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Hemispheric polymicrogyria and neonatal seizures: a potentially life-threatening combination

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ABSTRACT – Polymicrogyria (PMG) is a heterogeneous malformation of cortical development characterized by excessive gyration and abnormal cortical lamination. Typically, bilateral forms have more severe developmental delay and early-onset epilepsy, but the full spectrum of severity remains ill-defined. We report two cases of right hemispheric PMG and neonatal-onset, drug-resistant seizures culminating in early death. Case 1 began having seizures on Day 1 of life that intensified in severity and proved resistant to numerous antiepileptic drugs. He underwent right functional hemispherectomy but died three weeks post-operatively due to ongoing seizures. Case 2 presented with seizures on Day 3 of life and required respiratory support for prolonged ictal apnoeas. Seizures were resistant to antiepileptic drugs and eventually led to respiratory arrest, once aggressive resuscitative measures were withdrawn. In both cases, seizures seemingly originated independently in both hemispheres. These cases represent a severe phenotype of unilateral hemispheric PMG with bilateral seizures.

Key words: polymicrogyria, seizure, apnoea, unilateral, hemispherectomy

Polymicrogyria (PMG) is a malformation of cortical development characterized by numerous small gyri separated by shallow sulci with abnormal cortical lamination. MRI shows an abnormal gyral pattern with an irregular cortical surface, apparent cortical thickening, and a stippled grey-white junction (Leventer *et al*., 2010). The aetiology remains poorly understood, with evidence for both genetic and non-genetic aetiologies. The topographic extent of PMG is variable, leading to a spectrum of signs and symptoms. Bilateral forms of PMG generally have a more severe phenotype, with earlier-onset epilepsy and more severe developmental delay than unilateral forms. Median age at seizure onset in unilateral perisylvian PMG (8-11 years) is significantly higher than that of bilateral perisylvian PMG (three years) and generalized PMG (8-12 months) (Leventer *et al*., 2010;

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Shain *et al.*, 2013). Unilateral PMG is usually perisylvian in location and typically manifests with mild-to-moderate congenital hemiparesis and focal motor seizures (Pascual-Castroviejo *et al.*, 2001). However, the full spectrum of unilateral PMG is poorly defined, especially more severe forms with extensive hemispheric involvement. Here, we present two patients with right hemispheric PMG and neonatal onset of drug-resistant, bilateral seizures, leading to early death.

Case study 1

This male was the product of a normal pregnancy, born in good condition at 41 weeks by elective Caesarean section, with a birth weight of 4 kg. Family history was unremarkable. Seizures began on Day 1 with breath-holding events occurring two to three times per day and lasting 30 seconds. He was hospitalised for three weeks and treated with phenytoin and phenobarbitone. By 6 weeks of age, the seizures had become more prolonged, occurring multiple times weekly. They were characterized by eye deviation, bradycardia, cyanosis, apnoea, right arm jerking, and generalized tonic stiffening. Seizures were resistant to multiple antiepileptic drugs including sodium valproate, phenytoin, carbamazepine, vigabatrin, and lamotrigine, leading to repeated hospitalisations and admissions to intensive care.

By 3 months of age, there was severe global developmental delay. Head circumference was 42 cm (50th percentile). There were no dysmorphic features. Visual fixation and following was not sustained and there was an intermittent left esotropia. There was axial and appendicular hypotonia, poor head control, and minimal purposeful hand use. There was no evidence of hemiparesis.

Brain MRI at age 11 weeks showed right hemispheric polymicrogyria with no abnormality on the left and no other brain malformations (*figure 1*). PET scan showed right temporal, parietal, and central hypometabolism. Investigations including those for electrolytes and plasma amino acids, liver function tests, and urine metabolic screening were normal.

Interictal EEGs in the early neonatal period were normal. Video-EEG monitoring at age 11 weeks showed normal background without interictal epileptiform discharges and captured seizures with choreiform-like movements, leftward head rotation and eye deviation, unresponsiveness, and cyanosis. Ictal EEG showed no change early during the seizures, but showed pseudoperiodic, sharp slow-wave complexes late during the seizures in the left anterior temporal region for several minutes (*figure 2A, B*). Seizures lasted up to 20 minutes. Seizures remained drug-resistant and life-threatening, such that he underwent right functional hemispherectomy at age 4 months. Histopathology showed multiple small gyri, fusion of the molecular layer, and a two-layered cortex in right central and lateral

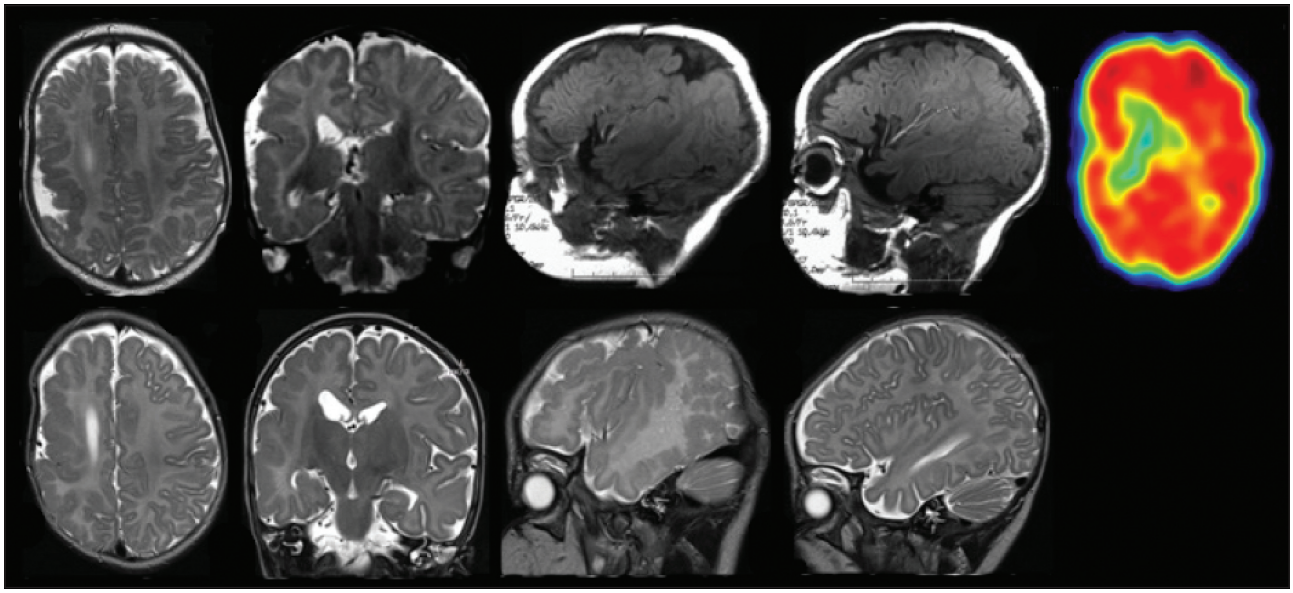

Figure 1. Brain magnetic resonance and FDG PET imaging of Case 1 (upper row) and Case 2 (lower row).
MR images (from left to right) are axial and coronal T2, and sagittal T1 and T2 sequences. MR imaging shows extensive right hemispheric PMG, maximal in the perisylvian region along an abnormally extended and Sylvian fissue, and extending well into the frontal, parietal, and temporal lobes. The images fourth from the left of each row show the apparently normal contralateral left hemisphere with normal Sylvian fissure morphology and no evidence of PMG. An axial FDG PET image from Case 1 (upper right) shows significant right hemisphere hypometabolism, maximum in the right perisylvian and insular regions.

temporal specimens, consistent with PMG and right hippocampal sclerosis.

There were a few focal seizures on the first post-operative day, with rhythmic movements of the right arm and leg and eye deviation. There was a prolonged 30-minute seizure post-operatively with tachycardia, hypertension, and generalized tonic stiffening. Seizure control improved prior to discharge. However, within two weeks of hemispherectomy he was re-admitted to the intensive care unit with refractory life-threatening seizures similar to his pre-operative events, occurring in long clusters of 50-90 minutes.

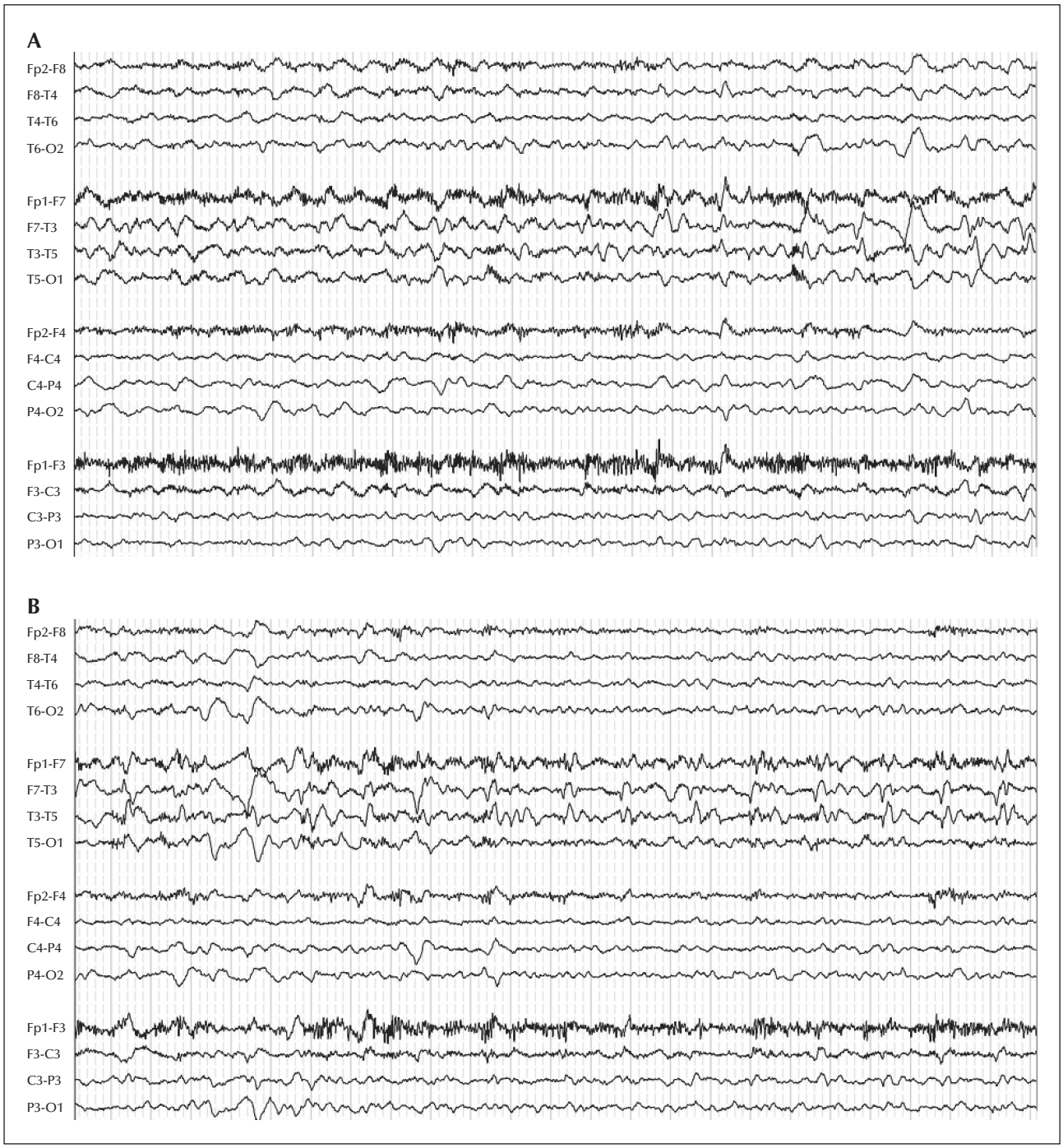

Figure 2. Video-EEG monitoring performed at age 11 weeks in Case 1 showing a left temporal seizure that commenced with a build-up of left temporal rhythmic theta-delta activity (A) that evolved to periodic high amplitude left temporal sharp and sharp-slow activity (B).

The patient died three weeks post-operatively when aggressive ventilatory support for seizures was withdrawn. Post-mortem examination was not performed.

Case study 2

This male was the product of a normal pregnancy, born in good condition at 40 weeks of gestation by uncomplicated spontaneous vaginal delivery, with a birth weight of 4.4 kg. Family history was unremarkable.

Seizure onset occurred on Day 3 and initially manifested with upward eye deviation, lip smacking, and dystonic posturing, and seizures were resistant to treatment with intravenous phenobarbital. Seizures evolved to longer episodes, up to 45 minutes duration, though most were one to two minutes with a frequency of one to six per day. At 5 weeks of age, he was admitted to the intensive care unit with status epilepticus requiring intubation. Typical events then consisted of behavioural arrest, tonic stiffening, profound cyanosis, oxygen desaturations to 40-60%, and apnoea or irregular breathing requiring oxygen, stimulation, bag-valve mask ventilation, and intranasal midazolam. Heart rate remained stable ictally. On some occasions, there was eye deviation to the right and right arm jerking.

By 3 months of age, there was significant global developmental delay. Head circumference was 39.5 cm (10^{th} percentile). There were no dysmorphic features. There was intermittent visual fixation and following. There was axial and appendicular hypotonia and poor head control with mild left-sided weakness. Nasogastric tube feeding was required.

Life-threatening apnoeic seizures remained resistant to trials of phenobarbitone, phenytoin, leviteracetam, clonazepam, midazolam, vigabatrin, sodium valproate, topiramate, zonisamide, high-dose steroids, and a ketogenic diet.

MRI showed right hemispheric polymicrogyria with no visible abnormality in the left hemisphere and no other brain malformations (*figure 1*).

Investigations including those for electrolytes, urine organic acids, plasma amino acids, very long chain fatty acids, and common mitochondrial point mutations and *POLG* mutations, as well as liver function tests, urine metabolic screening, CSF analysis (cell count, protein, glucose, lactate, and amino acids), chromosome microarray, and CMV PCR from the neonatal blood spot were all normal. Later, whole-exome sequencing did not reveal any mutations in known genes associated with PMG.

Interictal EEGs showed right posterior quadrant slowing and epileptiform activity during wakefulness, and independent bilateral epileptiform activity during sleep (*figure 3A*) . Video-EEG monitoring at 9 weeks of age captured three subclinical, electrographic seizures with left central rhythmic theta activity lasting 20-30 seconds. Four electroclinical seizures were captured consisting of motionless staring, typically with lateralized head and eye deviation and prolonged apnoea/cyanosis. Ictal onset was right temporal in one (*figure 3B*), left temporal in two (*figure 3C*), and left central in one. The longer seizures with pronounced apnoea and desaturations showed contralateral spread. Video-EEG monitoring at 14 weeks captured five electroclinical seizures with profound desaturations to 40-80% despite ongoing respiratory effort, motionless staring, and cycling movements. The electrographic changes began with rhythmic delta over the left hemisphere and subsequent sharp and fast activity over the left temporal area. No independent right hemisphere seizures were recorded on this occasion.

The child died due to pneumonia and respiratory arrest after a decision to withdraw aggressive resuscitation efforts at 4 months of age. Post-mortem examination limited to the brain showed bilateral hippocampal sclerosis and extensive PMG in the right hemisphere, manifesting with microgyration and fusion of the molecular layer and areas of both four-layered and poorly laminated cortex, sparing the right frontal pole and most of the right occipital lobe. There were no areas of left hemisphere cortical malformation or other brain abnormalities.

Discussion

The variable extent and topography of PMG leads to phenotypic diversity, making prognostication a challenge. It is generally accepted that patients with isolated focal PMG have milder symptoms than those with more extensive and bilateral PMG, PMG associated with other brain malformations, or PMG associated with a severe underlying aetiology such as a genetic syndrome, a metabolic disorder, or congenital CMV infection. In contrast, the two cases we describe suggest that isolated, non-syndromic, extensive unilateral PMG presenting with seizures in the neonatal period can have a devastating outcome.

While PMG is known to be a highly epileptogenic cortical malformation, little is known about the seizure manifestations of these lesions (Teixeira *et al*., 2007; Leventer *et al*., 2010). The epilepsy presentation of patients with varying topographic patterns of PMG has been explored in a large multi-centre cohort (Shain *et al*., 2013). Twenty-six patients in the cohort had extensive multlilobar unilateral lesions; 96% of these had focal epilepsies with a median age at onset of 3 years (Shain *et al*., 2013). There was a preponderance of right hemisphere lesions among the unilateral cases.

Notably, most of these had concordant seizure lateralization to the MRI abnormality, unlike the patient in Case 2. In another large unilateral PMG cohort, 80% of patients had focal motor seizures with and without secondary generalization, with a mean age at seizure onset of 6.5 years (Caraballo *et al*., 2013). Of this group, 65% eventually developed encephalopathy with status epilepticus during sleep (ESES) but prognosis was generally favourable, with most reaching full remission (Caraballo *et al*., 2013). We have not identified any reports of seizure severity to the extent seen in our cases.

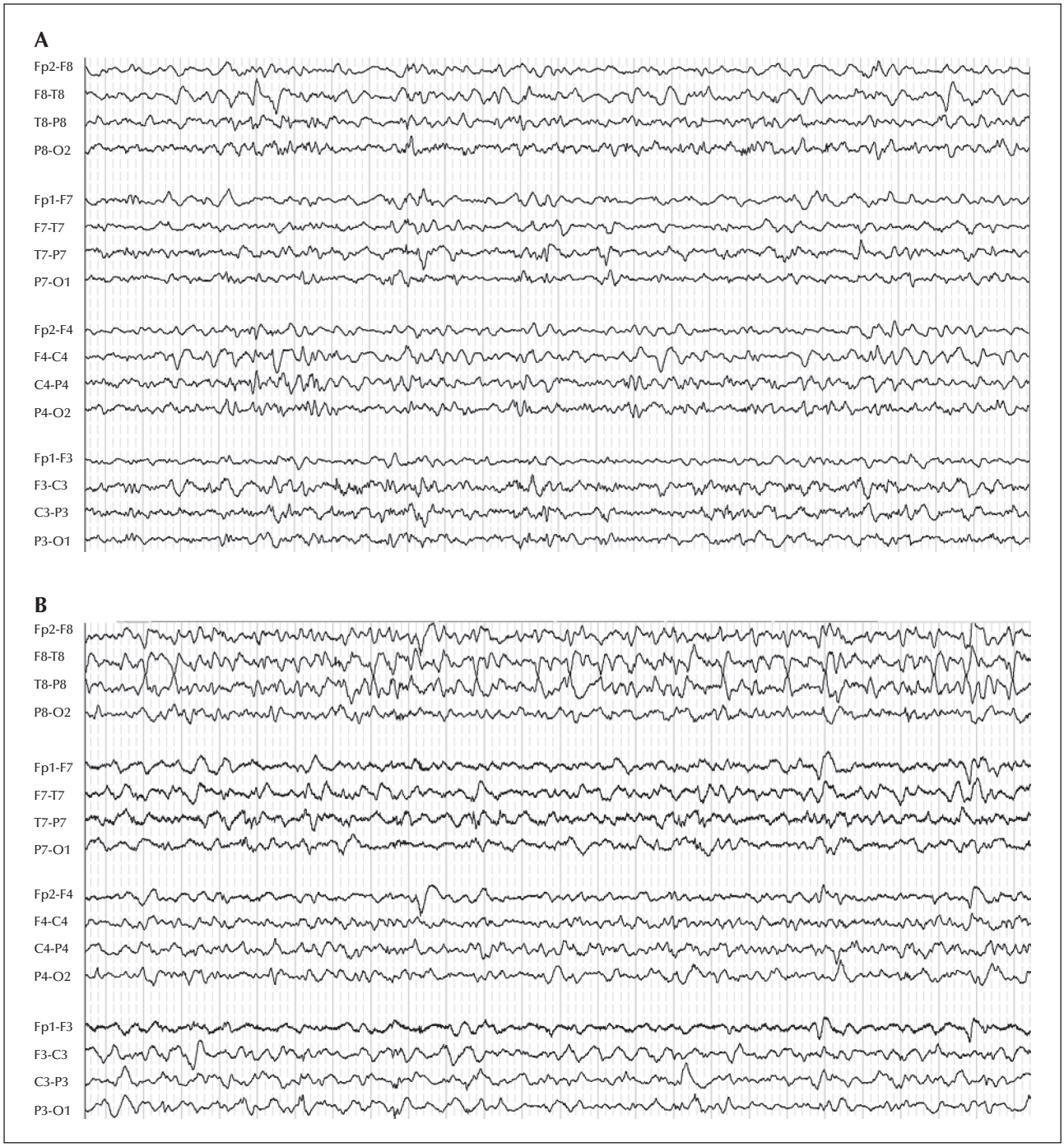

Figure 3. Video-EEG monitoring performed at age 9 weeks in Case 2. The interictal sleep EEG (A) shows a continuous but asymmetric background with higher voltage slower rhythms on the right, and focal epileptiform discharges arising independently from the right and left temporal, central and posterior regions. Clinical and subclinical seizures were recorded with ictal rhythms arising seemingly independently from the right temporal (B), right central, right occipital and left temporal (C) regions.

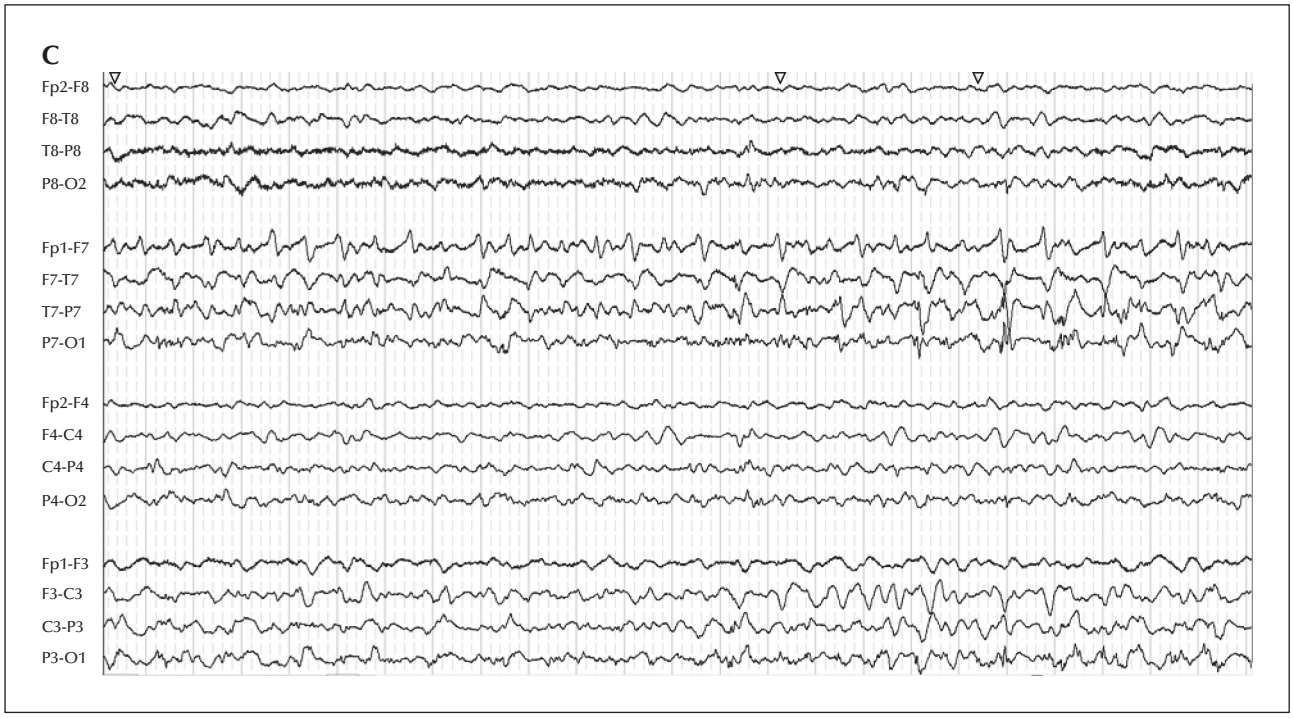

Figure 3. (*Continued*).

Autonomic manifestations occur in 37% of subtle seizures in infancy, and may include respiratory changes and bradycardia (Fenichel *et al*., 1980). However, severe and recurrent apnoeic events are not a common manifestation and mortality from such events is very uncommon (Ramelli *et al*., 1998; Freed and Martinez, 2001; Hosain *et al*., 2003). Lachhwani reported a single case of an extensive malformation of cortical development whose seizures were life-threatening, but this patient was also found to have a co-existing airway malformation (Lachhwani, 2008). In Case 2, we witnessed prominent autonomic features of cyanosis and desaturation prior to any apparent clinical apnoea which may have been due to limbic or insula involvement. These life-threatening seizures were seen to arise independently from the left and right temporal regions on scalp EEG. Interictally, the EEGs were relatively normal; a common finding in PMG (Teixeira *et al*., 2009). There are occasional reports of focal electrographic status and ESES among patients with unilateral PMG, but this was not seen in our patients (Teixeira *et al*., 2009).

Apart from the severity of seizures, likely related to autonomic manifestations, the cause of the catastrophic outcomes in our patients is unclear. For Case 1, it is possible that the hemispheric disconnection was incomplete or that there was an abnormality of the left hemisphere which was not seen on MRI. In the absence of a post mortem, this could not be determined. For both patients, it is possible that the PMG was part of a genetic syndrome that may have resulted in subtle developmental abnormalities of the contralateral hemisphere, impaired intrinsic seizure suppression mechanisms, or atypical inter-hemispheric spread of seizures. It is also possible that other organs, such as the heart, may have been involved, as neither patient had an echocardiogram to exclude this. The presence of bilateral hippocampal sclerosis in both cases would not explain their seizure semiologies or poor outcomes. Despite extensive investigations including brain post mortem, metabolic studies, and whole-exome sequencing, we did not find evidence of an underlying genetic or metabolic disorder in Case 2. Case 1 died prior to the discovery of any known genes for PMG.

Extensive malformations of cortical development, such as hemimegalencephaly, frequently lead to severe, drug-resistant seizures. Therefore, a large hemispheric malformation and catastrophic epilepsy may prompt consideration of epilepsy surgery. Hemispherectomy is an effective therapy for children with refractory seizures and major hemispheric lesions (Wyllie *et al*., 1998; Hamiwka *et al*., 2007). In a large series of patients undergoing hemispherectomy for intractable "unilateral" epilepsy, there were 3/111 post-operative deaths in those with migrational disorders; two had hemimegancephaly and one died with intractable seizures with PMG (Kossoff *et al*., 2003). A cautious approach to surgery for unilateral PMG may be warranted as there may be prominent epileptic activity

in an apparently structurally normal hemisphere. One may need to be concerned about prominent interictal and ictal EEG activity contralateral to the apparent unilateral PMG, in contrast to other major hemispheric lesions in infants where contralateral or generalized interictal discharges may not preclude a hemispherectomy (Doring *et al*., 1999).

In summary we present two infants with severe, life-threatening and intractable early-onset epilepsy, secondary to extensive unilateral PMG. We propose that this is a rare and severe syndrome of PMG which presents in the neonatal period and is distinct from other unilateral forms. Due to the possibility of independent seizure onset in the contralateral hemisphere, caution should be taken before embarking on procedures such as hemispherectomy, even in the presence of apparently normal contralateral imaging. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) Which distributions of polymicrogyria are usually associated with the most severe phenotypes?

(2) What should make one cautious in proceeding to hemispherectomy in a child with drug-resistant seizures secondary to unilateral PMG?

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