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Epilepsy prevalence and severity predictors in MRI-identified focal cortical dysplasia

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ABSTRACT

Objectives: To determine the prevalence of epilepsy and drug-resistant epilepsy in pediatric patients with focal cortical dysplasia (FCD) identified by magnetic resonance imaging (MRI). To determine clinical and imaging differences between those with drug-resistant epilepsy, drug-responsive epilepsy, and no epilepsy among children with MRI-identified FCD.
Methods: A keyword search of a hospital radiology database identified 97 study participants for inclusion in this retrospective study. Participants were included if they were under 18 years of age at time of database query and had an MRI between 2004 and 2013 showing FCD. Exclusion was based on imaging and clinical characteristics. Data was gathered using a chart review and supplemental questionnaire.
Results: In this cohort of patients with imaging findings compatible with FCD, 29% had not developed epilepsy. The prevalence of epilepsy and drug-resistant epilepsy was 71.13% (95% C.I. = 61.05–79.89%) and 32.99% (95% C.I. = 23.78–43.27%), respectively. Patients with epilepsy were more likely to have temporal ($p = 0.029$) or frontal ($p = 0.044$) lobe lesions and a family history of seizures ($p = 0.003$) than those without epilepsy. Age of seizure onset was later in those with drug-responsive epilepsy than those with drug-resistant epilepsy ($p = 0.0002$). A later age of seizure onset (OR = 1.22, $p = 0.0441$, 95% C.I. = 1.00–1.486) and absence of developmental delay (OR = 3.624, $p = 0.0497$, 95% C.I. = 1.002–13.110) predicted a less severe epilepsy phenotype.
Conclusions: Previous studies have only assessed patient cohorts with FCD and epilepsy, limiting the data on "asymptomatic" or "atypically presenting" FCD. Identifying a surprisingly large, novel cohort of children with FCD that had not developed epilepsy helps define prognosis and inform clinical management of children with FCD on imaging.

1. Introduction

Focal cortical dysplasia (FCD) is a malformation of cortical development that typically presents with childhood epilepsy (Blümcke et al., 2011; Sarnat and Flores-Sarnat, 2014; Sisodiya et al., 2009). Of patients with epilepsy, 5–10% also have FCD (Bast et al., 2006; Leach et al., 2014a). In pediatric cohorts with severe focal epilepsy, such as surgical candidates with drug-resistant epilepsy, up to 50% of patients have magnetic resonance imaging (MRI) visible FCD (Bast et al., 2006; Leach et al., 2014a). Onset of epilepsy was reported to be before age 5 for 60%, before 16 for 90%, and in adulthood for 10% of patients with FCD (Bast et al., 2006; Fauser et al., 2006; Sisodiya et al., 2014). A recent FCD study reported 6.3 years as the mean age of epilepsy onset in a cohort with drug-resistant epilepsy (Fauser et al., 2015).

Although pathology is the only means to confirm FCD, MRI is a recognized and widely used diagnostic tool for identifying FCD (Colombo et al., 2009; Lee and Kim, 2013; Leach et al., 2014a; Leventer et al., 1999; Madan and Grant, 2009; Mellerio et al., 2012; Widdess-Walsh et al., 2006). A study by Leach et al. (2014b) correlated FCD imaging features with pathology features. Of the three types and multiple subtypes of FCD classified by the International

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League Against Epilepsy (ILAE) classification system (Blümcke et al., 2011), MRI abnormalities were seen in 30% of FCD Type I cases, 55% of Type IIa, and 80% of Type IIb (Leach et al., 2014b).

FCD studies using surgical cohorts are limited by the potential to miss individuals with atypically presenting or asymptomatic FCD (Bast et al., 2006; Fauser et al., 2006; Widdess-Walsh et al., 2005). Because most healthy individuals do not undergo a brain MRI, the prevalence of FCD in the general population is unknown and difficult to assess (Holthausen et al., 2014). Large studies performing brain MRIs on healthy individuals have not identified FCD as a common finding (Sisodiya et al., 2009; Vernooji et al., 2007). However, one case study reported asymptomatic FCD identified by MRI in a 74-year-old male (Tezer-Filik et al., 2010). Other case studies document atypical clinical presentation of FCD such as two seizures and slow, progressive aphasia in a 32-year-old woman (Forgacs et al., 2014) and a single seizure in a 49-years-old male (Labate et al., 2015).

We hypothesized that an "atypical clinical presentation" of FCD without epilepsy is not rare, just rarely reported. There are no studies which describe the prevalence of epilepsy among those with MRI-identified FCD because all previous studies to our knowledge used cohorts of individuals that presented clinically with epilepsy and subsequently found to have FCD. Understanding the clinical spectrum of FCD helps define prognosis and inform clinical management of children with FCD on imaging. The purpose of this study was to determine the prevalence of epilepsy and drug-resistant epilepsy in patients with MRI-identified FCD and to describe a population of patients with FCD without epilepsy. We hypothesized there are differences between patients with an MRI-identified FCD who have drug-resistant epilepsy, drug-responsive epilepsy and no epilepsy. We aimed to determine the clinical and imaging differences that differentiate the epilepsy phenotype of children with imaging identified FCD.

2. Methods

The Institutional Review Board approved this retrospective, case-control study.

2.1. Participants and imaging review

A keyword search of the radiology database (Illuminate Insight, Softek, Kansas City, KS, U.S.A.) at a large tertiary care pediatric medical center using the term "cortical dysplasia" identified potential participants. Individuals between the age of 0 and 17 years at the time of the query who received a brain MRI between January 1, 2004 and December 31, 2013 showing single or multiple FCD(s) were eligible for inclusion. The index MRIs were all evaluated as a part of routine clinical practice by a group of experienced radiologists with training in Pediatric Neuroradiology. In each case, the imaging reviewer evaluated the examinations and categorized the findings in strict accordance with published criteria from our group (Leach et al., 2014b; Radhakrishnan et al., 2016). A board certified neuroradiologist with 20 years of experience interpreting MRIs for epilepsy surgery reviewed and classified all participant MR images, blinded to the epilepsy phenotype of the potential participants. For participants with more than one MRI available, the index cases identified by the keyword search and all prior and follow up MR imaging was reviewed.

Imaging protocols included the following: 1) Routine without contrast: Sagittal T1 (1 mm volumetric–4 mm slice thickness), Axial T2 (3–5 mm slice thickness), Axial T2 FLAIR (4–5 mm slice thickness), coronal T2 (4 mm slice thickness), Axial DTI (15–24 directions, 3 mm slice thickness), 2) Routine without and with contrast: without contrast study with additional volumetric 1 mm T1 and axial 4 mm T1 images post contrast, 3) Seizure protocol: Sagittal or Coronal T1 (1–1.25 mm volumetric with multiplanar reformations), Axial T2 (3–5 mm slice thickness), Axial T2 FLAIR (4–5 mm slice thickness), coronal oblique T2 FLAIR (3–4 mm slice thickness), coronal oblique T2 or STIR (3–4 mm slice thickness), Axial DTI (15–24 directions, 3 mm slice thickness) and 4) Seizure protocol with volumetric T2 FLAIR. Seizure protocol with added volumetric 1 mm isotropic sagittal T2 FLAIR and multiplanar reconstructions. The highest quality and field strength exam was used for lesion characterization.

Participants were excluded if they had genetic diagnoses associated with syndromic FCD (such as tuberous sclerosis complex) since the natural histories of these disorders are better understood than non-syndromic FCD. Participants with non-English speaking parents/guardians were excluded. Participants were excluded if the imaging review showed lesions that were 1) in the brain stem and/or cerebellum only, 2) potentially representative of a tumor as defined by mass effect, growth over time, radiologist recommendations for follow-up, and associated enhancement, 3) typical for remote insult as defined by cortical thinning and marked localized volume loss, or 4) gyral malformations involving greater than one brain quadrant or typical of lissencephaly, bilateral extensive polymicrogyria or hemimegalencephaly. Participants with technically inadequate studies (only one sequence or plane of acquisition, marked motion, or artifacts) were not included in the study.

During review of participant MRIs, FCD classification as "definite", "probable", or "possible" and lesion location were determined. FCD was defined as a localized disorder of the cortex and/or subjacent white matter typical of pathologically proven FCD seen in patients with drug-resistant epilepsy undergoing surgical resection (Blümcke et al., 2011; Leach et al., 2014a, 2014b). MRI characteristics of FCD, adapted from those previously developed and reported by our group (Leach et al., 2014b), included these features: 1) localized increased cortical signal without other known cause, 2) localized increase in cortical thickness, 3) ill-defined or irregular cortical-white matter junction, 4) localized subcortical signal located at the bottom of a sulcus, 5) asymmetric gyral pattern and/or depth, 6) transmantle signal changes related to a gyrus, and/or 7) subcortical heterotopic gray matter. FCD by MRI was "Definite" when feature 6 was seen with any two other features, "Probable" when feature 6 was seen with either feature 2, 3, 5, or 7 or when any three features were seen without feature 6, and "Possible" when any two features were seen without feature 6. Isolated heterotopias were not considered FCD.

During the imaging review, five distinct imaging themes defined by predominant imaging finding emerged. Anterior temporal lobe theme was defined by increased cortical or subcortical signal in the anterior temporal lobe and loss of gray matter-white matter differentiation which are typical of Type IIIa CD (Blümcke et al., 2011; Garbelli et al., 2012; Johnson et al., 2014). Gyral malformation predominant theme was abnormal sulcal or gyral pattern localized to one brain region and abnormal thickness or lobularity of the cortex which could be focally thickened or resemble polymicrogyria. This could be isolated or associated with 1) adjacent subcortical or periventricular heterotropia, which were commonly "transmantle" and nodular or ill-defined, 2) signal changes, or 3) both. Cortical signal predominant theme was defined by increased or decreased cortical signal which could be associated with gyral thickening and less impressive white matter signal. Cortical signal predominant theme typically lacked more extensive gyral malformations and irregularities. Subcortical predominant theme cases had localized subcortical signal abnormalities localized to a gyrus as the dominant imaging finding. The majority were associated with adjacent gray matter or white matter signal and ill-defined gray matter/white matter junction on T1 or T2 FLAIR. The imaging categorized under this theme do not have the typical tapering deep