Searching for the Lesion in "MRI-Normal" Neocortical Epilepsy—Plumb the Depths!

Small Focal Cortical Dysplasia Lesions Are Located at the Bottom of a Deep Sulcus. Besson P, Andermann F, Dubeau F, Bernasconi A. *Brain* 2008;131(Pt 12):3246–3255. Focal cortical dysplasia (FCD) is often characterized by minor structural changes that may go unrecognized by standard radiological analysis. Visual assessment of morphological characteristics of FCD and sulci harboring them is difficult due to the complexity of brain convolutions. Our purpose was to elucidate and quantify the spatial relationship between FCD lesions and brain sulci using automated sulcal extraction and morphometry. We studied 43 consecutive FCD patients using high-resolution MRI. Lesions were classified into small and large using qualitative (detection on initial clinical assessment of conventional MRI) and quantitative (volume) criteria. Sulci were identified and labeled automatically using an algorithm based on a congregation of neural networks. Segmented FCD lesions and sulci were then simultaneously visualized in 3D. We measured mean and maximum depth of sulci related to each FCD and of the corresponding sulci in 21 healthy controls. In addition, we calculated sulcal depth within the FCD neighborhood. Twenty-one (21/43 = 49%) patients had small FCD lesions (volume range: 128–3093 mm (3)). Among them, 17 (81%) had been overlooked during initial radiological evaluation and were subsequently identified using image processing. Eighteen (18/21 = 86%) small FCD lesions were located at the bottom of a sulcus. Two others were related to the walls of two sulci and one was located at the crown of a gyrus. Mean and maximum depth of sulci related to the FCD was higher than that of the corresponding sulci in controls ($p < 0.008$). Sulcal depth within lesional neighborhood had larger mean depth than that of the entire sulcus ($p < 0.0002$). Evidence that small FCD lesions are preferentially located at the bottom of an abnormally deep sulcus may be used to direct the search for developmental abnormalities, particularly in patients in whom large-scale MRI features are only mildly abnormal or absent.

COMMENTARY

The brain MRI may be assessed as normal on initial interpretation for as many as one-quarter of patients with pharmacoresistant epilepsy, who are referred for possible neurosurgical treatment (1). However, there is a significantly lower chance of postsurgical seizure freedom among patients for whom a relevant cerebral lesion has not been identified (2). Fortunately, the ability to detect subtle lesions in patients with neocortical epilepsy is rapidly evolving, and more and more often they are being identified during the presurgical evaluation. Focal cortical dysplasia is the most common subtle lesion that is discovered, and, in one classification system (3), it is divided into two types: type 1—no dysmorphic neurons or balloon cells, but with dyslamination (type 1A) or dyslamination plus giant or immature neurons (type 1B); and type 2 (Taylor type)—dyslamination plus dysmorphic neurons, without balloon cells (type 2A) or with balloon cells (type 2B). Compared with type 1, patients with type 2 cortical dysplasia present at a younger age, have higher seizure frequencies, and are extratemporal (4). Type 1 dysplasia more frequently is found in adult patients and is located in the temporal lobe. While only a subset of patients with type 1 dysplasia will develop medically intractable epilepsy, type 2 is highly epileptogenic, with electrocorticography over the lesion usually showing continuous spiking (3). When identified, complete resection of type 2 focal cortical dysplasia leads to good seizure control for most patients (4,5).

On occasion, focal cortical dysplasia is detected when careful reinspection of the fluid-attenuated inversion-recovery (FLAIR) MRI reveals a characteristic hyperintense funnel-shaped subcortical zone that tapers towards the lateral ventricle, representing transmantle dysplasia (4). Nonetheless, in many cases, the lesion cannot be detected on simple visual inspection. A number of investigators, including Besson et al., the authors of this study, have adapted a variety of image processing and analysis techniques to reveal more subtle abnormalities. One method is curvilinear reformatting, which creates planes that slice in a curved fashion parallel to the surface of the hemispheric convexity (6). Since the sulci tend to be perpendicular to the cortical surface, the curvilinear plane cuts directly across them, which reduces effects of oblique sectioning and volume averaging when assessing cortical thickness (6). Another approach is voxel-based morphometry, in which portions of the T1-weighted image are classified as gray matter, white matter, and CSF; the gray matter concentration map is subtracted from an averaged map of control images to identify areas of hyperintensity, which would presumably be areas of dysplasia (7). Finally, textural analysis and morphological processing have been developed to map gray matter thickness and detect blurring of the gray–white matter junction that may also indicate a region of dysplasia (8).

In the current paper, the three methods discussed were applied and coregistered with the results of image processing to extract the sulcal features. Small focal cortical dysplasia was

Epilepsy Currents, Vol. 9, No. 6 (November/December) 2009 pp. 160–161
Wiley Periodicals, Inc.

detected in many patients and was located primarily at the bottom of unusually deep sulci. The finding led to a proposed new class of type 2 focal cortical dysplasia termed, "bottom-of-sulcus dysplasia" (9). The occurrence of this developmental malformation can be understood in terms of the Van Essen hypothesis that sulci are formed and shaped as a result of mechanical tension along axons in the white matter, with strongly connected regions pulled closer to each other during development (10). The weak local cortical connectivity of the area of focal cortical dysplasia would result in the unopposed effects of longer corticothalamic connections pulling down on such a region during development, resulting in its ultimate location at the bottom of a deep sulcus.

This work by Besson et al. implies that subtle, bottom-of-sulcus focal cortical dysplasia is not uncommon, but is a frequently overlooked cause of medically intractable epilepsy, and has profound implications for the surgical workup. Small, deep focal cortical dysplasia cannot be consistently and reliably detected by electrocorticography alone, because subdural grid or strip electrodes record from a distance at the crowns of gyri, and depth electrodes can only be appropriately placed with prior knowledge of the lesion location. Wider availability of improved imaging processing methods, such as those used by Besson et al., will be key to detecting bottom-of-the-sulcus focal cortical dysplasia. Identification of these lesions will mean that a significant subgroup of patients who were originally thought to be poor surgical candidates, with cryptogenic neocortical epilepsy, will be found instead to have this well-defined, surgically remediable focal cortical dysplasia syndrome.

by John W. Miller, MD, PhD

References

1. Berg AT, Vickrey BG, Langfitt JT, Sperling MR, Walczak TS, Shinnar S, Bazil CW, Pacia SV, Spencer SS. The multicenter study of epilepsy surgery: Recruitment and selection for surgery. *Epilepsia* 2003;44:1425–1433.
2. Jeha LE, Najm I, Bingaman W, Dinner D, Widdess-Walsh P, Lüders H. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain* 2007;130:574–584.
3. Palmini A, Majm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, Jackson G, Lüders HO, Prayson R, Spreafico R, Vinters HV. Terminology and classification of the cortical dysplasias. *Neurology* 2004;62:S2–S8.
4. Lerner JT, Salamon N, Hauptman JS, Velasco TR, Hemb M, Wu JY, Sankar R, Donald Shields W, Engel Jr. J, Fried I, Cepeda C, Andre VM, Levine MS, Miyata H, Yong WH, Vinters HV, Mathern GW. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: A critical review and the UCLA experience. *Epilepsia* 2009 Jan 19.
5. Urbach H, Scheffler B, Heinrichsmeier T, von Oertzen J, Kral T, Wellmer J, Schramm J, Wiestler OD, Blümcke I. Focal cortical dysplasia of Taylor's balloon cell type: A clinicopathological entity with characteristic neuroimaging and histopathological features, and favorable postsurgical outcome. *Epilepsia* 2002;43: 33–40.
6. Bastos AC, Comeau RM, Andermann F, Melanson D, Cendes F, Dubeau F, Fontaine S, Tampieri D, Olivier A. Diagnosis of subtle focal dysplastic lesions: Curvilinear reformatting from three-dimensional magnetic resonance imaging. *Ann Neurol* 1999;46:88–94.
7. Colliot O, Bernasconi N, Khalili N, Antel SB, Naessens V, Bernasconi A. Individual voxel-based analysis of gray matter in focal cortical dysplasia. *NeuroImage* 2006;29:162–171.
8. Bernasconi A, Antel SB, Collins DL, Bernasconi N, Olivier A, Dubeau F, Pike GB, Andermann F, Arnold DL. Texture analysis and morphological processing of magnetic resonance imaging assist detection of focal cortical dysplasia in extra-temporal partial epilepsy. *Ann Neurol* 2001;49:770–775.
9. Barkovich AJ, Kuzniecky RI, Jackson GC, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. *Neurology* 2005;65:1873–1887.
10. Van Essen DC. A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 1997;383: 313–318.