



Imaging Focal Cortical Dysplasia in Refractory Epilepsy

Neuroimaging in Identifying Focal Cortical Dysplasia and Prognostic Factors in Pediatric and Adolescent Epilepsy Surgery.

Kim YH, Kang H-C, Kim D-S, Kim SH, Shim K-W, Kim HD, Lee JS. *Epilepsia* 2011;52:722–727.

PURPOSE: The purpose of this study is to determine the sensitivity of each imaging tool in identifying focal cortical dysplasia (FCD) in children and adolescents with epilepsy and to define the prognostic factors of pediatric and adolescent epilepsy surgery. **METHODS:** We identified 48 children with FCD who underwent resective surgery and analyzed their preoperative data. The results of various anatomic and functional neuroimaging studies were compared for accuracy in locating the lesion. We also investigated clinical factors that affected the outcome of surgical treatment. **KEY FINDINGS:** Brain magnetic resonance imaging (MRI) was able to localize FCD in 30 patients and fluorodeoxyglucose positron emission tomography (FDG-PET) and/or subtraction ictal single photon emission computed tomography (SPECT) coregistered with MRI provided additional information that helped to define the lesion in 13 patients. When comparing the pathologic results between a mild malformation of cortical development (MCD) and FCD type I and II, we noted a strong tendency for patients with FCD to have MRI abnormalities ($p = 0.005$). In addition, severe pathologic features (Palmini's classification, FCD type II) ($p = 0.025$) showed significant correlation with a better surgical outcome. To define the primary epileptogenic area, various interictal epileptiform discharges and the results of multimodal neuroimaging studies were helpful, and younger age at the time of operation could aid in more favorable surgical outcomes ($p = 0.048$). **Significance:** Our study showed a significant relationship between pathologic grade and the detectability of FCD by brain MRI. In addition, early surgery can be justified by showing that advanced neuroimaging studies in children with FCD and even with extensive epileptiform discharges have a higher rate of success.

Commentary

Cortical dysplasia (CD) is a developmental abnormality of cortical organization (1, 2) and a common cause of drug-resistant epilepsy. CD is a very common pathology identified in pediatric epilepsy surgery (3, 4). One of the primary challenges facing pediatric epileptologists caring for these patients is localization of epileptogenic structural lesions. In patients with well-defined structural lesions, resective epilepsy surgery can be curative. Unfortunately, the success of epilepsy surgery in patients with CD is often limited by absence of a MRI lesion and multifocal pathology. Even when a focal MRI lesion is identified, the spatial extent of the underlying pathology may not be evident. This "tip of the iceberg" phenomenon, where the lesion visualized on MRI represents only a portion of the underlying structural pathology, serves as a point of caution. Because of limitations in structural imaging in patients with CD, functional imaging and electrophysiology studies are very important. As was found in the study reviewed here (5), unfortunately scalp EEG is often complicated and may show generalized epileptiform abnormalities despite focal lesions (6). The use of intracranial EEG (iEEG) monitoring is often critical

in these patients for definitive localization. However, judicious use of iEEG requires a good hypothesis to guide intracranial electrode implantation. Otherwise, successful localization with iEEG requires more widespread implantation of intracranial electrodes, increasing cost, patient discomfort, and morbidity, and decreasing the successfulness of the procedure.

Functional neuroimaging can identify focal or regional abnormalities, even in the absence of a structural MRI lesion, and help focus the implantation of intracranial electrodes. Kim and colleagues (5) investigated prognostics of favorable surgical outcome and the ability of SPECT, PET, and structural MRI to localize epileptogenic cortical dysplasia.

To investigate the power of functional and structural imaging to localize CD, Kim and colleagues (5) identified 48 patients (primarily pediatric patients) with pathologically proven CD. The cohort of patients were clinically challenging, with ages 0.2 to 23 years, duration of epilepsy spanning 0.2 to 16 years, and with follow-up of 0.7 and 5.5 years (2.13 ± 1.23 years). Clinically, the patients represented a range of epilepsy syndromes, including infantile spasms, Lennox-Gastaut, and infantile epileptic encephalopathy. The scalp EEG showed a wide range of multifocal and generalized interictal epileptiform discharges in addition to focal epileptiform discharges.

Resected cortex was classified according to the staging scheme developed by Palmini and colleagues (2): 1) mild MCD if ectopically placed neurons only, 2) FCD type IA if isolated



architectural abnormalities, 3) FCD type IB if there were additional immature or giant neurons, 4) FCD type IIA if there were also dysmorphic neurons, and 5) FCD type IIB if there were additional balloon cells. They define severe pathological subtypes as FCD IIA and FCD IIB, and the rest as mild pathological subtypes for the purpose of identifying prognostic factors of epilepsy surgery outcome. The outcomes from epilepsy surgery were encouraging given the significant challenge these patients represent, with 56 percent (27/48 patients) Engel Class I and 14 patients off medications. Only 6 percent (3/48) of patients had no worthwhile improvement. Multivariate analysis demonstrated that a shorter duration of epilepsy at time of surgery and more severe subtype of FCD, that is, FCD IIA and FCD IIB, are associated with better outcomes.

All patients had structural imaging using 3 Tesla MRI, and a potentially epileptogenic lesion was identified in 62 percent (30/48) of patients. PET was obtained in 36 patients, and 83 percent (30/36) had a functional abnormality. Ictal and interictal SPECT was obtained in 27 patients, and using subtraction ictal-interictal SPECT coregistered to MRI (SISCOM), 89 percent (24/27) of patients demonstrated a functional abnormality. PET and SPECT both demonstrated better sensitivity compared with MRI for localizing an abnormality in patients with MCD, which not surprisingly has a high percentage (65%) of nonlocalizing structural imaging. Whereas PET and SPECT localized a region of functional abnormality in the majority of MCD cases, 77 percent and 75 percent, respectively, MRI identified a structural lesion in only 35 percent of MCD cases. There was not a significant difference between SPECT and PET for detection of functional abnormalities.

A PET abnormality was identified in 11 patients with normal MRI. Similarly, for SPECT, a SISCOM abnormality was identified in eight patients with normal MRI. Only two patients with normal PET and one with normal SISCOM had a lesional MRI. These results were used to show that PET ($p = 0.013$) and SPECT ($p = 0.020$) are more sensitive than MRI for detecting CD. There was no significant difference between PET and SPECT for detecting functional abnormalities in patients with CD. Investigating the sensitivity of structural and functional imaging based on pathologic subtypes showed that MRI was more sensitive for detection of FCD types I and II compared with MCD ($p = 0.005$). However, MRI sensitivity did not vary with specific FCD subtypes. Both SPECT and PET were more sensitive than MRI for detection of MCD and did not show a distinction for detecting MCD versus FCD lesions.

The study provides limited detail about electrophysiology and how resective margins were determined. The iEEG used to define the epileptogenic zone showed >3 Hz repetitive spikes, slow wave discharges, localized spindle-shaped fast discharges, and decremental fast discharges. Unfortunately, it is not clear which patients had spontaneous seizures recorded with chronic iEEG versus only interictal epileptiform abnormalities with intra-operative iEEG recordings.

Clinically, cortical dysplasia is associated with early seizure onset, developmental delay, and resistance to medical therapy. Epilepsy surgery is a viable option if the brain region generating seizures can be localized and resected (7). This study supports the importance of high-resolution MRI combined with PET and SISCOM to identify potentially epileptogenic structural and functional lesions. Complementing MRI, functional neuroimaging can provide critically important information for guiding implantation of intracranial electrodes. The prognostic factors associated with good surgical outcomes were found to be more severe pathologic grade (FCD IIA and FCD IIB) and younger age of operation.

It is interesting to speculate why more severe FCD is associated with better outcome. One possibility is that these lesions are better visualized on MRI and therefore completely resected at surgery. It would be interesting to know if this is supported by histology, that is, if the margins of the lesion defined by MRI are consistent with pathology. Recently, it has been reported that the majority of subtle CD are located in the sulcal depths (8), where electrophysiology is most limited. Given the convoluted structure of human brain, iEEG does not directly probe sulcal sources. Therefore, surgery relying on iEEG would be hampered by poor sampling of the sulcal regions. The association of surgical outcome with duration of epilepsy supports the emerging consensus that patients are better served with early evaluation for epilepsy surgery.

by Gregory A. Worrell, MD, PhD

References

1. Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. *J Neurol Neurosurg Psychiatry* 1971;34:369–387.
2. Palmieri A, Najm 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.
3. Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingman W, Ruggieri P. Seizure outcome after epilepsy surgery in children and adolescents. *Ann Neurol* 1998;44:740–748.
4. Kloss S, Pieper T, Pannek H, Holthausen H, Tuxhorn I. Epilepsy surgery in children with focal cortical dysplasia (FCD): Results of long-term seizure outcome. *Neuropediatrics* 2002;33:21–26.
5. Kim YH, Kang HC, Kim DS, Kim SH, Shim KW, Kim HD, Lee JS. Neuroimaging in identifying focal cortical dysplasia and prognostic factors in pediatric and adolescent epilepsy surgery. *Epilepsia* 2011;52:722–727.
6. Wyllie E, Lachhwani DK, Gupta A, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. *Neurology* 2007;69:389–397.
7. Duchowny M, Jayakar P, Resnick T, Harvey AS, Alvarez L, Dean P, Gilman J, Yalilali I, Morrison G, Prats A, Altman N, Birchansky S, Bruce J. Epilepsy surgery in the first three years of life. *Epilepsia* 1998;39:737–743.
8. Besson P, Andermann F, Dubeau F, Bernasconi A. Small focal cortical dysplasia lesions are located at the bottom of a deep sulcus. *Brain* 2008;131:3246–3255.



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