Since refractory seizure is always accompanied by a devastating prognosis, surgical access to status epilepticus in patients with HME should be considered actively, although it may result in surgery-related complications. If an mTOR inhibitor is introduced as an effective anti-epileptogenic agent, it can delay brain surgery, and might have benefits in terms of both seizure control itself and the reduction of complications due to early surgery. A recent study reported that mTOR inhibitors were effective for relapsed seizures 1 year after hemispherectomy in patients with TSC and HME.[15]

Lastly, we detected a novel heterozygous frameshift mutation in c.1743_1744insCAAGG (p.Thr582GlnfsTer49) of *TSC1* in our patient. No further genetic studies were conducted on the family because of parental refusal. However, there was no familial history of diagnosed TSC, and no family members had suspicious findings such as neurological symptoms or skin lesions.

To the best of our knowledge, there have been approximately 20 case reports of the association between TSC and HME. This is the first reported case in Korea, although its evaluation started immediately after birth and medical treatment was initiated before symptoms appeared, surgical treatment was eventually required under this diagnosis. Our patient was diagnosed with prenatal TSC accompanied by ventriculomegaly and HME was confirmed immediately after birth. On EEG monitoring, we found electrically intractable seizures, and used anti-epileptic drugs; however, there was no improvement. Early surgical intervention was performed, and clinical progress improved in the short term. In patients with the association of TSC and HME, early EEG monitoring might help to reveal subclinical seizures and status epilepticus even before clinical seizures appear. Early administration of anti-epileptic drugs and surgical intervention should be guaranteed, and frequent clinical follow-up and EEG monitoring are needed.

ORCID

Sungbo Shim, https://orcid.org/0000-0001-9703-7050
Jeong Eun Shin, https://orcid.org/0000-0002-4376-8541
Soo Min Lee, https://orcid.org/0000-0001-8777-425X
Seung Hwan Baek, https://orcid.org/0000-0002-7890-6916
Joon-Sik Park, https://orcid.org/0000-0002-4902-4770
Jung Ho Han, https://orcid.org/0000-0001-6661-8127
Min Soo Park, https://orcid.org/0000-0002-4395-9938
Hoon-Chul Kang, https://orcid.org/0000-0002-3659-8847
Eun Kyung Park, https://orcid.org/0000-0002-8777-3457
Ho Seon Eun, https://orcid.org/0000-0001-7212-0341

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Authors' Contributions

Conceptualization: HSE; Data curation: SS, SML, JSP; Investigation: SS, SHB, JHH; Methodology: JES; Supervision: HSE, JES; Validation: HCK, EKP, MSP; Visualization: SS; Writing–original draft: SS; Writing–review & editing: all authors.

References

1) Guerra MP, Cavalleri F, Migone N, Lugli L, Delalande O, Cavazzuti GB, et al. Intractable epilepsy in hemimegalencephaly and tuberous sclerosis complex. J Child Neurol 2007;22:80-4.
2) Sidira C, Vargiami E, Dragoumi P, Zafeiriou DI. Hemimegalencephaly and tuberous sclerosis complex: a rare yet challenging association. Eur J Paediatr Neurol 2021;30:58-65.
3) Cuddapah VA, Thompson M, Blount J, Li R, Guleria S, Goyal M. Hemispherectomy for hemimegalencephaly due to tuberous sclerosis and a review of the literature. Pediatr Neurol 2015;53:452-5.
4) Di Rocco C, Battaglia D, Pietrini D, Piastra M, Massimi L. Hemimegalencephaly: clinical implications and surgical treatment. Childs Nerv Syst 2006;22:852-66.
5) Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008;372:657-68.
6) Lee YJ, Lee EH, Jung MH, Yum MS, Ko TS. A case of tuberous sclerosis

with hemimegalencephaly. J Korean Child Neurol Soc 2009;17:231-6.
7) D'Gama AM, Poduri A. Precision therapy for epilepsy related to brain malformations. Neurotherapeutics 2021;18:1548-63.
8) Slowinska M, Jozwiak S, Peron A, Borkowska J, Chmielewski D, Sadowski K, et al. Early diagnosis of tuberous sclerosis complex: a race against time. How to make the diagnosis before seizures? Orphanet J Rare Dis 2018;13:25.
9) Xu Q, Uliel-Sibony S, Dunham C, Sarnat H, Flores-Sarnat L, Brunga L, et al. mTOR inhibitors as a new therapeutic strategy in treatment resistant epilepsy in hemimegalencephaly: a case report. J Child Neurol 2019;34:132-8.
10) Sakuma H, Iwata O, Sasaki M. Longitudinal MR findings in a patient with hemimegalencephaly associated with tuberous sclerosis. Brain Dev 2005;27:458-61.
11) Alfonso I, Vasconcellos E, Shuhaiber HH, Yaylali I, Papazian O. Bilateral decreased oxygenation during focal status epilepticus in a neonate with hemimegalencephaly. J Child Neurol 2004;19:394-6.
12) Salamon N, Andres M, Chute DJ, Nguyen ST, Chang JW, Huynh MN, et al. Contralateral hemimicrencephaly and clinical-pathological correlations in children with hemimegalencephaly. Brain 2006;129(Pt 2):352-65.
13) Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. Brain 2012;135(Pt 5):1348-69.
14) Griessenauer CJ, Salam S, Hendrix P, Patel DM, Tubbs RS, Blount JP, et al. Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: a systematic review. J Neurosurg Pediatr 2015;15:34-44.
15) Serletis D, MacDonald C, Xu Q, Kazina CJ, Dakshinamurti S, Marin S, et al. Hemispherectomy for hemimegalencephaly in a 6.5-week-old infant with tuberous sclerosis complex. Childs Nerv Syst 2022;38:1415-9.