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Surgical Resection of Focal Cortical Dysplasia in a Neonate with Novel TSC1 Mutation Leading to Resolution of Refractory Seizures: Case Report

Emily Garavatti, MD[1], Erin Yamamoto, MD, MS[2], Kelly Collins, MD[3], Nathan Selden, MD, PhD[3], and Ittai Bushlin, MD, PhD[4]

Abstract

We describe a neonate presenting on first day of life with refractory seizures secondary to a single, large area of focal cortical dysplasia (FCD) who underwent surgical resection at age 3 weeks leading to resolution of seizure activity and dramatic improvement in developmental trajectory. Surgical intervention for epilepsy is infrequently offered for neonates, often reserved only for those with catastrophic presentations. This case demonstrates that surgical intervention can be safe and efficacious in neonates for pharmaco-resistant seizures associated with a focal lesion. Rapid whole exome sequencing in this case yielded a germline novel de novo TSC1 mutation, leading to a genetic diagnosis of tuberous sclerosis complex (TSC). Our patient demonstrates an atypical neonatal presentation of TSC. Limited data is available for those with isolated FCD in TSC; this is the first reported case in a neonate.

Keywords

neonatal seizures, neonate, neurosurgery, tuberous sclerosis, tuberous sclerosis complex, epileptic encephalopathy, seizures, refractory, genetics, surgery

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Introduction

Seizures within the first day of life often occur secondary to acute brain injury, and therefore are classified as acute symptomatic seizures. Acute symptomatic seizures account for 75% of neonatal seizures.[1] Localized seizures that are refractory to medications raise suspicion for localization-related epilepsy. Catastrophic epilepsy, referring to frequent seizures with developmental regression or stagnation, can present in neonates and is an indication for surgical evaluation. In such cases, early surgical intervention is associated with improved cognitive outcomes.[2] This case demonstrates that surgical intervention can be effective for neonates with pharmaco-resistant seizures associated with focal lesions and that rapid whole exome sequencing can provide successful genetic diagnosis in the neonatal period.

Case

A male infant, conceived via *in vitro* fertilization (IVF), was born at 38 weeks by urgent c-section for placental abruption and met physiologic criteria for therapeutic hypothermia. Refractory seizures started within the first hour of life, arising from the left central region by scalp EEG. MRI on day of life 4 demonstrated a T1 hyperintense, T2 hypointense cortically based lesion in the posterior aspect of the left middle frontal gyrus suspected to represent focal cortical dysplasia (FCD; see Figure 1). Electrographic seizures persisted despite

[1]Neurodevelopmental Disabilities, Oregon Health & Science University School of Medicine, Portland, OR, USA
[2]Neurosurgery, Oregon Health & Science University School of Medicine, Portland, OR, USA
[3]Department of Neurosurgery, Oregon Health & Science University, Portland, OR, USA
[4]Department of Pediatric Neurology, Oregon Health & Science University, Portland, OR, USA

Corresponding Author:
Emily Garavatti, Neurodevelopmental Disabilities, Oregon Health & Science University School of Medicine, Portland, OR, USA
Email: garavatt@ohsu.edu

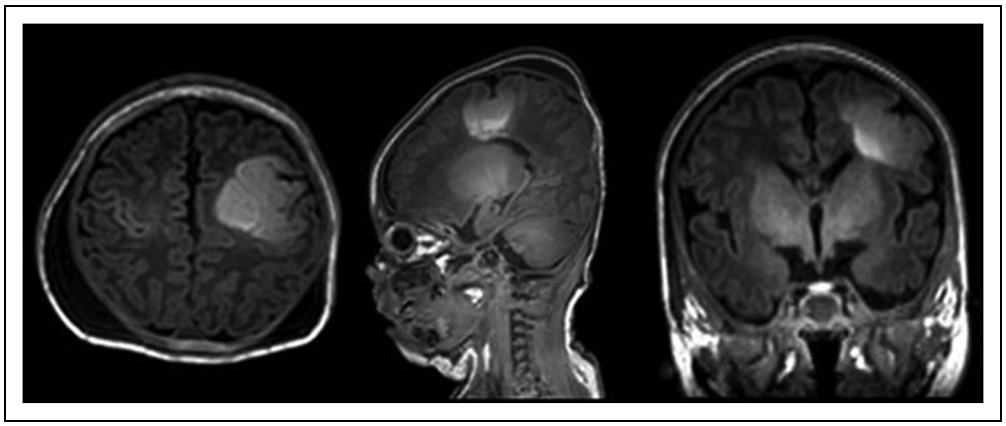

Figure 1. MRI obtained on day of life 4 demonstrated T1 hyperintensity in the left posterior frontal lobe associated with abnormal gyration pattern that may reflect an area of cortical dysplasia.

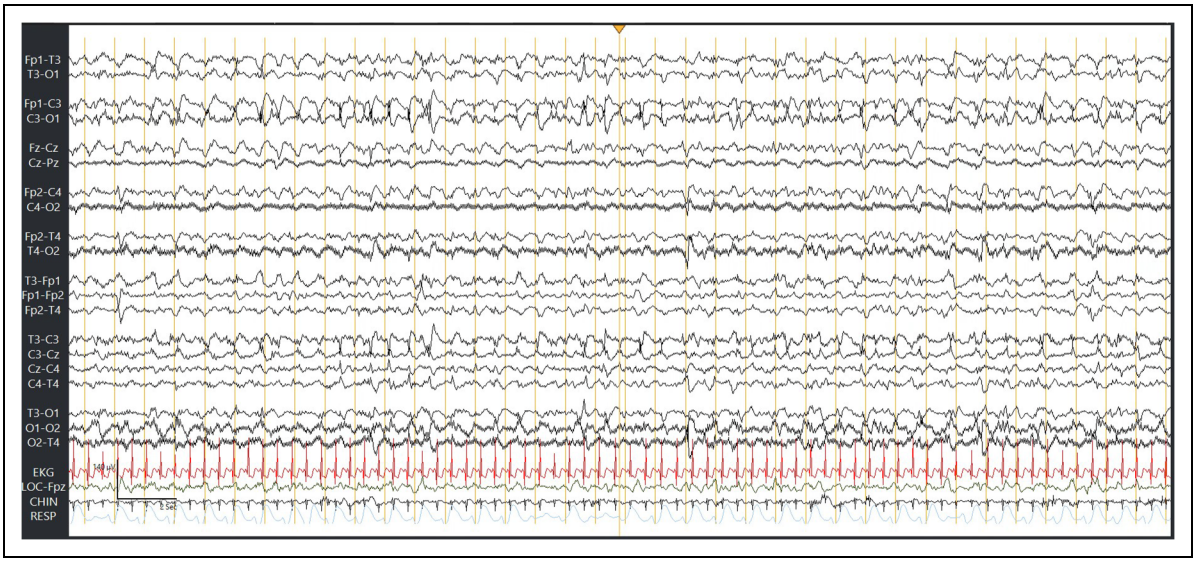

Figure 2. Focal spike discharges at C3 are at times nearly continuous, but arrhythmic and without focal evolution.

therapeutic dosing with phenobarbital, fosphenytoin, levetiracetam, topiramate and continuous midazolam infusion, which led to hemodynamic compromise requiring vasoactive support. In addition, therapeutic trials of pyridoxine, pyridoxal 5-phosphate, folinic acid, and biotin were attempted without response. On day 15, the patient was transferred to a tertiary care center. The neurological examination on arrival was notable for profound encephalopathy, diffuse hypotonia, absence of spontaneous movements, and sluggish response to noxious stimuli. EEG showed near-continuous spike discharges at C3 (see Figure 2). A craniotomy was performed with stereotactic guidance on day of life 18 with MRI-confirmed total resection of the radiographic lesion without complications, following which there was dramatic improvement in encephalopathy with spontaneous eye opening, visual fixation, and movement in all 4 extremities without any additional modification to the pre-operative schedule and dosing of anti-seizure medications. Pathology demonstrated dysplastic neurons and innumerable balloon cells, histologically consistent with focal cortical dysplasia IIb (FCDIIb). Rapid whole exome sequencing using peripheral blood demonstrated a novel de novo germline missense mutation in TSC1 (c.621C > A, p.(Y207X), pathogenic variant). Genetic testing from surgically resected tissue revealed 4 genetic variants including the same TSC1 mutation (TSC1 p.Y207*, FH p.S419L, FANCD2 splice site alteration, NBN p.R714*). The infant underwent screening with cardiac and renal ultrasound, skin exam with Wood's lamp, and ophthalmology evaluation and no other clinical characteristics of TSC were identified. There were no further concerns for clinical seizure activity, and given his dramatic clinical improvement, an EEG was not repeated during hospitalization. The infant was successfully weaned off respiratory support, oral feeding was advanced, antiseizure medications were weaned to levetiracetam monotherapy and he was discharged home on day of life 33. At the 3 month post-operative follow-up, he remains seizure-free and demonstrates age-appropriate developmental skills.

Discussion

Diagnostic uncertainty was one of the major challenges of this case. The initial presentation of clinical seizures and other physiologic criteria were concerning for the possibility of neonatal hypoxic-ischemic encephalopathy, which is one of the leading causes of neonatal seizures.[3] Therefore, this patient appropriately received therapeutic hypothermia. By contrast, the focality of the observed seizures raised concern for a possible underlying structural brain lesion, the presence of which was confirmed by MRI on day of life 4. The radiographic differential diagnosis for this epileptogenic lesion based on T1 hyperintensity included a melanocytic or a dysembryoplastic neuroepithelial tumor. Although it is atypical for malformations of cortical development to appear T1 hyperintense, the abnormal gyration pattern and the wedge-shaped signal abnormality extending to the ependymal surface had a similar appearance to the transmantle sign that is associated with FCDIIb (Figure 1). This led our team to suspect a malformation of cortical development,[4,5] which was confirmed after resection by histopathology. The classic radiographic appearance of FCDIIb is T1-hypointense and T2-hyperintense. By comparison our patient's lesion was T1 hyperintense, which is likely is related to the immature myelination pattern in neonates.[6,7]

Histopathologic and whole exome sequencing revealed the surprising result of FCDIIb and a germline mutation in TSC1. Singular areas of FCD are an uncommon manifestation of tuberous sclerosis complex (TSC), which is a condition associated with characteristic skin, kidney, lung, heart, and brain findings. A diagnosis of TSC is determined by either clinical criteria or identification of a pathogenic variant in the TSC1 or TSC2 genes. Genetic studies are typically initiated based on clinical suspicion. TSC1 and TSC2 code for hamartin and tuberin, respectively, which form a complex that inhibits mTOR signal pathways. Sixty percent of mutations that are associated with malformation of cortical development involve mTOR-MAP kinase pathways.[8] Mutations in these genes can result in FCDIIb with characteristic balloon cells and disruptions of cortical lamination, as seen with our patient.[8]

TSC gene mutations have been reported in isolated FCD.[9] These are often somatic mutations and not associated with syndromic TSC. It is likely that syndromic TSC occurs with germline mutations. However, hemimegalencephaly is an example of an extensive malformation of cortical development, which may occur with germline TSC mutations, but is not associated with syndromic TSC.[9] In these cases, hemimegaloencephaly occurs in the setting of a two hit phenomena, with both germline and somatic mutations. This suggests that the clinical spectrum of TSC may differ due to somatic, germline, or a combination of mutations. There have been few reports of individuals who have a single FCD as the only brain manifestation of TSC despite meeting the clinical criteria for TSC diagnosis based on cardiac, skin, lung or kidney findings. One study documents 5 children out of 105 that underwent presurgical evaluation for solitary FCD that were ultimately diagnosed with TSC based on other classic clinical criteria.[10] An isolated area of FCD associated with a germline TSC1 mutation has only been reported in 2 related patients with novel mutation, but has not previously been documented in a neonate.[11] Pathogenic mutations identified in FCD are more frequently somatic and therefore testing performed on blood or other genetic sampling, often may not be diagnostic.[9] Currently, genetic testing for malformations of cortical development is not standardized and it is possible that some individuals with isolated FCD and germline TSC mutation may be unrecognized. Diagnosis by genetic analysis may correspond with a broader TSC phenotype compared to diagnosis by clinical criteria. It is therefore uncertain whether existing data, based largely on clinical criteria, are accurate for counseling families of those patients diagnosed with TSC by genetic testing without other classical clinical features, as in our patient.

Neonatal onset epilepsy in the setting of TSC is rare, more commonly developing around 3-5 months of age.[12] In a large cohort of children with TSC, only 5.7% had onset of epilepsy in the neonatal period, and in those cases, children presented with multiple characteristic TSC brain lesions including cortical tubers, subependymal nodules, subependymal giant-cell astrocytomas.[12] Our case is unique in that there was neonatal presentation of refractory seizures associated with isolated FCD and a germline TSC1 mutation in absence of other clinical signs of TSC.

In a previous report, a cohort of 21 patients with TSC who developed seizures in the neonatal period, those with FCD were more likely to have drug resistant epilepsy and more likely to have severe intellectual disabilities.[12] Eleven patients showed large cortical malformations, and the majority of the children without FCD had experienced perinatal events that were independent risk factors for seizures. These findings suggest that large areas of FCD are commonly associated with a more severe clinical phenotype. Three children in this cohort received epilepsy surgery between 4-6 months of age, all of whom had improvement in seizure control. One patient who underwent FCD resection had normal psychomotor development, suggesting that relatively early surgical intervention for refractory seizures may be developmentally beneficial for children with TSC. Notably, all children in the reported cohort had multiple brain lesions characteristic of TSC.

Epilepsy surgery is infrequently performed within the first 30 days of life[12–14]; the youngest reported case of surgical resection of a focal lesion was 12 days old.[15] Surgical intervention in the neonatal/infant population poses special challenges including blood loss in the setting of very low circulating blood volume, and unmyelinated white matter that is delicate and difficult to manipulate without iatrogenic parenchymal injury. Surgical adjuncts, such as cranial fixation, image guided navigation, intra-operative imaging (including intra-operative MRI), and stereotactic EEG planning, may be more difficult or impossible to utilize.[16] Small size and low systemic blood volume pose additional challenges. The risks of surgery and anesthesia are therefore different than even in other older pediatric patients, and must be weighed against the benefits of early surgical intervention which include the potential for improved seizure control, maximizing developmental capacity, and overall reducing the effect of seizure burden on neurodevelopmental outcomes.[13]

Our team recommended surgical resection due to a substantial, refractory seizure burden despite maximal medical therapy, which itself was limited by the impact of this therapy on hemodynamic stability. The patient demonstrated remarkable clinical improvement and seizure freedom immediately post-operatively. He continues to be seizure free at 3-months post-surgical follow up.

The majority of individuals with TSC have epilepsy and mild to moderate intellectual disability. Recent investigations have been looking into whether early and aggressive treatment in TSC may reduce incidence or severity of neurodevelopmental sequala.[17,18] Everolimus, an MTOR inhibitor is a targeted treatment for TSC, has only been used in the neonatal period for treatment of cardiac rhabdomyomas. This treatment was not considered at initial presentation as TSC mutation was not known at the time of surgical intervention. In TSC, FCD has been associated with worse neurodevelopmental outcomes,[12] in the absence of genetic syndromes such as TSC, large FCD can be associated with intractable epilepsy and impaired neurodevelopment. Early surgical resection for FCD may significantly reduce or eliminate seizure burden and greatly improve neurodevelopmental outcomes,[13] though there is essentially no data on early surgical resection of FCD in TSC patients. Our patient's neonatal presentation of TSC is uncharacteristic. The isolated genetic basis for the TSC diagnosis in our case likely precludes counseling based either on FCD data or on more classic presentations of TSC in infancy.

Consent

Verbal informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

We confirm that guidelines on patient consent have been met and any details of informed consent obtained are indicated within the text of the submitted manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics

Our institution does not require ethical approval for reporting individual cases or case series.

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ORCID iD

Emily Garavatti https://orcid.org/0009-0008-4483-8602

References

1. Pisani F, Spagnoli C, Falsaperla R, Nagarajan L, Ramantani G. Seizures in the neonate: A review of etiologies and outcomes. *Seizure*. 2021;85:48–56.
2. Marashly A, Karia S, Zonjy B. Epilepsy surgery: Special circumstances. *Semin Pediatr Neurol*. 2021;39:100921.
3. Yozawitz E. Neonatal seizures. *N Engl J Med*. 2023;388(18):1692–1700.
4. Leventer R, Guerrini R, Dobyns W. Malformations of cortical development and epilepsy. *Dialogues Clin Neurosci*. 2008;10(1):47–62.
5. Bernasconi A, Bernasconi N, Bernhardt BC, Schrader D. Advances in MRI for "cryptogenic" epilepsies. *Nat Rev Neurol*. 2011;7(2):99–108.
6. Eltze CM, Chong WK, Bhate S, Harding B, Neville BGR, Cross JH. Taylor-type focal cortical dysplasia in infants: Some MRI lesions almost disappear with maturation of myelination. *Epilepsia*. 2005;46(12):1988–1992.
7. Miller E, Widjaja E. Neuroimaging in pediatric epilepsy. In: *Caffey's Pediatric Diagnostic Imaging*. 12th ed. Saunder; 2013:408–409.
8. Chung C, Yang X, Bae T, et al. Comprehensive multi-omic profiling of somatic mutations in malformations of cortical development. *Nat Genet*. 2023;55(2):209–220.
9. D'Gama AM, Woodworth MB, Hossain AA, et al. Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a Continuum of cortical dysplasias. *Cell Rep*. 2017;21(13):3754–3766.
10. Hirfanoglu T, Gupta A. Tuberous sclerosis complex with a single brain lesion on MRI mimicking focal cortical dysplasia. *Pediatr Neurol*. 2010;42(5):343–347.
11. Hoelz H, Coppenrath E, Hoertnagel K, et al. Childhood-Onset epileptic encephalopathy associated with isolated focal cortical dysplasia and a novel TSC1 germline mutation. *Clin EEG Neurosci*. 2018;49(3):187–191.
12. Kotulska K, Jurkiewicz E, Domanska-Pakiela D, et al. Epilepsy in newborns with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2014;18(6):714–721.
13. Makridis KL, Atalay DA, Thomale UW, Tietze A, Elger CE, Kaindl AM. Epilepsy surgery in the first six months of life: A systematic review and meta-analysis. *Seizure*. 2022;96:109–117.
14. Roth J, Constantini S, Ekstein M, et al. Epilepsy surgery in infants up to 3 months of age: Safety, feasibility, and outcomes: A multicenter, multinational study. *Epilepsia*. 2021;62(8):1897–1906.
15. Peterson C, Garling RJ, Asano E, et al. Successful surgical treatment of refractory Status epilepticus in a 12-day-old infant. *Pediatr Neurol*. 2019;92:73–75.
16. Trayner J, Nesbit G, Scott RM, Boulis NM, Selden NR. Clinical problem solving: Family matters case problems in neurosurgery case presentation. *Neurosurgery*. 2008;62(1):195–201.
17. Makridis KL, Klotz KA, Ramantani G, et al. Epilepsy surgery in early infancy: A retrospective, multicenter study. *Epilepsia Open*. 2023;8(3):1182–1189.
18. Kotulska K, Kwiatkowski DJ, Curatolo P, et al. Prevention of epilepsy in infants with tuberous sclerosis Complex in the EPISTOP trial. *Ann Neurol*. 2021;89(2):304–314.