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Meningeal defects and focal cortical dysplasia: an unrecognized relationship? Illustrative case

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BACKGROUND Focal cortical dysplasias (FCDs) are a heterogenous cluster of histopathologic entities classically associated with medically refractory epilepsy. Because there is substantial histopathologic variation among different types of FCD, there are likely multiple pathogenic mechanisms leading to these disorders. The meninges are known to play a role in cortical development, and disruption of meningeal-derived signaling pathways has been shown to impact neurodevelopment. To our knowledge, there has not yet been an investigation into whether genetic pathways regulating meningeal development may be involved in the development of FCD.

OBSERVATIONS The authors reported a patient with refractory epilepsy and evidence of FCD on imaging who received surgical intervention and was found to have an unusual dural anomaly overlying a region of type Ic FCD. To the authors' knowledge, this was the first report describing a lesion of this nature in the context of FCD.

LESSONS The dural anomaly exhibited by the patient presented what could be a potentially novel pathogenic mechanism of FCD. Resection of the cortical tissue underlying the dural anomaly resulted in improvement in seizure control. Although the pathogenesis is unclear, this case highlighted the importance of further investigation into the developmental origins of FCD, which may help elucidate whether a connection between meningeal development and FCD exists.

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KEYWORDS dural abnormalities; focal cortical dysplasia; epilepsy; cortical development; meninges

Focal cortical dysplasias (FCDs) are a heterogenous cluster of histopathologic entities characterized by abnormal cortical development.[1] They are classically associated with medically refractory epilepsy and often require surgical intervention to achieve seizure freedom.[2,3] Because there is substantial histopathologic variation among different types of FCD, there are likely multiple pathogenic mechanisms that lead to the development of these disorders.[1] Specific genetic alterations (germline and somatic mosaicism) have been associated with some forms of FCD. For example, the pathogenesis of FCD type IIb is believed to be due to mutations affecting the mTOR signaling pathway, and some evidence suggests a link between FCD types Ia and IIa and mutations in the sodium channel gene *SCN1A*.[2,3] Previous investigations have also suggested that defects in meningeal development may be responsible for some FCD subtypes because the meninges are heavily involved in regulating some pathways of cortical development.[4] Nevertheless, much about the pathogenesis of FCDs remains to be elucidated.

Illustrative Case

A 47-year-old, right-handed woman presented with medically refractory left temporal epilepsy with onset at 29 years of age. Her typical seizure presented as an auditory aura and inability to speak or comprehend speech, followed by right facial clonic seizure and occasional progression to generalized tonic-clonic (GTC) seizure. She experienced daily auras with seizures several times per year that lasted 2.5 to 3 minutes.

ABBREVIATIONS ECoG = electrocorticography; EEG = electroencephalography; FCD = focal cortical dysplasia; GTC = generalized tonic-clonic; MRI = magnetic resonance imaging.

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The patient was initially treated with antiepileptic drugs, including phenytoin, carbamazepine, lamotrigine, and levetiracetam. After failing to achieve desirable seizure control with medical interventions, surgical options were considered. A 5-day epilepsy monitoring unit evaluation at our institution revealed one habitual auditory aura of buzzing in the left ear without electroencephalography (EEG) change and four habitual seizures with focal onset, with two progressing to GTC. In most of her seizures, she reported a preceding buzzing sensation with a sense of fear and was unresponsive with fearful moaning sounds prior to seizure progression. With convulsive seizures, she progressed to right head version, a sign-of-four with right arm extended and left arm flexed, and a last clonic jerk on the left. These findings indicated seizure lateralization to the left hemisphere but did not provide more specific localization data. Interictally, she had frequent left hemispheric intermittent slowing as well as 2- to 3-second runs of sharply contoured paroxysmal theta/fast activity, which was primarily seen over the left temporal region. At times, fragmentary discharges were seen, which resembled longer bursts. These bursts were favored to represent epileptiform discharges, presumably with neocortical localization. Taken together, these findings implicated an epileptogenic zone over the left temporal region, with semiology showing concordant high-probability lateralization to the left hemisphere. Additionally, magnetic resonance imaging (MRI) revealed a subtle area of abnormal sulcation of the left inferior and middle temporal gyri (Fig. 1). The ictal single-photon emission computed tomography (injection 10 seconds after first EEG change) showed a focal hyperemic area on the left posterior temporal lobe, overlapping with the finding of possible dysplasia seen on MRI. Subtraction from interictal acquisition did not show any significant difference, however, indicating that the hyperemic area could be artifactual. Positron emission tomography and computed tomography imaging of the brain did not demonstrate any areas of hypometabolism to suggest a seizure focus in the interictal phase. Functional MRI indicated left hemisphere dominance for expressive and receptive language function, with language function localized posteriorly to the area of abnormal sulcation on structural imaging. The bilateral hippocampi were found to be within the normal range for volume without any evidence of asymmetry on volumetric analysis. Neuropsychological testing showed mild declines in auditory working memory and aspects of language processing consistent with mild acquired dysfunction within the frontotemporal neocortical networks of the language dominant hemisphere. After discussing the case at our institution's multidisciplinary epilepsy conference, the patient was deemed a suitable candidate for invasive EEG (iEEG) for long-term seizure monitoring, with the goal of localizing the seizure-onset zone with respect to eloquent cortex involvement.

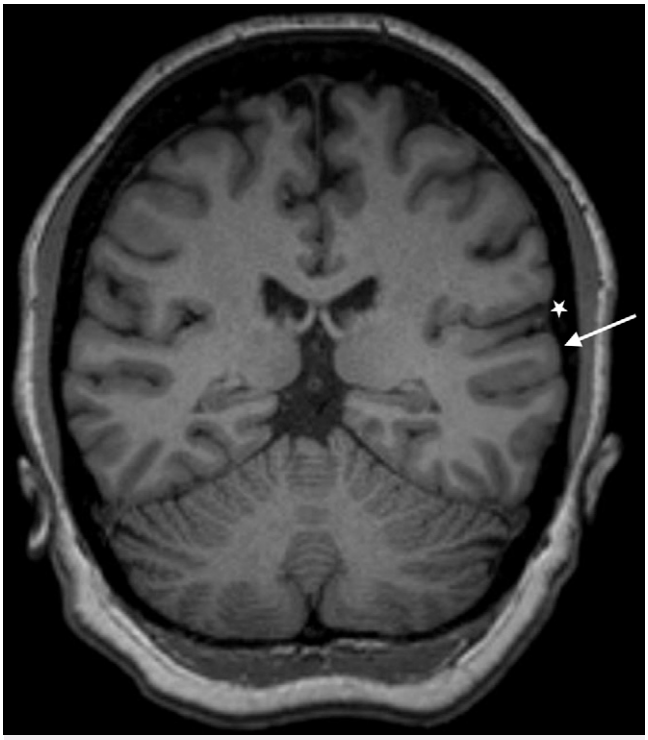

FIG. 1. Coronal T1-weighted MRI demonstrating a region of questionable abnormal sulcation (*star*) and cortical thickening (*arrow*) in the left superior and middle temporal gyri.

The patient underwent a left frontotemporal craniotomy for subdural grid placement and stereotactic placement of two depth electrodes. After removal of the bone flap, a distinct dural anomaly was observed in the area visually corresponding to the region of suspicion for focal cortical dysplasia. The dura in this region appeared abnormally thin and translucent upon gross examination (Fig. 2). The subdural electrode arrays were placed in the following fashion: 4×8 over the lateral temporal cortex, 1×4 over the temporal tip, 2×6 basal temporal, 1×6 posterior basal temporal, 2×6 inferior frontal, and 1×4 upfacing ground over the frontal pole (Fig. 3).

Postoperatively, iEEG monitoring localized the patient's region of seizure onset to the left lateral temporal cortex. Extraoperative low-frequency stimulation mapping of the lateral left temporal electrodes elicited the patient's habitual seizures from the same electrodes identified as the location of her spontaneous seizure onset. Extraoperative functional mapping showed no overlap between language or any other critical functions within the region of seizure onset. As such, the patient returned to the operating room for explantation of the iEEG electrodes and resection of the brain tissue identified to be the location of seizure onset within the left lateral temporal lobe. This cortical region was directly underlying the previously identified dural abnormality seen at the time of initial grid placement (Fig. 4). Preresection electrocorticography (ECoG) was collected and showed frequent interictal abnormalities in the cortex corresponding with the cortex marked for resection. The electrode grid was removed, and tissue was resected in two specimens to spare an en passage cortical vessel. Subpial aspiration and resection was taken down to the depth of the two adjacent sulci. Postresection ECoG was collected and demonstrated resolution of the previously seen interictal activity. Pathologic examination of the resected tissue showed abnormalities consistent with the International League Against Epilepsy classification of FCD type Ic, including evidence of radial and tangential cortical dyslamination. The patient was discharged home 3 days after explantation and resection. Postoperatively, she experienced transient mild word-finding difficulties and issues with auditory comprehension. She began a course of speech therapy approximately 6 weeks following surgery and made notable and significant improvements with this intervention. She and her husband were pleased with her postoperative speech function by 3 months postoperatively. She experienced two auras in the first month following surgery but had no other seizure activity since then. She has been seizure-free for approximately 10 months and continues to be monitored by her interdisciplinary epilepsy team.

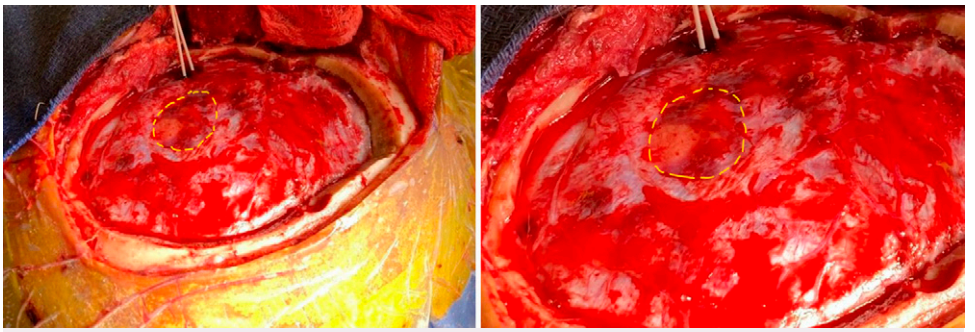

FIG. 2. Intraoperative photographs obtained prior to resection, showing the area of abnormal dura over the superior temporal gyrus (*dotted circle*). Depth electrodes seen in the inferior temporal gyrus.

Discussion

Observations

We report this case to highlight the unusual dural anomaly overlying a region of type Ic FCD in our patient. To our knowledge, this is the first report describing a lesion of this nature in the context of FCD.

The meninges are known to play an important role in the development of the cerebral cortex, and disruption of meningeal-derived cellular signaling pathways has been shown to substantially impact neurodevelopment.[4–6] In 2006, Borrell and Marín established that the meningeal-derived chemokine Cxcl12 and its receptors Cxcr4 and Cxcr7 are key components of the mechanism guiding migration of Cajal-Retzius cells within the cerebral cortex.[4,5] In addition, Siegenthaler et al. established that secretion of retinoic acid by the meninges is critical to the process of corticogenesis in the developing brain.[6] These studies demonstrate only a few of the neurodevelopmental pathways that are tightly regulated by the meninges, highlighting the crucial role the meninges play in cerebral development. Accordingly, congenital meningeal defects that interrupt such pathways may be a driving force in the pathogenesis of certain FCD subtypes. The case we present may be an example of such an event, in which the patient's dural anomaly may have contributed to the aberrant development of the underlying cortex, eventually resulting in FCD.

Type I FCD is characterized by abnormal cortical architecture and is divided into three subtypes based on the type of abnormality present. Type Ia FCD is defined by radial dyslamination, whereas type Ib FCD is defined by tangential dyslamination. Type Ic FCD is a combination of types Ia and Ib.[3] In the case presented, the patient's epileptogenic tissue showed evidence of both radial and tangential cortical dyslamination and is therefore considered type 1c FCD. In contrast to type II FCDs, a specific genetic pathway has not yet been identified in the pathogenesis of type I FCDs. This gap in knowledge was recently emphasized in the comprehensive review published by Jesus-Ribeiro et al., which found that previous investigations into the genetic cause of FCD type I have not been able to identify a consistent or reliable pathogenic mechanism.[7] To our knowledge, there has been no investigation into whether the genetic pathways regulating development of the meninges may be involved in the development of FCD. The case we present suggests that such an investigation is warranted in the future.

Although FCDs are a common cause of medically refractory epilepsy, they are not the only developmental anomalies associated with this disorder. Encephaloceles, particularly those of the temporal lobe, are also associated with pharmacoresistant epilepsy.[8] However, few investigations have explored a possible connection among

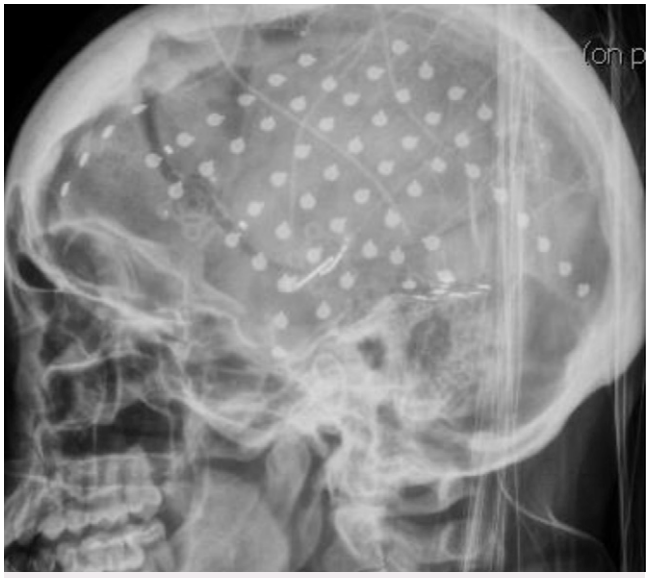

FIG. 3. Postoperative radiograph of the left lateral skull showing placement of the subdural grid.

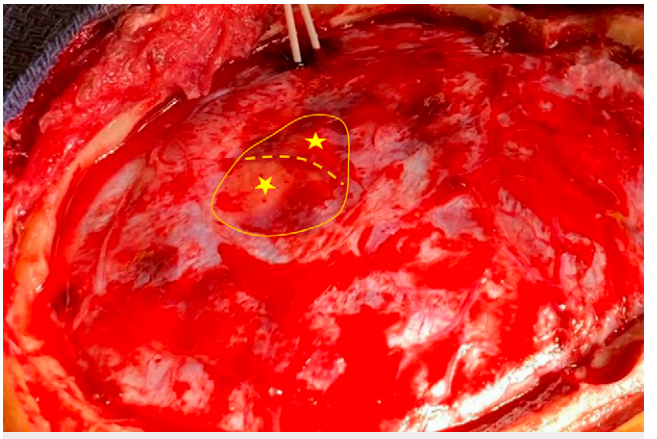

FIG. 4. Intraoperative photograph indicating the regions of resected cortical tissue (*stars*) and the en passage cortical vessel (*dotted line*).

encephaloceles, FCD, and the mechanisms of neurodevelopment that lead to these lesions. It has been established that encephaloceles are epileptogenic in nature, even in the absence of FCD.[8] However, the epileptogenicity of these lesions may be attributable to multiple pathogenic mechanisms. In 2018, de Souza et al. reported a case in which a patient with refractory temporal lobe epilepsy was found to have multiple encephalocele defects of the left temporal pole while undergoing resection. Interestingly, the surgical pathology from this patient's left temporal pole region also showed evidence of FCD.[9] Similarly to the patient we report, this case raises the question of whether certain cases of FCD may be related in some way to meningeal development.

Lessons

The dural anomaly exhibited by our patient presents what could be a potentially novel pathogenic mechanism of FCD. More detailed investigation of the dural anomaly itself was limited in our case because there were no samples collected from the dura for pathological examination during resection due to there being no clinical indication to do so. Because of this lack of samples, analysis of developmental pathways potentially involved in the development of the abnormality as well as the FCD was not feasible. Like other single-case reports, it is difficult to draw conclusions regarding the role of the meninges in FCD development based on our patient's findings alone. Although the proximity of the two lesions in this patient is certainly noteworthy, it is possible that the dural thinning occurred independently of the FCD. Reports of similar anomalies in other patients with or without FCD may help clarify whether an association between the lesions truly exists. Furthermore, if there is a connection between the dural thinning and FCD, many questions remain unanswered regarding the pathogenesis of this relationship. The possibility must be considered that the epileptogenicity of the dysplastic tissue potentially led to the gradual deterioration of the dura overlying it, although this has not often been reported or documented in our practice. Nonetheless, this case raises important questions regarding the developmental origins of focal cortical dysplasia, which warrant further exploration. Future investigation of these issues may help elucidate whether a connection between meningeal development and FCD exists and, if it does, where that connection lies.

References

1. 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):1348–1369.
2. Crino PB. Focal cortical dysplasia. *Semin Neurol.* 2015;35(3): 201–208.
3. Iffland PH 2nd, Crino PB. Focal cortical dysplasia: gene mutations, cell signaling, and therapeutic implications. *Annu Rev Pathol.* 2017; 12:547–571.
4. Siegenthaler JA, Pleasure SJ. We have got you 'covered': how the meninges control brain development. *Curr Opin Genet Dev.* 2011; 21(3):249–255.
5. Borrell V, Marín O. Meninges control tangential migration of hem-derived Cajal-Retzius cells via CXCL12/CXCR4 signaling. *Nature Neuroscience*. 2006;9(10):1284–1293.
6. Siegenthaler JA, Ashique AM, Zarbalis K, et al. Retinoic acid from the meninges regulates cortical neuron generation. *Cell*. 2009; 139(3):597–609.
7. Jesus-Ribeiro J, Pires LM, Melo JD, et al. Genomic and epigenetic advances in focal cortical dysplasia types I and II:. a scoping review. *Frontiers in Neuroscience*. 2021;14:580357.
8. Ramos-Fresnedo A, Domingo RA, McGeary RC, et al. Encephalocele-associated drug-resistant epilepsy of adult onset: diagnosis, management, and outcomes. *World Neurosurgery.* 2021;151:91–101.
9. de Souza JPSAS, Mullin J, Wathen C, et al. The usefulness of stereo-electroencephalography (SEEG) in the surgical management of focal epilepsy associated with "hidden" temporal pole encephalocele: a case report and literature review. *Neurosurgical Review.* 2018;41(1): 347–354.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Bandt, Ellis, Trybula. Acquisition of data: Bandt, Trybula, Adney, Lee. Analysis and interpretation of data: Bandt, Lee. Drafting the article: Ellis. Critically revising the article: all authors. Reviewed submitted version of manuscript: Bandt, Ellis, Trybula, Adney. Approved the final version of the manuscript on behalf of all authors: Bandt. Administrative/technical/material support: Bandt, Ellis. Study supervision: Bandt.

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