Epilepsy & Behavior Reports 19 (2022) 100560

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Epilepsy surgery in PCDH 19 related developmental and epileptic encephalopathy: A case report

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ARTICLE INFO

Article history:
Received 22 April 2022
Revised 26 June 2022
Accepted 3 July 2022
Available online 6 July 2022

Keywords:
PCDH19
DEE
Epilepsy surgery
Genetic epilepsy

ABSTRACT

We report a female child with PCDH19 related developmental and epileptic encephalopathy with drug-resistant seizures, cognitive and language impairment, autism spectrum disorder and sleep dysfunction. Her seizures, which started at 10 months of age, were resistant to multiple anti-seizure medications. Developmental stagnation followed by regression occurred after the onset of recurrent seizures. Her ictal EEGS suggested left temporal lobe origin for her recorded seizures. MRI upon expert re-review showed a subtle abnormality in the left temporal lobe.

In view of the severe nature and frequency of her seizures, a left temporal lobectomy was undertaken at the age of 2 years and 3 months. Though her seizure outcome was Engel class 3, her seizure frequency and severity were significantly reduced. She has been seizure-free for 10 months at her last outpatient assessment when she was 4 years and 8 months of age (2 years and 5 months after epilepsy surgery). However she recently had an admission for COVID19 infection, with a breakthrough cluster of seizures. Her developmental trajectory changed, though she is making good progress with her cognitive and language skills.

Introduction

PCDH19 (Protocadherin19) is a common and important epilepsy related gene, located on the X chromosome, with phenotypic heterogeneity and incomplete penetrance [42,34,14,25,7,35]. The condition is attributed to pathogenic loss-of-function variants in the PCDH19 gene. PCDH19 disorders have an unusual pattern of expression. It manifests in heterozygous females but hemizygous males are mostly unaffected [8,4,6,28]. Since heterozygous females have a mixture of cells that express either wild-type (WT) or mutant forms of PCDH19, due to random X-inactivation, the mosaic expression of PCDH19 is proposed to cause pathogenic symptoms. There is cellular interference between cells expressing either the intact or variant copy. A changed equilibrium between asymmetric and symmetric cell division may contribute to the pathogenesis in PCDH19 related disorders [26,23,3]. PCDH19 is expressed widely in the embryonic and adult brain, including the developing cortex and hippocampus, and in areas connected to the hippocampal formation such as entorhinal cortex, lateral septum, and basolateral amygdaloid complex. The gene encodes a transmembrane protein, Protocadherin 19, a calcium dependant cell adhesion molecule of the Cadherin family, which is involved in cell to cell interactions, signal transduction and development of neural connections. PCDH19 mutations disrupt brain development; abnormal proliferation and migration of neural progenitors, accelerated neurogenesis, accelerated asymmetric cell divisions and differentiations, and impaired synaptic development have been shown in animal and in-vitro studies [22,30,10,27,18,26,3,19,12,37,23].

Pathogenic variants in this gene may be associated with a wide spectrum of disorders including epilepsy [30,7]. Developmental

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https://doi.org/10.1016/j.ebr.2022.100560
2589-9864/

and epileptic encephalopathy (DEE) characterized by cognitive and language impairment, autism, and sleep abnormalities are seen in females. The severity of the associated epilepsy is extremely variable with drug resistant and progressive epileptic encephalopathy (such as Dravet syndrome and epilepsy with myoclonic-atonic seizures) to some self-limited forms. Neuropsychiatric disorders have been reported occasionally in males with mosaic PCDH19 pathogenic variants [39].

Seizure onset in girls is often in infancy [26,5,7,8]. Seizures may show clustering [17,3,38], and be triggered by fever [38,24,25]. Seizure types include focal and generalized seizures and maybe clonic, tonic-clonic, tonic, atonic, myoclonic and absences. Seizures are often resistant to anti-seizure medications, especially in the first decade of life and withdrawal of anti-seizure medication may not be possible even in those who become seizure-free [13,35,1].

In this case report we describe the features of DEE related to a PCDH19 de novo pathogenic variant in a female child. The child had drug-resistant epilepsy, with severe seizures that frequently needed resuscitation. She subsequently underwent a temporal lobectomy with significant benefit with regard to her seizures and the developmental profile.

Case report

We report on a female child, aged 4 years and 10 months, with PCDH19 related developmental and epileptic encephalopathy [31] with drug-resistant seizures, cognitive and language impairment, autism spectrum disorder and sleep dysfunction. Her seizures, which started at age 10 months, were resistant to multiple anti-seizure medications. Developmental stagnation followed by regression occurred after onset of seizures. Her ictal EEGs suggested left temporal lobe origin for her recorded seizures. MRI on expert re-review showed a subtle abnormality in the left temporal lobe.

In view of the severe nature and frequency of her seizures, a left temporal lobectomy was undertaken at the age of 2 years and 3 months. Though her seizure outcome was Engel Class 3 [9], her seizure frequency and severity have significantly reduced. She has been seizure-free for ten months, at last outpatient assessment when she was 4 years and 8 months of age (2 years and 5 months after epilepsy surgery). However she recently had an admission for COVID19 infection, with a breakthrough cluster of seizures. Her developmental trajectory changed, though she is making good progress with her cognitive and language skills.

Seizures

Seizures began at 10 months with a cluster of afebrile generalized tonic-clonic seizures. Over the next 2 years seizures increased in frequency and severity. She had generalized tonic-clonic seizures, tonic seizures, focal seizures with impaired awareness, seizures associated with apneas/hypopneas and significant oxygen desaturations that needed oxygen and bag and mask resuscitation. Seizures were frequently triggered by fever, though they also occurred when she was afebrile. There was clustering of seizures. Most seizures were brief and less than 5 min in duration. Her worst seizure frequency was in 2019, when she could have 13–15 seizures in a day. Seizure frequency at the time of surgery was ~12/-month, and her need for oxygen/bag and mask resuscitation ~4–5 times/month.

Seizures were reduced significantly after surgery, both in frequency and severity. There has been no need for bag and mask resuscitation after surgery. There have been varying periods of seizure freedom, interrupted by breakthrough seizures. The longest seizure-free duration has been ten months. However she was admitted this month, following a prolonged focal seizure, preceded by a cluster of brief generalized tonic-clonic seizures, in association with COVID19 infection and fever. She was loaded with levetiracetam. She did not need airway support or bag and mask ventilation.

Anti-seizure medications

She has tried many anti-seizure-medications (ASMs), including phenobarbital, carbamazepine, oxcarbazepine, levetiracetam, phenytoin, topiramate, clobazam, lamotrigine and valproate. These ASMs were often used in combinations, as monotherapy was ineffective. There were no ASM withdrawals due to adverse effects. She has also had a trial of pyridoxine. Attempts to reduce ASMs after surgery have been unsuccessful due to the recurrence of seizures. Currently she remains on valproate, lamotrigine, topiramate and clobazam. Her parents are not interested in changing her current ASMs, as they are very pleased with her developmental gains and seizure-free periods of several months. She has had multiple seizure types, as known to occur in females with PCDH19 pathogenic variants. Epilepsy with PCDH19 mutations is often drug-resistant. Her current ASMs include clobazam that has been reported to be one of the most effective as well as three others [16]. A ketogenic diet was considered but not attempted as it would have been very difficult to initiate and maintain.

Development

Early developmental milestones are reported to have been near age appropriate. She smiled at 6 weeks, vocalisations started at 3 months, and rolling at 6–7 months. She was referred to a physiotherapist at 9 months as she was not yet sitting. Retrospectively her mother feels vocalisations were immature for age at 9 months. Development was said to stagnate and then regress after seizure onset at ten months. With each cluster her skills were said to regress and then she would slowly regain some skills over the next few months. She is reported to have pulled to stand at one year, took her first steps and said the first word at around 14 months. At a chronological age of 23 months (Griffith's III) her general development quotient was <1 percentile. At 26 months of age, she was identified to have significant impairment of expressive and receptive language (based on the Preschool Language Scale: PLS-5).

She was also identified to have features consistent with autism. A diagnosis of autism spectrum disorder (ASD) was subsequently made. She has received early interventional therapy and is now registered with and receives services through the National Disability Insurance Scheme.

She had epilepsy surgery at 27 months. After surgery she made developmental gains. Verbal communication improved upon informal assessment, and she was observed to be more interactive with her parents, therapists, and carers despite remaining severely delayed overall. She was unable/unwilling to engage in formal assessment attempted at 6 and 24 months. At last outpatient review, at 56 months of age (29 months after epilepsy surgery), she was able to walk and run. She was reported to have 50 words in her vocabulary and was putting 4–5 words together. She recites the alphabet untill "g", the numbers from 1 to 10 and sings along the first sentence of several nursery rhymes. She has an individual education plan at the kindergarten. The impression of her family and health professionals is that she is making consistent developmental gains, albeit slowly.

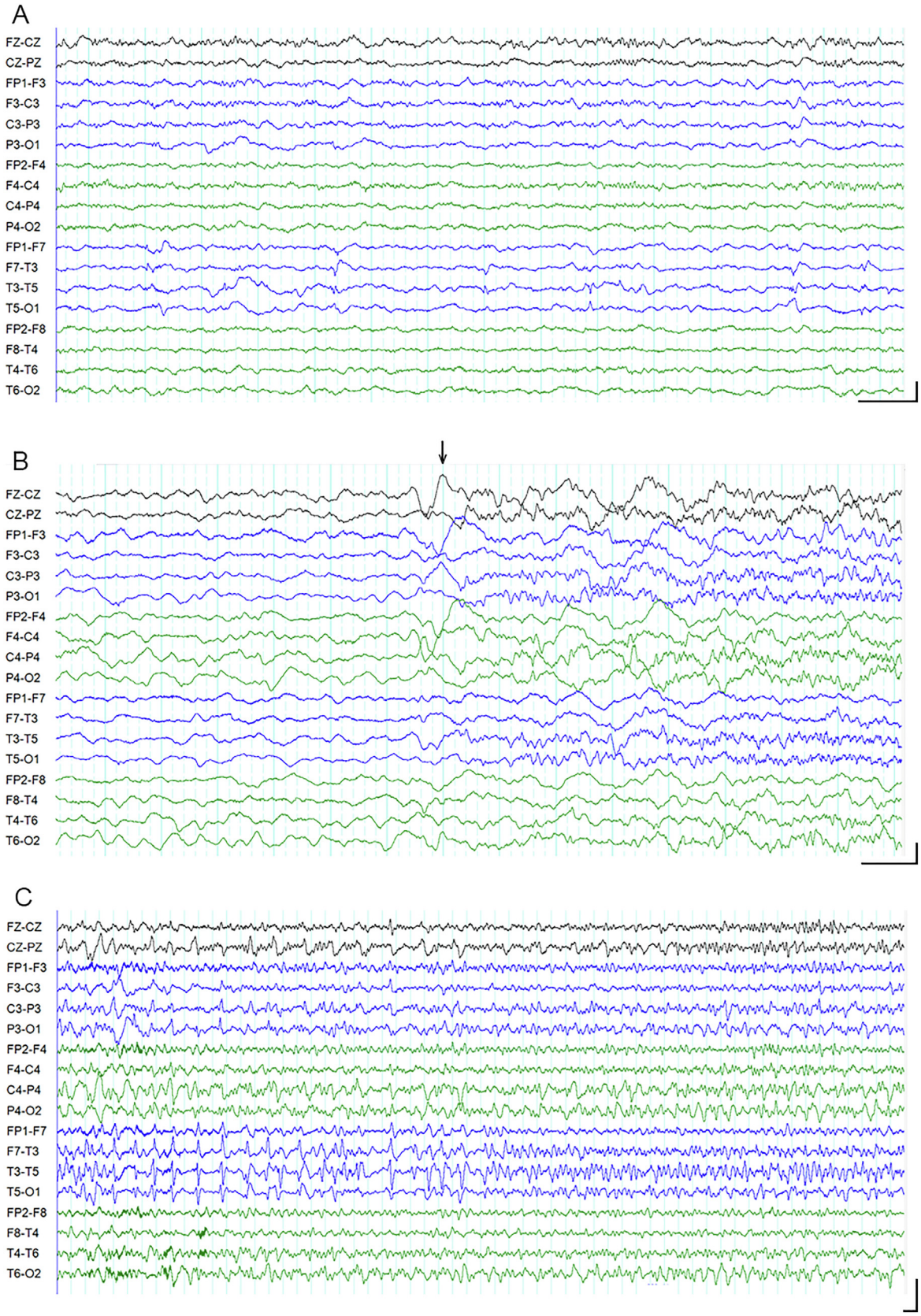

Fig. 1. Interictal and ictal EEG: All EEG epochs are displayed in a double-banana montage. Calibration bars are present in each subfigure: horizontal 1 s, vertical 200 μV. 1A. A 15 s epoch showing interictal epileptiform discharges from the left temporal and temporo-occipital regions. Intermittent left temporal slowing is also seen.1B. A 15 s epoch showing electrographic seizure onset from the left hemisphere (arrowhead). 1C. A 60 s epoch showing 6th minute of the seizure. Note prominent the left temporal epileptiform discharges.

Neurophysiology

She had two of three standard (about one hour) video-EEGs undertaken in our institution, prior to prolonged video-EEG monitoring that did not show any interictal epileptiform discharges. Left temporal slowing and left temporal and temporo-occipital spikes and sharps were present in one recording (see Fig. 1A). Interictal EEGs in PCDH19 mutations may be normal, or show increased slow activity and epileptiform activity [26].

On a 20-hour video-EEG obtained in the epilepsy monitoring unit in 2019, seven electro-clinical seizures were captured. Six of these seizures arose from sleep. Clinical features of the seizure started well after electrographic onset. The most prominent feature of the clinical semiology was oxygen desaturation. She had brief apneas, became dusky and was stiff. The increased tone at onset was more obvious in the seizure from the wake state. She slowly falls forward and her mother helps lie her down; she appears to have generalised increase in tone. Oxygen by mask corrected the desaturation. She was tachycardic during the seizure. Electrographically the seizures appeared to lateralize to the left hemisphere. EEG features at onset and into the seizure suggested left temporal localization (see Fig. 1 for the EEG features of one seizure). The electro-clinical features of the seizures captured on this study were stereotypical; we did not capture any of her other seizure types. She has had V-EEGs since her surgery, including an 18 h monitoring; no seizures have been captured. At times, there was

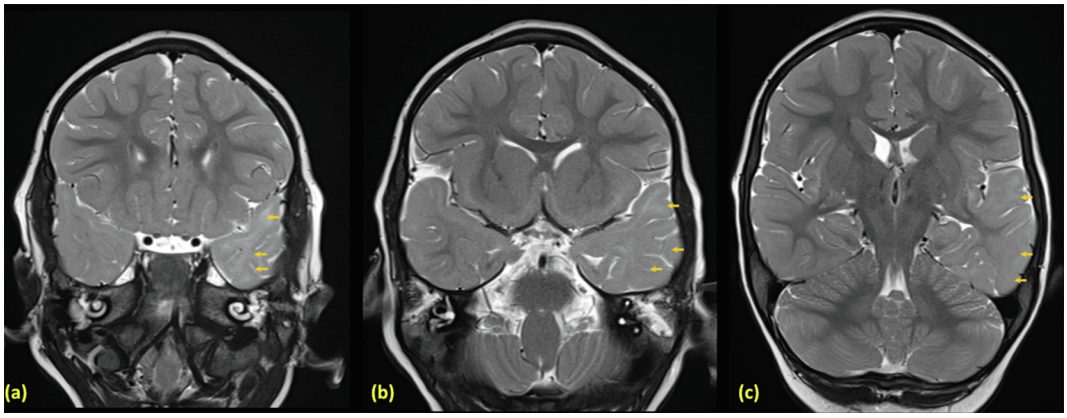

Fig. 2. MRI Brain with coronal oblique T2 images of the temporal lobes from anterior to posterior (a) – (c): There is asymmetric T2 high signal within the left anterior temporal lobe and polar white matter (arrows) consistent with an underlying cortical dysplasia. The hippocampi have a normal appearance. The right temporal lobe myelination is within normal limits for age.

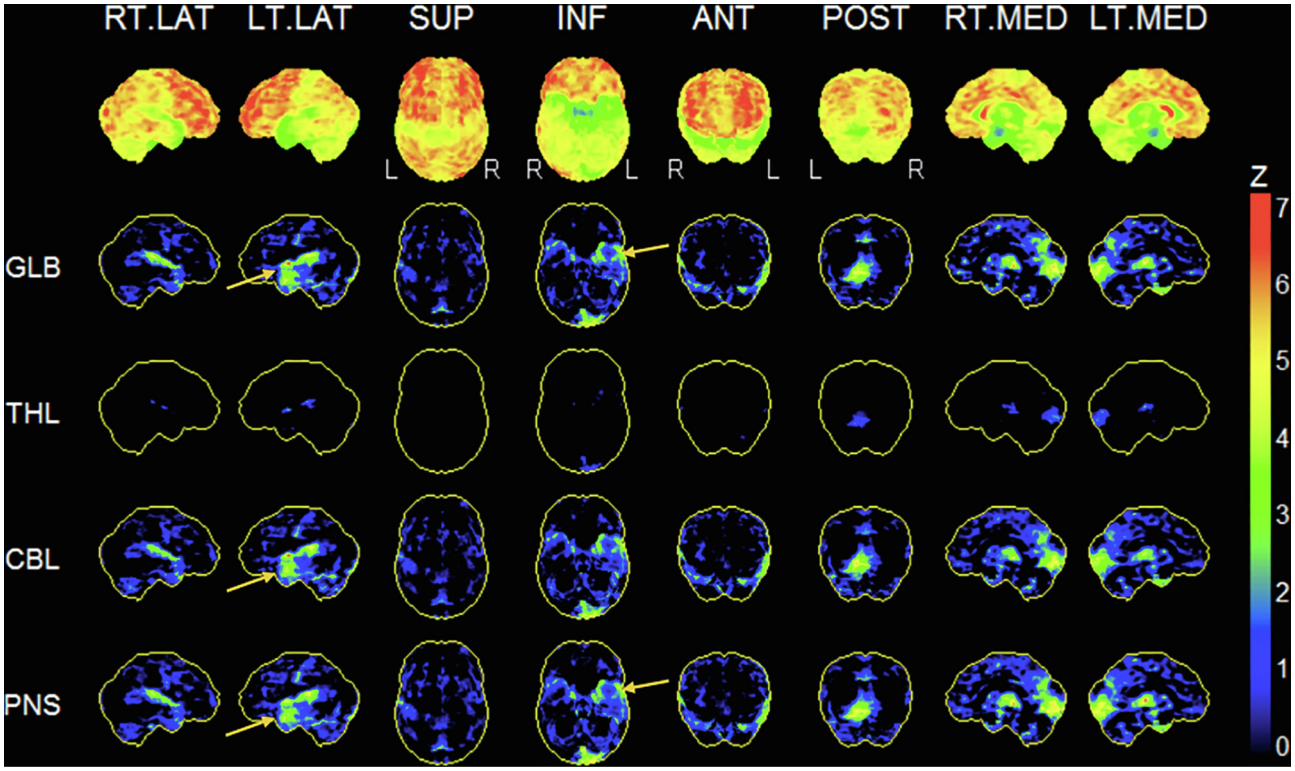

Fig. 3. Fluorine – 18- fluorodeoxyglucose positron-emission tomography / computed tomography (FDG PET/CT) 3D stereotactic surface projection and normal database comparison (Neurostat): Localized hypometabolism in the left temporal lobe (arrows). Visual cortex hypometabolism related to general anaesthesia.

mild increase in occipital slowing, and mild asymmetry of the background consistent with the prior left temporal lobectomy.

Neuro-imaging

MRIs (2018, 2019) were initially reported as not showing a malformation of cortical development or grey matter heterotopia. However on expert re-review, after video-EEG monitoring localized seizures to the left temporal region, there appeared to be some abnormalities in the left anterior temporal lobe and pole suggesting cortical dysplasia. A repeat MRI in 2019 confirmed subtle abnormalities (abnormality of left temporal pole involving white matter. There was hyperintensity and relatively unmyelinated or poor myelination of the terminal rami within the anterior temporal lobe (see Fig. 2). A PET scan showed mild diffuse hypometabolism (Fig. 3) involving the anterior and lateral left temporal lobe. Symmetrical reduced activity in the visual cortices seen may have reflected involvement of a larger network but was initially felt to be more likely related to the general anesthesia.

Epilepsy gene panel

An epilepsy gene panel detected a pathogenic loss-of-function heterozygous PCDH19 gene variant, c.2463dup and p.(Pro822Allafs*8), with the full Human Genome Variation Society nomenclature description of the variant NM_001184880.2(PCDH19):c.[2463dup];[2463 =]. Familial evaluation determined this to be a *de-novo* variant.

Surgery

An initial standard anterior temporal lobectomy was performed. Electrocorticography with a 4-contact subdural strip placed along the posterior superior margin of the resection showed epileptiform activity over two contact points. A sliver of extension was undertaken over the middle temporal gyrus to include this area in the resection. Inspection at surgery suggested gross total resection of the abnormality though confirmation by postoperative MRI imaging was not obtained. There were extra-axial fluid collections on postoperative CT scan, with a pseudo meningocele that resolved with conservative management.

Histology

The histology was consistent with a malformation of cortical development [21]. Focal cortical dysplasia (FCD Type 1b) was seen in the left medial temporal lobe and features of mild malformation of cortical development (mMCD types I and II) were seen in the lateral temporal areas (see Fig. 4).

The medial temporal lobe showed abnormal tangential cortical lamination with subtotal absence of neurons in cortical layer IV [21]. There were features of a neuronal migration disorder with persistence of neuronal precursors within the subventricular region of the temporal horn of the lateral ventricle, including subtle periventricular nodular heterotopia forming aggregates within layer II of the entorhinal cortex. There were no balloon cells or dysmorphic neurons. There was gliosis in Ammon's horn of the hippocampus, most marked within CA4, and mild granule cell dispersion in the dentate gyrus without hippocampal sclerosis. In

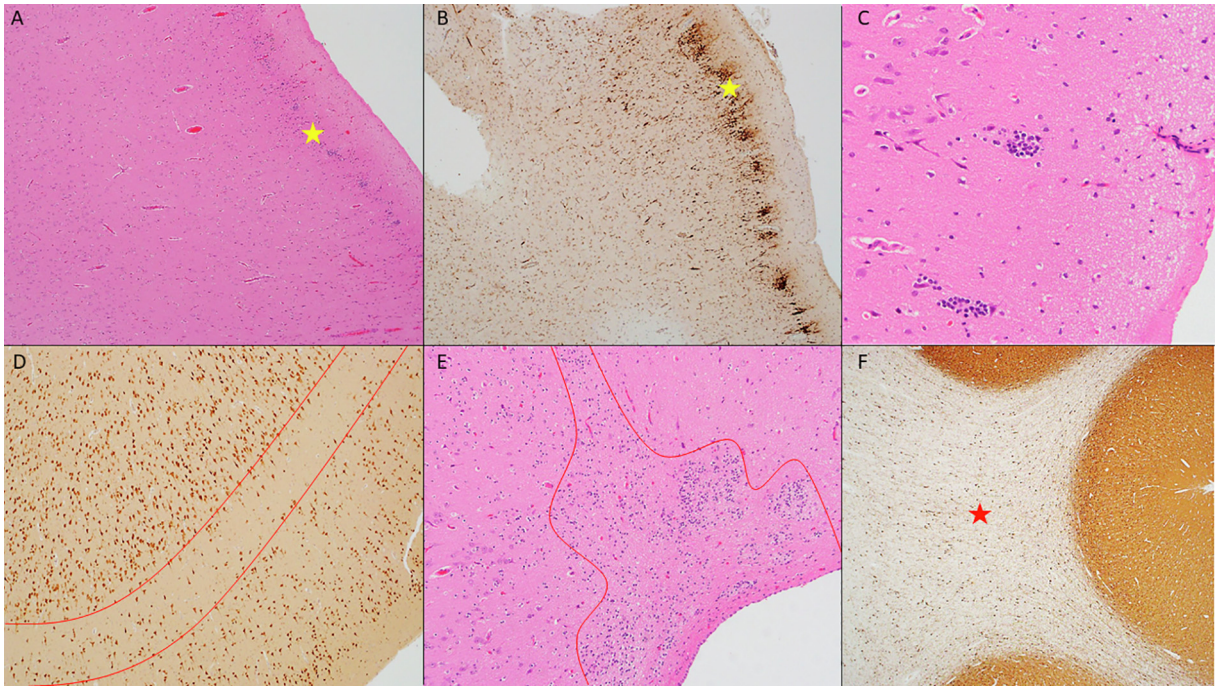

Fig. 4. Histopathology. A-C. Medial temporal lobe entorhinal cortex showing neuronal precursors forming a linear band within layer II. A. Low magnification, the asterisk is at a band of neuroblasts (H&E, 40x). B. BCL2 immunohistochemical stain highlighting band-like distribution (asterisk) of neuroblasts (BCL2, 40x). C. High magnification showing clustered neuroblasts in the region of layer II (H&E, 200x). D. Subtotal absence of neurons within cortical layer IV of the distal entorhinal cortex, more than the usual reduction in layer IV neuronal density in this region. This is sufficient for abnormal tangential lamination, or focal cortical dysplasia type 1B by the ILAE classification (NeuN immunohistochemical stain, red lines show position of layer IV, 40x). E. Persistent periventricular neuronal precursors near the temporal horn of the lateral ventricle, with linear extension into the adjacent deep temporal lobe white matter in keeping with an abnormality of neuronal migration (red lines show the distribution of the neuronal precursors, H&E, 100x). F. Increased numbers of single heterotopic neurones within the subcortical and deep white matter of the temporal lobe (asterisk), amounting for to a mild malformation of cortical development (mMCD) (MAP2A immunohistochemistry, 20x). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the anterior and posterolateral temporal regions there were increased numbers of isolated heterotopic neurons within the deep white matter (>500 μm deep to the grey-white interface) and within the cortical layer I (mMCD types I and II).

Discussion

We report a case involving epilepsy surgery in a female child with a PCDH19 mutation, showing many of the features (multiple seizure types, clustering of seizures, fever triggered seizures, drug-resistant epilepsy, epileptic encephalopathy, developmental impairment, cognitive and language delay, autism spectrum disorder) described in PCDH19 related neurodevelopmental disability [5,4,7,8,11,13,14,16,17,22,25,26,35,42]. The role of epilepsy surgery in drug-resistant genetically mediated epilepsies is still being elucidated. Success rates of epilepsy surgery varies widely among patients with different genetic causes [32]. The best outcomes are seen in those with mTOR and GATOR pathway related gene abnormalities and focal cortical dysplasia (e.g., tuberous sclerosis). There is only limited information available regarding successful surgery in drug-resistant epilepsies associated with the genetic mutations related to altered synaptic function and transmission [32]. The available literature suggests complete seizure control is not commonplace (less than 15% of cases) after epilepsy surgery of patients with gene involvement from SCN1A, SCN1B, CNTNAP2 and STBXP1 [32,40,33,2,29,11]. MRI negative patients with genetic epilepsies also have less favorable outcomes compared to MRI positive patients [32]. Lotte et al [16], in their paper entitled "Effectiveness of antiepileptic therapy in patients with PCDH 19 mutations", mention a relatively high proportion of abnormal MRI findings (focal cortical dysplasia diagnosed or suspected in several patients) but is without specific details.

The decision to undertake a temporal lobectomy in this case was challenging, and her parents played an integral role. In our experience [20] 76% of children with seizures and resective brain surgery have become seizure-free (Engel class 1) on long term follow up. A Cochrane review regarding surgery for epilepsy concluded that seizure freedom was seen in 64% of cases; however, the range of success varied from 13.5 to 92.5% [41]. Initially our patient was reported to have a normal MRI which would have reduced the chances for a successful outcome from surgery. Expert re-review revealed subtle abnormalities on the MRI. Hypometabolism in the left temporal lobe seen in the PET scan provided additional data supporting neuroimaging abnormality. The result of the gene panel testing was received after we had initiated the discussion on epilepsy surgery. There was very little literature regarding the outcome of epilepsy surgery in PCDH19 related DEE [35,36]. Kurian et al [15] assessed the occurrence of cortical malformations in early infantile epilepsy related to PCDH19 pathogenic variants. They report neuroradiological abnormalities in all five cases in their series, confirmed by histology in two. Surgery in two cases (Patients 3 and 4) resulted in improvement of seizures, but not in seizure freedom. Patient 3 had an extended temporo-parieto-occipital resection and Patient 4 had a right frontal lobe resection.

Conclusion

We report a 4 year 10-month-old girl with PCDH19 related drug-resistant epilepsy who benefited from epilepsy surgery, both regarding seizures and development. Parents report improvement in quality of life for the whole family. Our case report adds to the literature regarding the promising role of epilepsy surgery in PCDH19 related epilepsy. It also emphasizes the wide clinical spectrum and complexity associated with management of the genetic epilepsies. Future reports and larger case series detailing neurophysiology, imaging, pathology, and outcomes may help delineate the role of surgery in children with PCDH19 related epilepsy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the family for consent to publish this case report. We thank all the clinicians and health professionals involved in the management and care of this child.

References

[1] Aledo-Serrano Á, Del Ser T, Gil-Nagel A. Antiseizure medication withdrawal in seizure-free patients with PCDH19-related epilepsy: A multinational cohort survey. Seizure 2020;80:259–61.
[2] Barba C, Parrini E, Coras R, Galuppi A, Craiu D, Kluger G, et al. Co-occurring malformations of cortical development and SCN1A gene mutations. Epilepsia 2014;55(7):1009–19.
[3] Borghi R, Magliocca V, Petrini S, Conti LA, Moreno S, Bertini E, et al. Dissecting the role of PCDH19 in clustering epilepsy by exploiting patient-specific models of neurogenesis. J Clin Med 2021;10(13):2754.
[4] Breuillard D, Leunen D, Chemaly N, Auclair L, Pinard JM, Kaminska A, et al. Autism spectrum disorder phenotype and intellectual disability in females with epilepsy and PCDH-19 mutations. Epilepsy Behav 2016;60:75–80.
[5] Chemaly N, Losito E, Pinard JM, Gautier A, Villeneuve N, Arbues AS, et al. Early and long-term electroclinical features of patients with epilepsy and PCDH19 mutation. Epileptic Disord 2018;20(6):457–67.
[6] de Lange IM, Rump P, Neuteboom RF, Augustijn PB, Hodges K, Kistemaker AI, et al. Male patients affected by mosaic PCDH19 mutations: five new cases. Neurogenetics 2017;18(3):147–53.
[7] Dell'Isola GB, Vinti V, Fattorusso A, Tascini G, Mencaroni E, Di Cara G, et al. The broad clinical spectrum of epilepsies associated with protocadherin 19 gene mutation. Front Neurol 2021;12:780053.
[8] Dibbens LM, Tarpey PS, Hynes K, Bayly MA, Scheffer IE, Smith R, et al. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. Nat Genet 2008;40(6):776–81.
[9] Engel JCG, Ness PCV, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J, editor. Surgical treatment of the epilepsies. New York: Raven Press; 1993. p. 609–22.
[10] Gerosa L, Francolini M, Bassani S, Passafaro M. The role of protocadherin 19 (PCDH19) in neurodevelopment and in the pathophysiology of early infantile epileptic encephalopathy-9 (EIEE9). Dev Neurobiol 2019;79(1):75–84.
[11] Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130(3):843–52.
[12] Hoshina N, Johnson-Venkatesh EM, Hoshina M, Umemori H. Female-specific synaptic dysfunction and cognitive impairment in a mouse model of PCDH19 disorder. Science 2021;372(6539).
[13] Ikeda H, Imai K, Ikeda H, Shigematsu H, Takahashi Y, Inoue Y, et al. Characteristic phasic evolution of convulsive seizure in PCDH19-related epilepsy. Epileptic Disord 2016;18(1):26–33.
[14] Jamal SM, Basran RK, Newton S, Wang Z, Milunsky JM. Novel de novo PCDH19 mutations in three unrelated females with epilepsy female restricted mental retardation syndrome. Am J Med Genet A 2010;152A(10):2475–81.
[15] Kurian M, Korff CM, Ranza E, Bernasconi A, Lübbig A, Nangia S, et al. Focal cortical malformations in children with early infantile epilepsy and PCDH19 mutations: case report. Dev Med Child Neurol 2018;60(1):100–5.
[16] Lotte J, Bast T, Borusiak P, Coppola A, Cross JH, Dimova P, et al. Effectiveness of antiepileptic therapy in patients with PCDH19 mutations. Seizure 2016;35:106–10.
[17] Lyons S, Marnane M, Reavey E, Williams N, Costello D. PCDH19-related epilepsy: a rare but recognisable clinical syndrome in females. Pract Neurol 2017;17(4):314–7.
[18] Mancini M, Bassani S, Passafaro M. Place at the right time: how changes in protocadherins affect synaptic connections contributing to the etiology of neurodevelopmental disorders. Cells 2020;9(12):2711.
[19] Mincheva-Tasheva S, Nieto Guil AF, Homan CC, Gecz J, Thomas PQ. Disrupted excitatory synaptic contacts and altered neuronal network activity underpins the neurological phenotype in PCDH19-clustering epilepsy (PCDH19-CE). Mol Neurobiol 2021;58(5):2005–18.
[20] Nagarajan L, Lee M, Palumbo L, Lee S, Shah S, Walsh P, et al. Seizure outcomes in children with epilepsy after resective brain surgery. Eur J Paediatr Neurol 2015;19(5):577–83.

[21] Najm IM, Sarnat HB, Blümcke I. Review: The international consensus classification of Focal Cortical Dysplasia – a critical update 2018. Neuropathol Appl Neurobiol 2018;44(1):18–31.
[22] Niazi R, Fanning EA, Depienne C, Sarmady M, Abou Tayoun AN. A mutation update for the PCDH19 gene causing early-onset epilepsy in females with an unusual expression pattern. Hum Mutat 2019;40(3):243–57.
[23] Pederick DT, Richards KL, Piltz SG, Kumar R, Mincheva-Tasheva S, Mandelstam SA, et al. Abnormal cell sorting underlies the unique X-linked inheritance of PCDH19 epilepsy. Neuron 2018;97(1):59–66.e5.
[24] Rakotomamonjy J, Sabetfakhri NP, McDermott SL, Guemez-Gamboa A. Characterization of seizure susceptibility in Pcdh19 mice. Epilepsia 2020;61(10):2313–20.
[25] Rampazzo ACM, dos Santos RRP, Maluf FA, Simm RF, Marson FAL, Ortega MM, et al. Dravet syndrome and Dravet syndrome-like phenotype: a systematic review of the SCN1A and PCDH19 variants. Neurogenetics 2021;22(2):105–15.
[26] Samanta D. PCDH19-related epilepsy syndrome: a comprehensive clinical review. Pediatr Neurol 2020;105:3–9.
[27] Serratto GM, Pizzi E, Murru L, Mazzoleni S, Pelucchi S, Marcello E, et al. The epilepsy-related protein PCDH19 regulates tonic inhibition, GABA(A)R kinetics, and the intrinsic excitability of hippocampal neurons. Mol Neurobiol 2020;57(12):5336–51.
[28] Shibata M, Ishii A, Goto A, Hirose S. Comparative characterization of PCDH19 missense and truncating variants in PCDH19-related epilepsy. J Hum Genet 2021;66(6):569–78.
[29] Skjei KL, Church EW, Harding BN, Santi M, Holland-Bouley KD, Clancy RR, et al. Clinical and histopathological outcomes in patients with SCN1A mutations undergoing surgery for epilepsy. J Neurosurg Pediatr 2015;16(6):668–74.
[30] Smith L, Singhal N, El Achkar CM, Truglio G, Rosen Sheidley B, Sullivan J, et al. PCDH19-related epilepsy is associated with a broad neurodevelopmental spectrum. Epilepsia 2018;59(3):679–89.
[31] Specchio N, Curatolo P. Developmental and epileptic encephalopathies: what we do and do not know. Brain 2021;144(1):32–43.
[32] Stevelink R, Sanders MW, Tuinman MP, Brilstra EH, Koeleman BP, Jansen FE, et al. Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review. Epileptic Disord 2018;20(2):99–115.
[33] Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, et al. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med 2006;354(13):1370–7.
[34] Trivisano M, Lucchi C, Rustichelli C, Terracciano A, Cusmai R, Ubertini GM, et al. Reduced steroidogenesis in patients with PCDH19-female limited epilepsy. Epilepsia 2017;58(6):e91–5.
[35] Trivisano M, Pietrafusa N, Terracciano A, Marini C, Mei D, Darra F, et al. Defining the electroclinical phenotype and outcome of PCDH19-related epilepsy: A multicenter study. Epilepsia 2018;59(12):2260–71.
[36] Trivisano M, Specchio N. Focal cortical dysplasia in genetic epilepsy: new insights from PCDH19-related epilepsy. Dev Med Child Neurol 2018;60(1):11–2.
[37] Tsai T-C, Sikora M, Xia P, Colak-Champollion T, Knaut H, Heisenberg C-P, et al. An adhesion code ensures robust pattern formation during tissue morphogenesis. Science 2020;370(6512):113–6.
[38] van Roest A, Van de Vel A, Lederer D, Ceulemans B. The clinical and genetic spectrum in infants with (an) unprovoked cluster(s) of focal seizures. Eur J Paediatr Neurol 2020;24:148–53.
[39] Vlaskamp DRM, Bassett AS, Sullivan JE, Robblee J, Sadleir LG, Scheffer IE, et al. Schizophrenia is a later-onset feature of PCDH19 Girls Clustering Epilepsy. Epilepsia 2019;60(3):429–40.
[40] Weckhuysen S, Marsan E, Lambrecq V, Marchal C, Morin-Brureau M, An-Gourfinkel I, et al. Involvement of GATOR complex genes in familial focal epilepsies and focal cortical dysplasia. Epilepsia 2016;57(6):994–1003.
[41] West S, Nevitt SJ, Cotton J, Gandhi S, Weston J, Sudan A, et al. Surgery for epilepsy. Cochrane Database Syst Rev 2019;6(6):Cd010541.
[42] Yang Li, Liu J, Su Q, Li Y, Yang X, Xu L, et al. Novel and de novo mutation of PCDH19 in girls clustering epilepsy. Brain Behav 2019;9(12):e01455.