■ Clinical commentary

*Epileptic Disord 2021; 23 (1): 167-172*

Epileptic Disorders

# Clinical seizure manifestations in the absence of synaptic connections

Emma Macdonald-Laurs [1], Catherine A. Bailey [1], Sarah Barton [1,2,3], Joseph Yuan-Mou Yang [2,3,4], Simone Mandelstam [2,3,5], Duncan Macgregor [2,3,6], Paul J. Lockhart [2,3], Richard J. Leventer [1,2,3], Wirginia J. Maixner [2,3,4], A. Simon Harvey [1,2,3]

[1] Department of Neurology, The Royal Children's Hospital, Parkville, Victoria, Australia
[2] The University of Melbourne, Parkville, Victoria, Australia
[3] Murdoch Children's Research Institute, Parkville, Victoria, Australia
[4] Department of Neurosurgery, The Royal Children's Hospital, Parkville, Victoria, Australia
[5] Department of Medical Imaging, The Royal Children's Hospital, Parkville, Victoria, Australia
[6] Department of Anatomical Pathology, The Royal Children's Hospital, Parkville, Victoria, Australia

Received June 8, 2020;
Accepted October 20, 2020

**ABSTRACT** – We report a child with a history of temporal-parietal-occipital disconnection for epilepsy secondary to posterior quadrantic dysplasia who developed recurrent and prolonged bouts of distress and autonomic disturbance associated with EEG and PET evidence of status epilepticus confined to his disconnected cortex. These bouts were refractory to antiseizure medications but resolved following resection of the disconnected cortex. In the absence of synaptic connections, we hypothesise that his seizure-related symptoms were mediated either by neurochemical transmission in preserved vascular and lymphatic channels or by ephaptic transmission to trigeminal nerve fibres in overlying dura, producing symptoms akin to migraine. The case highlights potential means by which seizures may manifest clinically, without synaptic connections, and adds to the differential for symptoms post-disconnection surgery.

**Key words:** epilepsy; migraine; neurochemistry; neurosurgery

• **Correspondence:**
Emma Macdonald-Laurs
Department of Neurology, Royal Children's Hospital, 50 Flemington Road, Parkville, VIC, 3052, Australia
<emma.macdonald-laurs@rch.org.au>

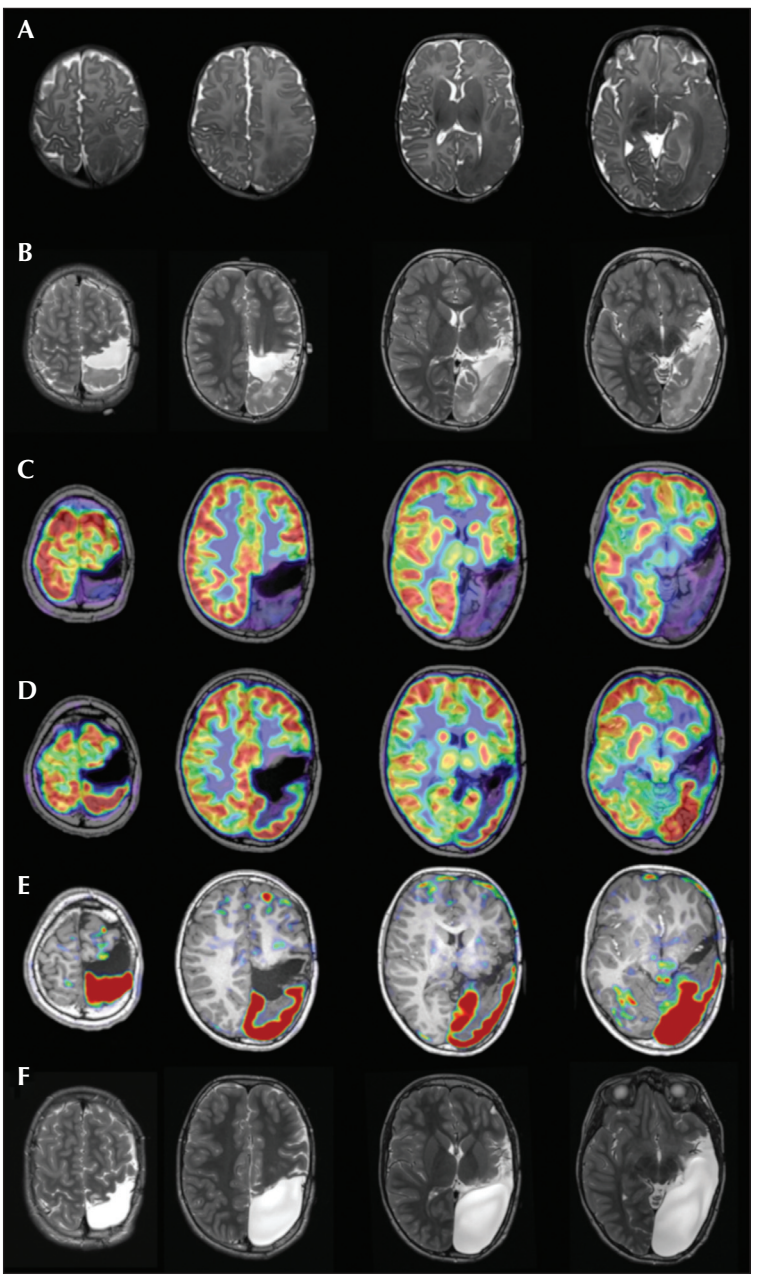
doi:10.1684/epd.2021.1252

In multilobar and hemispheric epileptic syndromes, disconnection rather than resection is often preferred, due to fewer postoperative complications [1]. Disconnected epileptic cortex survives on its vascular pedicle and continues to produce electrographic seizures, but without clinical manifestations given the absence of synaptic connections with the remainder of the brain. Postoperative seizures suggest incomplete disconnection, remote pathology or secondary epileptogenesis [2].

We report a child with symptomatic bouts of status epilepticus in his disconnected and dysplastic posterior cortex in whom clinical manifestations ceased only after the disconnected cortex was resected. We postulate mechanisms by which his electrographic seizures were clinically manifest in the absence of synaptic connections.

## Case study

We report an 11-year-old boy with intellectual disability, autism and mild right hemiparesis who presented at age four days with focal and tonic seizures. EEG showed burst-suppression in the left posterior quadrant and MRI demonstrated enlargement, cortical thickening and signal change involving the left temporo-parieto-occipital (TPO) lobes (*figure 1A*) . TPO disconnection was performed in two stages, at ages of two and seven months, to the level of the central sulcus anteriorly (*figure 1B*).




■ **Figure 1.** Axial MRI and PET imaging before and after disconnection and resection of the dysplastic left temporal-parietal-occipital lobes (all MRI acquired at 3T; axial images are in radiological view from superior to inferior). (A) T2-weighted MRI at age one month showing cortical dysplasia throughout the left temporal, parietal and occipital lobes. (B) T2-weighted MRI at age nine years and five months, showing the disconnected and dysplastic left posterior quadrant and the normal-appearing cortex in the left frontal lobe and right hemisphere. (C) FDG-PET overlaid on co-acquired T1-weighted MRI at age eight years during an asymptomatic period, showing hypometabolism of the left temporal, parietal and occipital lobes and normal metabolism in the left insula, basal ganglia and frontal lobe and the right hemisphere. (D) FDG-PET overlaid on co-acquired T1-weighted MRI at age nine years and five months during a typical bout, showing hypermetabolism of the left temporal, parietal and occipital lobes and normal metabolism in the left insula, basal ganglia and frontal lobe and the right hemisphere. (E) Subtraction FDG-PET coregistered with T1-weighted MRI accentuating the bout-related hypermetabolism in the left temporal, parietal and occipital lobes and absence of significant metabolic change elsewhere. (F) T2-weighted MRI at age nine years and 10 months, showing resection of the left temporal, parietal and occipital lobes.

Histopathology revealed focal cortical dysplasia (FCD) type IIb. Genetic testing identified a mosaic somatic variant in *PIK3CA* [NM_006218.4:c.3140A>G: p.(His1047Arg)], pathogenic for brain overgrowth syndromes.

Post-operatively, he was seizure-free and antiseizure medications (ASM) were ceased. Early postoperative EEGs showed periodic interictal epileptiform discharges (IEDs) over the left posterior quadrant and normal rhythms elsewhere.

At age 3.5 years, he began having bouts of distress, potentially due to headache, during which he would hold his head, scream and have intermittent eye deviation, facial pallor, anorexia, vomiting and somnolence. These lasted several hours, occurred multiple times per day for one to four weeks, recurred every two to six months, and often prompted hospitalisation for distress, obtundation and weight loss.

Four video-EEG recordings performed during typical bouts at ages 4.9, 5.7, 7.2, and 8.3 years each demonstrated electrographic seizures every few minutes in his left posterior quadrant (*figure 2B*). Four recordings performed during asymptomatic periods at ages 4.3, 5.6, 6.4 and 8.0 years each showed periodic IEDs in the left posterior quadrant, without electrographic seizures (*figure 2A*). In no recordings was there propagation of electrographic seizures or IEDs to the left frontal region or right hemisphere. Some recordings showed independent IEDs in the left central, right frontal and right occipital regions, similar in appearance to the IEDs of self-limited focal epilepsies of childhood.

3T MRI, performed at ages 5.6, 6.4, 8.0 and 9.4 years (*figure 1B*), showed no evidence of dysplasia in the left frontal or insula lobes, and complete TPO disconnection (*supplementary figure 1*). No MRI showed ventricular dilation suggestive of raised intracranial pressure.

Seed-based, probabilistic fibre tracking [3], from multiple regions in the left TPO lobes, showed no residual fibre connections. Compared to conventional diffusion tensor imaging (DTI) that models per MRI voxel single fibre orientation, our tractography utilised multi-tissue constrained spherical deconvolution [4, 5] that estimates white matter microstructural organisation more accurately over crossing-fibre brain regions [6], as well as minimises false reconstructions due to modelling of non-white matter brain tissues or CSF.

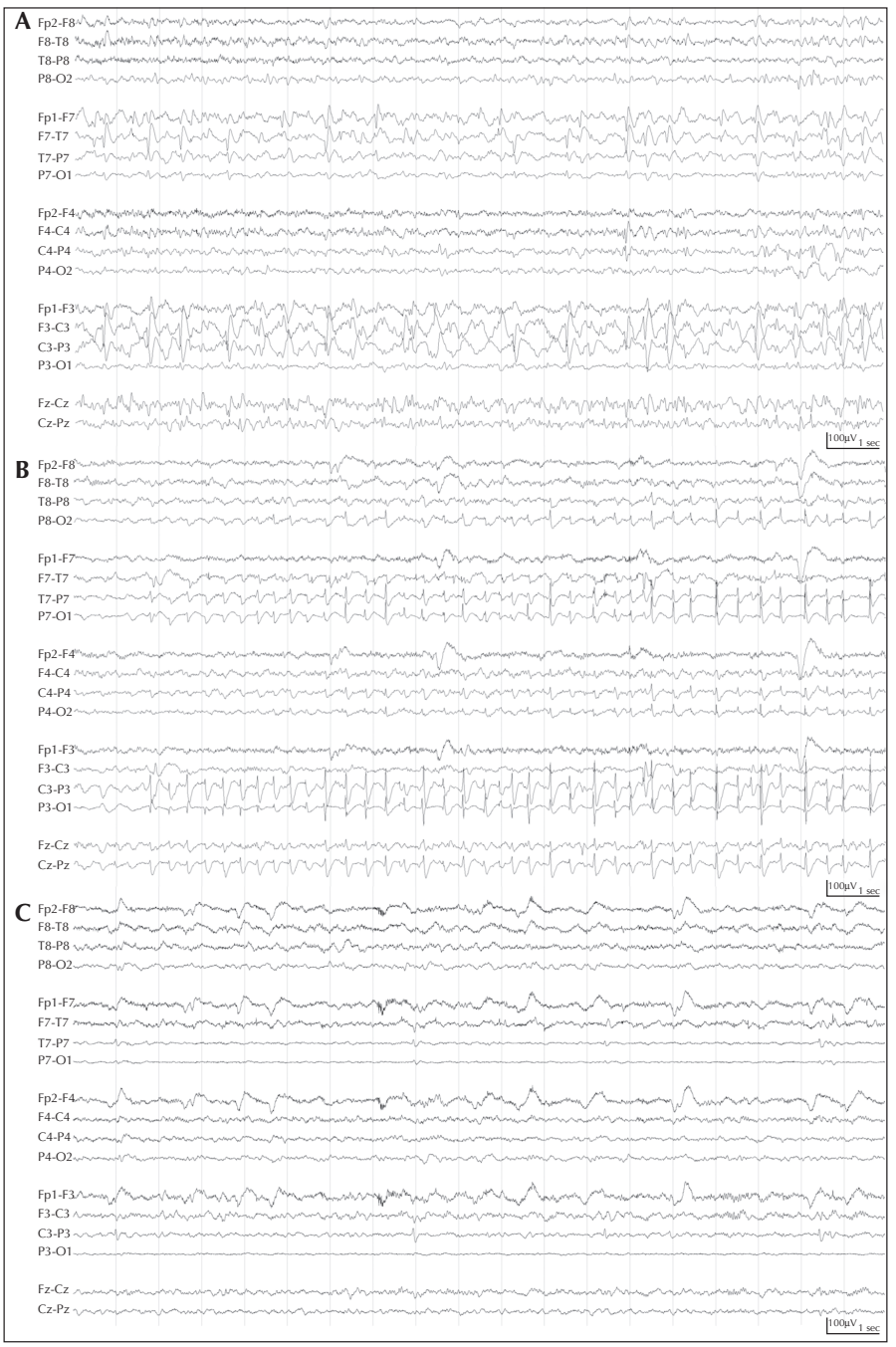
FDG-PET was performed at age 8.0 years, during an asymptomatic period with only left posterior quadrant IEDs on EEG (*figure 1C*), and at age 9.5 years, during a typical bout in which six left posterior quadrant seizures lasting 1-3 minutes occurred during the half hour following FDG injection (*figure 1D*). PET during the asymptomatic period showed marked hypometabolism and PET during the bout showed marked hypermetabolism in the disconnected left TPO lobes; the difference emphasized with subtraction (*figure 1E*). Normal metabolism with no change was seen in the left basal ganglia, insula and frontal lobe, and right hemisphere.

Several ASMs were trialled over the years, some given intravenously during bouts, without clinical or EEG improvement. During this period, he had two further surgeries. The first at age 5.3 years was a small corticectomy of residual medial postcentral gyrus, anterior to the disconnection margin, completing the disconnection to the level of the central sulcus throughout. The second, at age 6.2 years, was a resection of some residual amygdala tissue at the disconnection margin. Histopathology was negative from both surgeries and the bouts of distress continued. At age 9.5 years, he underwent resection of the disconnected left TPO lobes. No neural or glial connections were identified along the previous disconnection planes, only pial strands and blood vessels.

No further bouts occurred during the two years following the left TPO resection. His general health, weight and behaviour improved, and his ASMs were reduced to clobazam monotherapy, continued for behaviour management. A 120-hour EEG performed three months after TPO resection showed absent EEG activity in the left posterior quadrant and normal background activity over the left frontal region (*figure 2C*). Stereotyped, sleep-activated IEDs were recorded in the left central and right occipital regions as seen on his previous EEGs. MRI, three months following TPO resection, showed removal of the left TPO lobes to the level of the central sulcus and lateral fissure, and normal-appearing left insula and frontal lobe (*figure 1F*).

## Discussion

The child's recurrent and prolonged bouts of presumed pain with autonomic dysfunction were temporally associated with electrographic and metabolic evidence of status epilepticus in his disconnected left TPO lobes, the ictal EEG and FDG-PET abnormalities not being present when he was asymptomatic. Thus, his bouts were clearly related to the prolonged periods of recurrent electrographic seizures. However, no residual neural connections were evident on conventional anatomical MR imaging, on tractography exploration, or at surgery. Additionally, there was no evidence of left frontal, left insular or right hemispheric seizure activity on ictal EEG or ictal PET, or dysplasia on MRI. It is unlikely that his symptoms were of left basal ganglia origin, in the absence of ictal dystonia and basal ganglia hypermetabolism. The resolution of the bouts following resection of the disconnected, dysplastic




■ **Figure 2.** Examples of EEG recordings before and after disconnection and resection of the dysplastic left temporal-parietal-occipital lobes. (A) EEG performed awake during an asymptomatic period at age eight years, showing continuous slowing and sharp-slow wave discharges over the right hemisphere, maximal in the centrotemporal region. Independent right occipital and centrotemporal spikes are seen in the latter few seconds. (B) EEG performed during a typical bout at age nine years and five months, showing electrographic seizure activity in the left posterior quadrant with a field to the right posterior quadrant. A left centro-temporal spike is seen in the 14th second. (C) EEG performed awake following resection of the left temporo-parieto-occipital lobes, showing attenuation of the background rhythms over the left posterior quadrant without the previous sharp-slow-wave discharges and electrographic seizures. Intermittent, sleep activated, left centro-temporal and right occipital discharges (not shown) remained.

and periodically seizing cortex is compelling evidence that intermittent status epilepticus in the left TPO lobes was the basis of his symptoms. However, it is difficult to understand the mechanism by which he was symptomatic in the absence of synaptic connections between his left TPO lobes and the rest of his brain. Seizure-related activation of the trigemino-vascular system by cortical spreading depression (CSD)-triggered neurochemical release or ephaptic transmission are possible mechanisms.

CSD, a propagating wave of transient hyperexcitability followed by sustained hypoexcitation, is a well understood mechanism of migraine. CSD results in stimulation of the trigemino-vascular system via vasodilation of local dural and pial blood vessels and release of proinflammatory molecules and neuropeptides, such as calcitonin gene-related peptide (CGRP), leading to pain and autonomic dysfunction [7]. Seizures and CSD can co-occur and facilitate each other. Ictal and postictal migraine occur in occipital and temporal lobe seizures, the posterior cortex being more susceptible to initiation of CSD than other brain regions [7]. Subclinical, posterior cortex seizure activity is postulated as the basis of the migraine-like or stroke-like episodes in Sturge-Weber syndrome [8]. It is possible that seizure-related CSD in the disconnected left TPO lobes resulted in release of neurochemicals which travelled through preserved arterial, venous or meningeal lymphatic pathways, or into the subarachnoid space, to activate the trigemino-vascular system [7].

Another potential mechanism is ephaptic stimulation of trigeminal nerve fibres in the dura of the middle cranial fossa, by high-voltage seizure activity in the left temporal lobe, causing sustained trigemino-vascular disturbance. Such non-synaptic communication between nerve cells is postulated to mediate hemifacial spasm, hemifacial seizures in infants with cerebellar ganglioglioma [9] and ipsilateral ictal blinking in patients with epileptogenic lesions in the middle cranial fossa [10].

Migraine-like episodes, occurring because of seizure activity in disconnected cortex, are reported in the literature and may be under-recognised. Four of 24 children in a hemispherotomy series developed ``migraines'' following surgery, most of whom had dysplasia [1]. Fusco *et al*. reported a patient with Rasmussen syndrome who developed ``migraines'' two years following hemispherotomy which were associated with sub-continuous seizure activity in the disconnected hemisphere and SPECT hyperperfusion in the occipital lobe during the migraine, suggesting it was related to seizure activity in the disconnected occipital cortex [11].

## Conclusion

Our and the aforementioned cases demonstrate how seizure activity following disconnection may manifest with migraine-like episodes, through possible neurochemical or ephaptic, rather than synaptic, transmission. In our case, the tight correlation of symptoms with EEG and PET evidence of seizures, the absence of residual neural connections, and the resolution of symptoms following resection of disconnected cortex provide evidence for such a phenomenon and add to the diagnostic possibilities for neurological episodes following disconnection surgery. ■

**Supplementary data.**
Supplementary figure is available on the www.epilepticdisorders.com website.

**Acknowledgements and disclosures.**
We are grateful for the support of the Australian Government National Health and Medical Research Council GNT1128933, the Murdoch Children's Research Institute, the Campbell Edwards Trust and the Brain Foundation and the Victorian Government Operational Infrastructure Support Program.
None of the authors have any conflict of interest to declare.

## References

1. Basheer SN, Connolly MB, Lautzenhiser A, Sherman EMS, Hendson G, Steinbok P. Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function. *Epilepsia* 2007; 48: 133-140.

2. 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.

3. Yang JY-M, Beare R, Seal ML, Harvey AS, Anderson VA, Maixner WJ. A systematic evaluation of intraoperative white matter tract shift in pediatric epilepsy surgery using high-field MRI and probabilistic high angular resolution diffusion imaging tractography. *J Neurosurg Pediatr* 2017; 19: 592.

4. Tournier JD, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *NeuroImage* 2007; 35: 1459-72.

5. Dhollander T, Raffelt D, Connelly A. *Unsupervised 3-tissue response function estimation from single-shell or multi-shell diffusion MR data without a co-registered T1 image*. ISMRM Workshop on Breaking the Barriers of Diffusion MRI 2016. Lisbon, Portugal.

6. Tournier J-D, Calamante F, Connelly A. MRtrix: diffusion tractography in crossing fiber regions. *Int J Imag Syst Tech* 2012; 22: 53-66.

7. Parisi P, Striano P, Kasteleijn D, Verrotti A, Martelletti P, Villa M, *et al*. Ictal epileptic headache: recent concepts for new classifications criteria. *Cephalalgia* 2012; 32: 723-4.

8. Sethi M, Kowalczyk MA, Dalic LJ, Archer JS, Jackson GD. Abnormal neurovascular coupling during status epilepticus migrainosus in Sturge-Weber syndrome. *Neurology* 2017; 88: 209-11.

9. Harvey AS, Arzimanoglou A. Cerebello-pontine hamartoma. In: Arzimanoglou, A, Cross, JH, Gaillard, WD, Holthausen, H, Jayakar, P, Kahane, P & Mathern, G (eds.) *Pediatric Epilepsy Surgery*. Montrouge: John Libbey Eurotext, 2016.

10. Jadhav T, Bailey C, Maixner W, Harvey AS. Ictal unilateral blinking is an unreliable lateralizing sign in tuberous sclerosis complex. *Epilepsy Res* 2016; 125: 58-61.

11. Fusco L, Specchio N, Ciofetta G, Longo D, Trivisano M, Vigevano F. Migraine triggered by epileptic discharges in a Rasmussen's encephalitis patient after surgery. *Brain Dev* 2011; 33: 597-600.

## TEST YOURSELF

**(1) What are the potential reasons for persistent seizures or seizure-related symptoms following peri-insular hemispherotomy for hemispheric FCD1 during early childhood?**

A. Incomplete fronto-basal disconnection
B. Basal ganglia involvement
C. Non-synaptic transmission
D. Neurochemically-mediated
E. Ephaptic transmission

**(2) How is cortical spreading depression (CSD) related to epileptic seizures?**

A. CSD may be facilitated by epileptic seizures
B. Epileptic seizures may facilitate CSD
C. Ictal and postictal migraine may be related to CSD
D. CSD is involved in all epileptic seizures
E. None of the above

*Note: Reading the manuscript provides an answer to a ll questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".*