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Cutting-Edge Classification of Focal Cortical Dysplasia for Epilepsy Surgery

Toward a Better Definition of Focal Cortical Dysplasia: An Iterative Histopathological and Genetic Agreement Trial

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Objective: Focal cortical dysplasia (FCD) is a major cause of difficult-to-treat epilepsy in children and young adults, and the diagnosis is currently based on microscopic review of surgical brain tissue using the International League Against Epilepsy classification scheme of 2011. We developed an iterative histopathological agreement trial with genetic testing to identify areas of diagnostic challenges in this widely used classification scheme. Methods: Four web-based digital pathology trials were completed by 20 neuropathologists from 15 countries using a consecutive series of 196 surgical tissue blocks obtained from 22 epilepsy patients at a single center. Five independent genetic laboratories performed screening or validation sequencing of FCD-relevant genes in paired brain and blood samples from the same 22 epilepsy patients. Results: Histopathology agreement based solely on hematoxylin and eosin stainings was low in Round 1, and gradually increased by adding a panel of immunostainings in Round 2 and the Delphi consensus method in Round 3. Interobserver agreement was good in Round 4 (kappa = .65), when the results of genetic tests were disclosed, namely, MTOR, AKT3, and SLC35A2 brain somatic mutations in 5 cases and germline mutations in DEPDC5 and NPRL3 in 2 cases. Significance: The diagnoses of FCD 1 and 3 subtypes remained most challenging and were often difficult to differentiate from a normal homotypic or heterotypic cortical architecture. Immunohistochemistry was helpful, however, to confirm the diagnosis of FCD or no lesion. We observed a genotype–phenotype association for brain somatic mutations in SLC35A2 in 2 cases with mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy. Our results suggest that the current FCD classification should recognize a panel of immunohistochemical stainings for a better histopathological workup and definition of FCD subtypes. We also propose adding the level of genetic findings to obtain a comprehensive, reliable, and integrative genotype–phenotype diagnosis in the near future.

Commentary

The practice of clinical medicine has always relied upon both correct diagnosis and proper treatment. In response to evolving scientific evidence it is therefore essential to continuously revise both disease classification systems and clinical practice guidelines so that health care providers can provide optimal care to patients. Focal cortical dysplasia (FCD) is a common cause of medication resistant epilepsy in both children and adults.[1] Surgical resection results in seizure freedom in in some, but not all, patients with FCDs. It may be possible to improve the percentage of patients who are seizure free if clinicians have better tools to diagnose and classify FCDs before surgery.

Diagnostic features of FCDs on brain MR imaging may include cortical thickening, blurring of the grey-white matter junction, lesions located at the bottom of a sulcus, and a transmantle sign, but these lesions can be small and exhibit subtle findings thereby making them difficult to identify. In recent years, the use of advanced MRI acquisition sequences and post-acquisition image processing methods has improved the ability to detect FCDs before surgery. Separately, ongoing studies of FCD surgical specimens are revealing a growing number of both germline and somatic mutations that appear to be pathogenic.[2] Based on the latter it may be time to update the classification of FCDs. The novel study by Blümcke et al[3] is a significant step forward in the diagnosis and classification of patients with FCDs who may undergo surgical resection to treat epilepsy because it combines standard histological findings with immunohistology and genetic features.

Focal cortical dysplasia was described in a seminal paper by David Taylor and colleagues in 1971.[4] Shortly thereafter, FCDs were subclassified as Type I and Type II based on the degree of abnormality seen using standard histopathology techniques. In 2011 the International League Against Epilepsy published a consensus classification of the spectrum of FCDs that broadened the types of FCDs from 2 to 3.[5] Type I was defined as an isolated type with either abnormal radial cortical lamination (Ia), abnormal tangential cortical lamination (Ib) or abnormal radial and tangential cortical lamination (Ic). Type II was considered to also be an isolated type with either dysmorphic

neurons (DN) (Type IIa) or dysmorphic neurons and balloon cells (BC) (Type IIb). The new category, Type III, was defined as cortical lamination abnormalities associated with a principal lesion. It was broken into 4 subtypes: associated with hippocampal sclerosis (IIIa), adjacent to a glial or glioneuronal tumor (IIIb), adjacent to a vascular malformation (IIIc) and adjacent to any other lesion acquired in early life, eg trauma, ischemic stroke, encephalitis (IIId). In a broader context, FCDs are classified in the 2012 Developmental and Genetic Classification for Malformations of Cortical Development (MCD) among the "Group I.C: cortical dygeneses with abnormal cell proliferation."[6]

Surgical success appears to depend in part on FCD type. For example, seizure-free outcomes are less common with Type I than with Type II FCDs, and the outcome with Type III lesions appears to predominantly depend upon the principal lesion rather than the dysplasia.[3,7] Any presurgical diagnosis requires pathologic confirmation using histologic confirmation from the surgical tissue removed.[1] In addition to standard hematoxylin and eosin stains, many immunohistochemical stains like glial fibrillary acidic protein, microtubule, neurofilament, synaptophysin, vimentin, and cresyl violet–Luxol fast blue may be used.

Extensive research over the last decade has improved our understanding of the genetics and molecular biology of these lesions. For example, in FCD Type II, dysmorphic neurons are quite different from balloon cells. DN are cytomegalic, are rich in neurofilament, have excessive mammalian target of rapamycin (mTOR) activity, and are hyperexcitable (epileptogenic). By contrast, BC are also large and mTOR hyperactive, but are electrically silent. Mammalian target of rapamycin is a serine/threonine-specific protein kinase that regulates cellular metabolism, growth, apoptosis and proliferation. Rapamycin, a macrolide discovered in 1975 in soil samples from Easter Island, demonstrates both antifungal and immunosuppressant properties. Additionally, rapamycin (sirolimus) and its analog everolimus inhibit cell cycle progression and proliferation. Everolimus is approved in the United States to treat both epileptic seizures and subependymal giant cell astrocytomas in patients with tuberous sclerosis complex (TSC). Everolimus is believed to act via inhibition of the mTOR complex 1 (mTORC1) which is normally inhibited by the protein complex of TSC1 (hamartin), TSC2 (tuberin) and TBC1D7. Interestingly, TSC cortical tubers show striking histopathologic similarities to FCD Type IIb.[8] Moreover, many Type IIb (especially bottom-of-the sulcus frontal lobe) lesions are found to contain germline and/or somatic gain-of-function mutations in the mTOR pathway.[1,2,8] A newer entity called mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE) is often also located in the frontal lobe and is frequently associated with somatic mutations in the SLC35A2 gene affecting the glycosylation pathway. In contrast, genetic mutations have not commonly been seen thus far in FCD Type I lesions, but recent unpublished data, reviewed by Blümcke and colleagues,[1] suggest that DNA methylation patterns could distinguish Type Ia from other FCD types.

In 2016 the World Health Organization revised its Classification of Tumors of the Central Nervous System to add molecular genetic parameters to histology to define many tumor types.[9] This integrated phenotype – genotype classification has helped lead patients toward more effective therapies for their specific tumor type. Blümcke and colleagues[3] logically recommend that we add this approach to the diagnosis and treatment of FCDs. They took formalin fixed, paraffin embedded surgical sections from 22 patients with FCDs at 1 epilepsy center and submitted them to 20 neuropathologists worldwide. After this first round of review interobserver agreement was poor (kappa = .16). In the next two rounds, a review of immunostained sections and a Delphi consensus process improved agreement. The important finding was that after genetic testing (of both fresh-frozen brain specimens and matched blood samples) results were disclosed, interobserver agreement was substantially better (kappa = .65). They found mutations in 31.7% of the patients: brain somatic mutations in mTOR, AKT3 and SLC35A2 genes, and germline mutations in DEPDC5 and NPRL3 genes. DEPDC5 mutations may involve a "second-hit" mechanism in which a germline mutation (seen in the blood specimen) and a somatic mutation is found in brain cells. Interestingly, both BCs and DNs carry aberrant DEPDC5 genes suggesting that the somatic mutation occurs early in a progenitor of both glia and neurons.[2,10]

It is time to heed the call of these investigators[3] and refine the immunohistochemical diagnostic strategy for, and add genetic information to, the classification of FCDs. Doing so will be a step forward on the path to more personalized medical care for persons with epilepsy.

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