FULL-LENGTH ORIGINAL RESEARCH

Temporal lobe epilepsy and focal cortical dysplasia in children: A tip to find the abnormality

*Luca Bartolini, †Matthew T. Whitehead, ‡§Cheng-Ying Ho, *Leigh N. Sepeta, *Chima O. Oluigbo, *Kathryn Havens, *Emily R. Freilich, *John M. Schreiber, and *William D. Gaillard

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Dr. Luca Bartolini is a neuroscience research fellow at Children's National Health System.

Summary

Objective: To demonstrate an association between magnetic resonance imaging (MRI) findings and pathologic characteristics in children who had surgery for medically refractory epilepsy due to focal cortical dysplasia (FCD).

Methods: We retrospectively studied 110 children who had epilepsy surgery. Twenty-seven patients with FCD were included. Thirteen had temporal lobe epilepsy (TLE) and 14 had extra-temporal lobe epilepsy (ETLE). Three patients had associated mesial temporal sclerosis. Preoperative 3T MRIs interleaved with nine controls were blindly re-reviewed and categorized according to signal alteration. Pathologic specimens were classified according to the 2011 International League Against Epilepsy (ILAE) classification and compared to MRI studies.

Results: Rates of pathology subtypes differed between TLE and ETLE ($\chi^2(3) = 8.57$, $p = 0.04$). FCD type I was more frequent in TLE, whereas FCD type II was more frequent in ETLE. In the TLE group, nine patients had temporal tip abnormalities. They all exhibited gray–white matter blurring with decreased myelination and white matter hyperintense signal. Blurring involved the whole temporal tip, not just the area of dysplasia. These patients were less likely to demonstrate cortical thickening compared to those without temporal tip findings ($\chi^2(1) = 9.55$, $p = 0.002$). Three of them had FCD Ib, three had FCD IIa, two had FCD IIIa, and one had FCD IIb; MRI features could not entirely distinguish between FCD subtypes. TLE patients showed more pronounced findings than ETLE on MRI ($\chi^2(1) = 11.95$, $p = 0.003$, odds ratio [OR] 18.00). In all cases of FCD, isolated blurring was more likely to be associated with FCD II, whereas blurring with decreased myelination was seen with FCD I ($\chi^2(6) = 13.07$, $p = 0.042$).

Significance: Our study described associations between MRI characteristics and pathology in children with FCD and offered a detailed analysis of temporal lobe tip abnormalities and FCD subtypes in children with TLE. These findings may contribute to the presurgical evaluation of patients with refractory epilepsy.

KEY WORDS: Focal cortical dysplasia, MRI, Temporal lobe epilepsy, Pathology, Children, Epilepsy surgery.

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*Center for Neuroscience, Children's National Health System, George Washington University, Washington, District of Columbia, U.S.A.; †Department of Diagnostic Imaging and Radiology, Children's National Health System, George Washington University, Washington, District of Columbia, U.S.A.; ‡Department of Pathology, Children's National Health System, George Washington University, Washington, District of Columbia, U.S.A.; and §Department of Pathology, University of Maryland, Baltimore, Maryland, U.S.A.

Address correspondence to Dr. Luca Bartolini, Center for Neuroscience, Children's National Health System, George Washington University, 111 Michigan Ave NW, Washington, DC 20010, U.S.A. E-mail: lbartoli@childrensnational.org

Key Points

- FCD I predominates in the temporal lobe and FCD II in extratemporal locations
- Temporal tip abnormalities in TLE include blurring of the gray–white matter junction with regionally decreased myelination and white matter hyperintensity.
- Blurring involves the whole temporal tip, not just the area of dysplasia. This can help identifying the epileptogenic focus in TLE.
- In all cases of FCD, isolated blurring is associated with FCD II, whereas blurring with decreased myelination is seen with FCD I.
- Patients with TLE due to FCD are 18 times more likely to have more pronounced findings on MRI than patients with ETLE

Focal cortical dysplasia (FCD), a common cause of medically refractory epilepsy,[1] is characterized by abnormalities of neuronal maturation, differentiation, and cortical layering.[2] Up to 50% of cases of FCD are located in the temporal lobe,[3] and are commonly associated with temporal lobe epilepsy (TLE). In 2011, the International League Against Epilepsy (ILAE) redefined the subtypes of FCD to improve categorization of the pathologic findings and reduce interobserver variability.[4] However, there remains a lack of well-defined neuroradiologic features associated with different types of FCD, especially type I.[5] Magnetic resonance imaging (MRI) findings include blurring of the gray–white matter junction, subcortical white matter volume loss, white matter T_2 hyperintensity, abnormal gyration, and cortical thickening.[6] The ability to consistently detect FCD type I and II appears limited, even with 3T MRI.[5]

We aim to characterize differences in FCD MRI findings in TLE and extra-temporal lobe epilepsy (ETLE), and to identify imaging features that predict histology.

Methods

Subjects

We retrospectively analyzed 110 consecutive children, from a prospectively maintained quality assurance epilepsy surgery database, who had epilepsy surgery from March 2011 to August 2015 (after introduction of 3T MRI). All patients underwent long-term video–electroencephalography (EEG) monitoring, high-resolution epilepsy protocol 3T MRI, and in selected cases, functional MRI, neuropsychological evaluation, and phase II invasive monitoring prior to surgery. Nine patients had 18-Fluorodeoxyglucose–positron emission tomography (FDG-PET). We included 27 patients with pathologically confirmed FCD: 13 had TLE (which included 3 cases of associated mesial temporal sclerosis [MTS]), and 14 had ETLE. Demographic and clinical data recorded included age, sex, age at seizure onset, seizure duration, age at surgery, outcome according to the Engel Epilepsy Surgery Outcome Scale (from last clinic visit and at least 1 year following surgery).[7]

Children's National Health System Institutional Review Board (IRB) approved the study.

MRI

A board-certified pediatric neuroradiologist blindly re-reviewed preoperative 3T epilepsy protocol MRI studies from the 27 epilepsy surgery patients with FCD, interleaved with 9 epilepsy patients with normal MRI. The neuroradiologist was not aware of the clinical indication for the MRI studies. We categorized images as follows: (0) normal, (1) presence of gray–white matter blurring only, (2) gray–white matter blurring associated with regionally decreased myelination, (3) marked signal prolongation (hyperintense signal relative to normal gray matter), (4) transmantle sign (abnormal trailing signal toward the ventricle or touching the ventricle) and (5) white matter hyperintense signal on T_2-weighted Imaging (T2WI) and T_2–fluid-attenuated inversion recovery (FLAIR). Categories 2 and 3 were considered to represent more pronounced signal alterations. MRI studies were also classified according to the presence of cortical thickening (defined as a visually apparent difference compared to the thickness of the cortex in a nonaffected area of the same gyrus and to the same area contralateral to the lesion). T_1-weighted Imaging (T1WI) was the only sequence available for one patient in the TLE group, and he was included only in the analysis of cortical thickening. All exams were performed on a 3 Tesla magnet (General Electric, Milwaukee, WI, U.S.A.) with a 32-channel head coil. All studies employed an epilepsy high-resolution protocol that contained the following pulse sequences: three-dimensional (3D) volumetric spoiled gradient-echo (SPGR) T1WI, fast spin-echo (FSE) T2WI or fast relaxation fast spin echo (FRFSE) T2WI, axial diffusion-weighted images (DWI) or diffusion tensor images (DTI), coronal T2WI (either fat saturation T2WI or inversion recovery T2WI), and high-resolution oblique coronal FSE WI thorough the hippocampi (3 mm). Magnetization transfer (MT) T1WI and arterial spin-labeling (ASL) perfusion sequences were protocol additions for certain cases. Each pulse sequence was adjusted manually for window/level to ensure the contrast resolution was personalized to the reader's visual system.

Pathology

All specimens were re-reviewed by a board-certified neuropathologist according to the 2011 ILAE classification of FCD. Palmini classification was used to allow comparison with prior studies which utilized this classification. Routine histologic examination included hematoxylin and eosin stain in addition to immunohistochemical analysis with NeuN, Neurofilament-200 (NF-200), synaptophysin, and glial fibrillary acidic protein (GFAP) stains.

Statistical analysis

Descriptive statistics including median, interquartile range, and frequencies are reported for demographic and outcome variables: age of seizure onset, seizure duration, age at surgery, pathologic findings, and Engel outcome for the TLE and ETLE groups (separately). We examined the sensitivity of conventional visual analysis of 3T MRI in detecting areas of FCD for the following groups: (1) combined TLE and ETLE, (2) TLE, (3) temporal tip subgroup, (4) ETLE, and (5) FCD I subgroup (including both TLE and ETLE). We used likelihood ratios to examine the rates of specific pathology subtypes and Palmini categories for MRI findings within different patient groups, as well as the association between pathology subtype and MRI findings within those groups because in some cases the cell count was <5 due to the small sample size. First, we compared pathology subtypes in TLE and ETLE patients. Second, we examined the prevalence of cortical thickening in patients with and without temporal tip involvement in the TLE group. Third, we investigated rates of MRI findings (using the six MRI categories previously delineated) in patients with TLE compared to those with ETLE. We also examined the likelihood of more pronounced MRI findings (MRI categories 2 and 3) compared to less evident results (MRI categories 0 and 1) in TLE and ETLE. Third, we compared the rates of abnormality detection (using the six MRI categories) in T_2-FLAIR and T2WI in the (1) combined TLE and ETLE group and (2) temporal tip subgroup. Finally, we examined the association between MRI findings and pathology within the following groups: (1) TLE, (2) TLE with temporal tip involvement, (3) TLE and ETLE combined, and (4) ETLE. Statistical analyses were conducted using SPSS version 23.0 (IBM Corp., Armonk, NY, U.S.A.).

Results

Data for all 27 patients, including clinical, MRI, and pathological findings, are summarized in Table 1.

Clinical data

In the TLE group (n = 13), median age at seizure onset was 24 months (interquartile range [IQR] 51), median seizure duration was 5.9 years (IQR 8.9), and median age at surgery was 7.6 years (IQR 11.0). FCD type Ib was the most common pathologic finding in the TLE group (n = 5). Two cases of FCD Ib were associated with MTS, hence they were classified as FCD IIIa. One case of FCD IIa had also MTS and was classified as dual pathology.[4] Engel outcome was: class I (n = 10), class II (n = 2), and class III (n = 1). Of the nine patients with temporal tip abnormalities, seven had class I and two had class II outcome.

In the ETLE group (n = 14), median age at seizure onset was 44 months (IQR 54), median seizure duration was 7.3 years (IQR 5.2), and median age at surgery was 12.9 years (IQR 7.9). FCD types IIa and IIb were the most common pathologic findings (type IIa: n = 7; IIb: n = 6). Engel outcome was as follows: class I (n = 10, including two patients with only 1 year of postoperative follow-up), class II (n = 2, including one patient with 1-year follow-up), and class III (n = 2, including one patient with 1-year follow-up).

Conventional visual analysis of 3T MRI had a sensitivity of 89% for combined TLE and ETLE groups in detecting areas of FCD. The sensitivity for the TLE group was 92%, and for the temporal tip subgroup was 100%. The sensitivity for the ETLE group was 86%. Sensitivity for the FCD I subgroup (including both TLE and ETLE) was 83%.

Ipsilateral MTS occurred in three patients and bilateral hippocampal malrotation (defined as a rounded shape of the hippocampus in at least one plane or incomplete hippocampal inversion) in three other patients in the TLE group. All three patients with hippocampal malrotation had Engel I outcome. Of all nine patients with temporal pole abnormalities, only one had a history of febrile seizures and also had evidence of MTS. The median age at onset for patients with temporal tip abnormalities and no evidence of MTS was 36 months (IQR 55), median age at surgery was 8.4 years (IQR 11.5), and median seizure duration was 5.2 years (IQR 10.3). For patients with MTS, median age at onset was 20 months (IQR 12), median age at surgery was 7.6 years (IQR 2.4), and median seizure duration was 6.6 years (IQR 2.1).

T_2-FLAIR sequence was more likely to detect an abnormality in the area of FCD than T2WI sequence in the combined TLE and ETLE group ($\chi^2(16) = 44.32$, $p < 0.000$). In particular, T_2-FLAIR detected gray–white matter blurring associated with regionally decreased myelination, whereas the same patient's scans were read as normal using T2WI (combined TLE and ETLE: n = 3). All three of those patients were in the temporal lobe tip subgroup.

Pathologic findings and location

The rates of pathology subtypes differed between the TLE and ETLE groups ($\chi^2(3) = 8.57$, $p = 0.04$). Overall, FCD I was more frequent in the TLE group (5 patients vs. one in the ETLE group), whereas FCD II was more frequent in the ETLE group (13 cases vs. 6 in the TLE group). FCD subtypes were as follows: in the TLE group, five patients had FCD Ib (Fig. 1), four had FCD IIa, two patients had FCD IIb, and two patients FCD IIIa. Three patients had MTS: one had dual pathology with FCD IIa and MTS and two had FCD IIIa (both had FCD Ib and MTS). Three patients with temporal tip involvement were found to have FCD Ib, three patients had FCD IIa, two had FCD IIIa, and one had FCD IIb. Nine patients in the TLE group had signs of regionally decreased myelination, especially in the temporal tip, with vacuolated white matter, ectopic neurons, and gliosis. In the ETLE group, one patient had FCD Ib,

Table 1. Clinical, MRI, and pathologic findings in TLE and ETLE patients

Temporal lobe epilepsy (TLE) patients (n = 13)

Pt	Age at onset (m)	Age at surgery (y)	Temporal tip (yes/no)	Engel	T_2-FLAIR	T2WI	T_2 fatsat	T1WI	MT	DTI	Path
1	24	8.6	Yes	1	BD	BD	NA	N	N	N	IIa + MTS (DP)
2	60	17.0	Yes	1	BD	BD	BD	N	N	N	Ib
3	30	6.3	Yes	2	BD	N	BD	N	N	N	IIb
4	42	18.8	Yes	1	BD	N	BD	N	A	N	IIa
5	95	10.4	Yes	2	BD	N	NA	N	N	N	Ib
6	3	18.2	Yes	1	BD	BD	BD	N	N	DA	Ib
7	8	5.2	Yes	1	BD	BD	BD	BD	N	N	IIa
8	20	6.2	Yes	1	BD	BD	BD	N	N	N	IIIa
9	60	17.5	No	1	NA	NA	NA	B	NA	NA	Ib
10	12	7.6	Yes	1	BD	BD	BD	BD	N	DA	IIIa
11	56	6.4	No	1	B	B	B	B	N	B	IIb
12	3	5.9	No	3	N	N	N	N	N	N	Ib
13	6	6.4	No	1	B	B	B	B	E	B	IIa

Extra-temporal lobe epilepsy (ETLE) patients (n = 14)

Pt	Age of onset (m)	Age at surgery (y)	Location	Engel	T_2-FLAIR	T2WI	T_2 fatsat	T1WI	MT	DTI	Path
14	52	15.2	PL	1	B	B	B	B	N	B	IIa
15	0	6.9	FL	1	B	B	NA	B	N	B	IIa
16	17	7.8	PL	1	B	B	B	B	E	B	IIa
17	64	13.0	FL	1	BD	BD	BD	N	E	N	Ib
18	87	13.6	PL	1	B	B	B	B	E	B	IIb
19	2	0.6	FL	1	N	B	B	B	NA	N	IIb
20	6	16.3	FL	3	M	M	M	M	A	B	IIb
21	30	5.0	OL	1	B	B	B	B	A	B	IIb
22	40	21.8	FL	1	B	B	B	B	N	B	IIa
23	3	7.7	FL	2	B	B	B	B	N	B	IIa
24	84	14.0	FL	1	B	B	B	B	NA	N	IIb
25	48	15.9	FL	2	N	N	N	N	N	N	IIa
26	48	12.7	PL	1	N	N	N	N	N	N	IIa
27	57	9.4	FL	3	B	B	B	B	A	B	IIb

Pt, patient; m, months; y, years; T_2 FLAIR, T_2 fluid-attenuated inversion recovery; T2WI, T_2-weighted imaging; T_2 fatsat, T_2 fat saturation; T1WI, T_1-weighted imaging; MT, magnetization transfer; DTI, diffusion tensor imaging; Path, pathology; MTS, mesial temporal sclerosis; DP, dual pathology; BD, gray–white matter blurring associated with decreased myelination; N, normal; NA, not available; M, marked signal prolongation; A, abnormal; DA, decreased apparent-diffusion coefficient; B, gray–white matter blurring only; E, equivocal; PL, parietal lobe; FL, frontal lobe; OL, occipital lobe.

Data are represented in median. Five TLE and four ETLE patients had FDG-PET.

seven patients had FCD IIa (Fig. 2), and six patients had FCD IIb.

MRI characteristics of the temporal tip

In the TLE group, MRI abnormalities occurred predominantly in the temporal lobe tip (n = 9) (Fig. 3). Temporal tip abnormalities all exhibited gray–white matter blurring with regionally decreased myelination (n = 9) and white matter hyperintense signal (n = 9). These MRI findings were not pathognomonic for a specific FCD subtype, but six patients with temporal tip involvement demonstrated FCD Ib or IIa. Within the TLE group, patients with temporal tip involvement were less likely to demonstrate cortical thickening compared to those without temporal tip findings ($\chi^2(1) = 9.55$, $p = 0.002$).

MRI findings in TLE versus ETLE

MRI rates for categories 0–3 were different for TLE compared to ELTE ($\chi^2(4) = 14.46$, $p = 0.002$). TLE patients were more likely to have gray–white matter blurring associated with regionally decreased myelination, whereas ETLE subjects were more likely to have gray–white matter blurring only. TLE patients were 18 times more likely than ETLE patients to have more pronounced MRI findings ($\chi^2(1) = 11.95$, $p = 0.003$, OR 18.00). Only one patient in the TLE group (with no temporal tip involvement) had evidence of transmantle sign. In the ETLE group; six patients had white matter hyperintensity on MRI and four had transmantle sign. Comparison of FLAIR white matter hyperintensity and transmantle sign between TLE and ETLE revealed no differences ($p = 0.165$ and $p = 0.150$, respectively), potentially owing to the sample size.

Association between FCD classification and MRI findings

Within the TLE group as a whole, we found no relationship between FCD classification and MRI findings. In the ETLE group, we found a trend for a relationship between

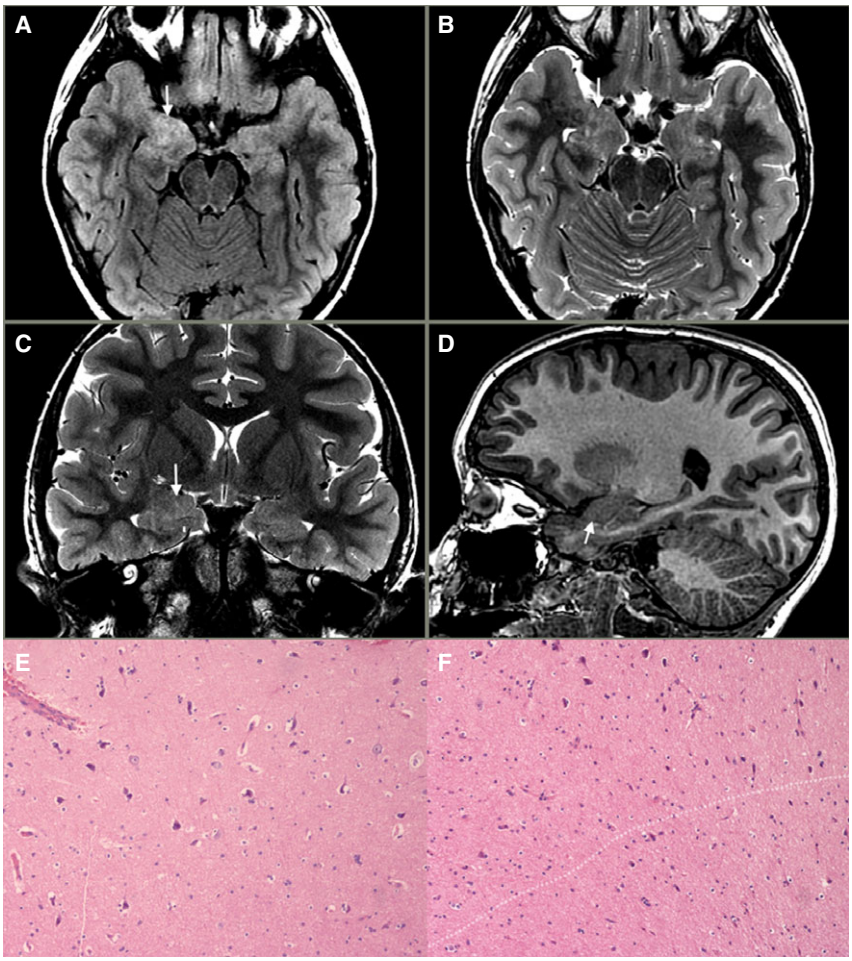

Figure 1.
MRI and pathologic findings from a 10-year-old patient with temporal lobe epilepsy. Axial T_2-FLAIR (repetition time [TR]/echo time [TE]/inversion time [IT] msec, 10,000/126/2,250) (**A**), axial T2WI (TR/TE msec, 5,928/91) (**B**), and coronal T2WI (TR/TE msec, 2,850/115) (**C**) reveal abnormal hyperintense signal infiltrating the right temporal uncus, obscuring the normal corticomedullary interfaces between the amygdala, cortex, and intervening white matter (arrows). Sagittal SPGR T1WI (TR/TE/IT msec, 8/3/450) (**D**) shows abnormal signal that is isointense to gray matter, masking the distinction between the amygdala and overlying cortex (arrow). Pathologic findings from the same patient: hematoxylin and eosin (H&E) stain, 10× magnification showing disorganized architecture of the cortex and paucity of neurons (**E**) and blurring of the gray–white matter junction (faint dotted line) with presence of ectopic neurons in the subcortical white matter (**F**). Final diagnosis is FCD type Ib.
Epilepsia © ILAE

FCD classification and T_2-FLAIR MRI findings ($\chi^2(3) = 7.21$, $p = 0.066$). When all cases of FCD including TLE and ETLE were combined, a finding of gray–white matter blurring only was more likely to be seen in association with FCD II, whereas gray–white matter blurring associated with decreased myelination was more likely to be seen with FCD I ($\chi^2(6) = 13.07$, $p = 0.042$).

Postoperative MRI evaluation and reoperation

Two-thirds of patients (n = 18) had intraoperative neuronavigation to guide surgery, 14 had intraoperative MRI, and all patients had postoperative 3T MRI to confirm resection of the targeted abnormality. In the TLE group, nine patients had expected postoperative changes with no identifiable residual FCD. Of the four patients who had evidence of residual FCD, three underwent successful re-resection. In the ETLE group, 10 patients had only post-operative changes on MRI; three patients had residual FCD, and two of them underwent successful re-resection.

Discussion

Imaging abnormalities in patients with TLE predominantly occurred in the temporal lobe tip, and consisted of gray–white matter blurring with regionally decreased myelination and white matter hyperintense signal, without evidence of cortical thickening. Blurring was not confined to the area of focal cortical dysplasia but extended to the whole temporal tip. The majority of patients with temporal tip abnormalities were found to have FCD Ib or IIa, but MRI features could not help distinguish between the two subtypes.

FCD I predominated in the temporal lobe and FCD II in extratemporal locations. Patients with TLE due to FCD were more likely to have more pronounced findings on MRI than patients with ETLE.

Explanation and importance of temporal tip abnormalities

The literature describes blurring of the gray–white matter interface in FCD lesions located in the temporal pole.[8] Table 2 summarizes published studies that evaluate temporal tip imaging and pathology. There is still debate on the exact mechanism that could account for the imaging changes seen in these patients.[9,10]

From a pathologic standpoint, it is likely that the uneven thickness of the cortex accounts for the blurring of the gray–white junction seen on MRI. This finding was rarely seen in

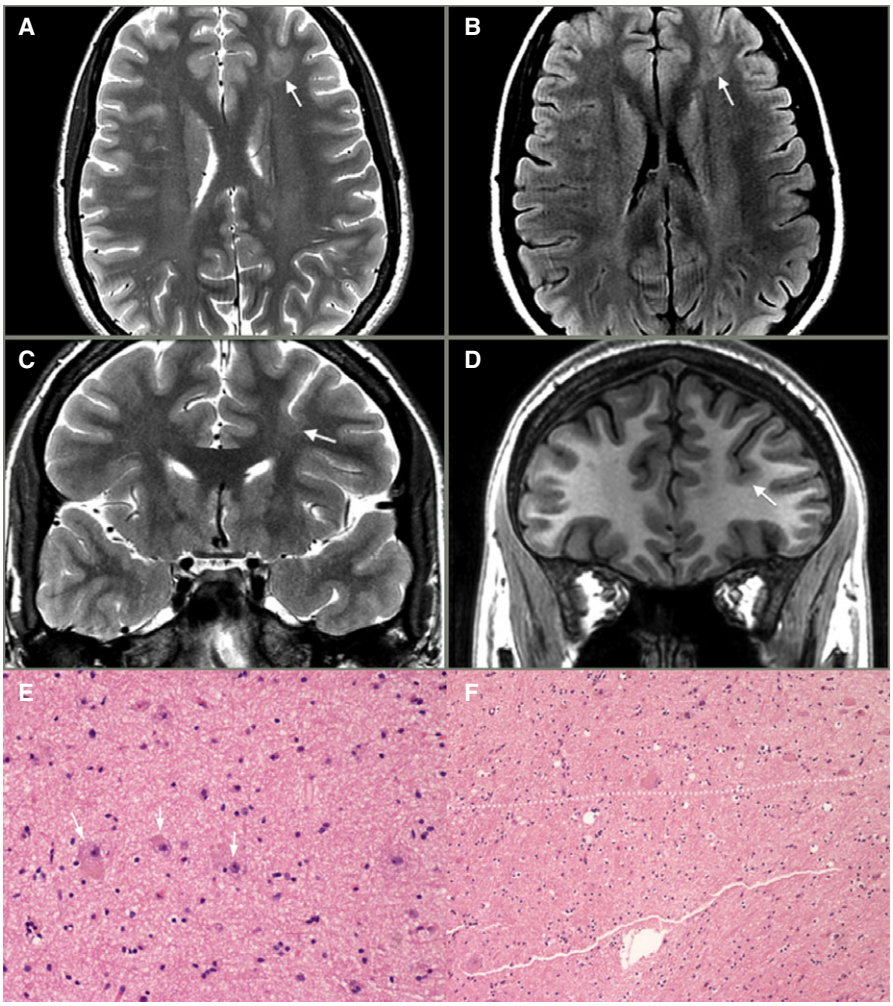

Figure 2.
MRI and pathologic findings from a 21-year-old patient with ETLE. Axial T2WI (TR/TE msec, 3,500/99) (**A**), axial T_2-FLAIR (TR/TE/IT msec, 10,000/145/2,250) (**B**), and coronal T2WI (TR/TE msec, 3,000/102) (**C**) depict abnormal ill-defined hyperintense signal extending from the juxtacortical white matter in the depth of the left superior frontal sulcus toward the lateral ventricular margin, with overlying cortical thickening (arrows). Coronal SPGR T1WI (TR/TE/IT msec, 8/3/450) (**D**) shows focal blurring of the corticomedullary interface in the deep left superior frontal sulcus with associated cortical thickening (arrow). Pathologic findings from the same patient: H&E stain, 10× magnification showing dysmorphic neurons (white arrows) (**E**) and blurring of the gray–white matter junction (faint dotted line) with vacuolated white matter (**F**). Final diagnosis is FCD type IIa.
Epilepsia © ILAE

isolation in our cohort of patients with TLE. In the majority of cases, blurring was associated with regionally decreased myelination, especially in the temporal tip, characterized by the presence of vacuolated white matter, ectopic neurons, and gliosis, which are common findings, but not present in all cases. In our cohort of ETLE, vacuolated white matter was not seen as often as in cases of TLE.

In the study by Di Gennaro,[11] several patients with MTS were found to have ectopic neurons in the white matter on pathologic evaluation and blurring with atrophy of the temporal pole on MRI. Meiners[12] found that a lower myelin density was the only pathologic change associated with the MRI findings observed in the temporal pole. Choi[13] described a higher number of ectopic neurons assessed via quantitative measurement in the temporal tip white matter of patients with MRI changes.

Other studies found no explanation for the temporal tip changes. Mitchell[9] analyzed specimens from patients with temporal tip MRI changes, and despite finding significant gliosis in the temporal pole, they could not demonstrate a difference in the density of glial cell nuclei in patients with or without blurring. Garbelli[14] reported that patients with and without blurring of the gray–white junction in the temporal pole may have similar neuropathological features, with no difference in terms of gliosis or white matter neuronal density. The same authors proposed that the blurring is the result of myelin bundle degeneration in the temporal pole with resulting abnormal configuration of the fibers, and they utilized the term "dysmyelination" to describe this process.

Embryonic development and maturation of the temporal lobe may place the temporal tip at greater risk for migrational abnormalities. Different brain regions have specific periods of myelin maturation.[15] The temporal tip undergoes slower myelination than other brain regions, particularly during the first 2 years of life, which may account for potential vulnerability to chronic insult of this area.[16] The absence of macrophage infiltration in our study group argues against a mechanism of ongoing insult as the cause of temporal tip findings.

Temporal tip MRI changes are usually described in association with MTS.[4,17,18] Two thirds of our patients with temporal tip abnormalities did not have evidence of MTS, which supports the notion that the pathologic

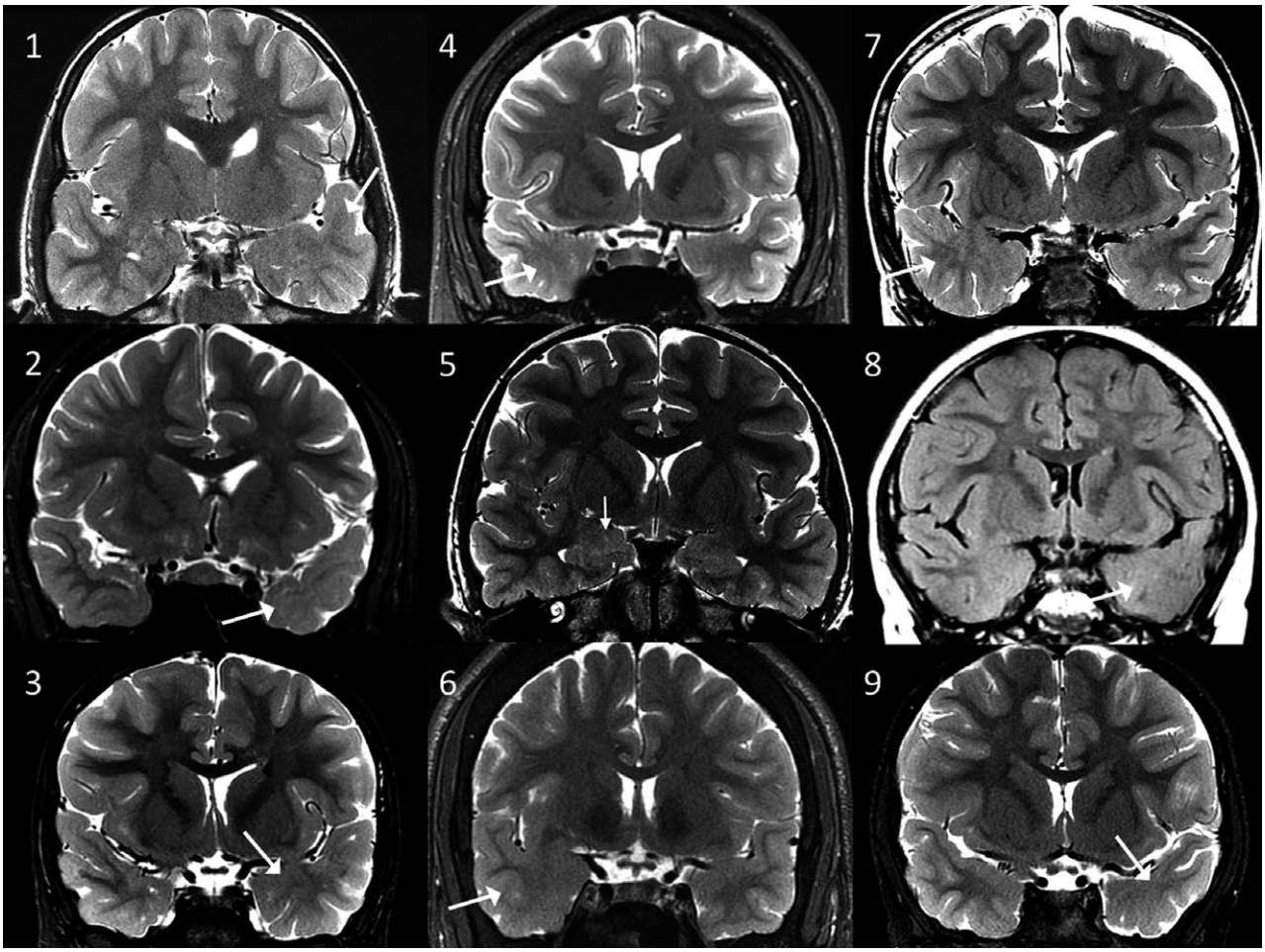

Figure 3.
MRI findings of the nine patients with temporal lobe epilepsy and temporal tip abnormalities. Coronal T2WI (1–7, 9), and coronal T_2-FLAIR (8) images through the temporal lobes of nine patients with temporal lobe epilepsy demonstrating asymmetric hyperintense temporal white matter signal and regional obscuration of corticomedullary interfaces in the temporal tip representing cortical dysplasia (arrows).

Table 2. Studies that describe temporal pole MRI abnormalities in patients with temporal lobe epilepsy

Study	No. of patients	Children (n, %)	Seizure duration (y, range)	Magnet	Temporal tip abnormalities (n, %)	MTS (n, %)	G/W blurring ± hypom (n, %)
Bartolini (this study)	13	13 (100)	6 (0–17)	3 T	9 (69)	3 (23)	12 (92)
Garbelli[14]	32	0	29 (5–54)	1.5 T	18 (56)	32 (100)[a]	13 (40)
Caboclo[37]	35	0	26 (5–49)	1.5 T	21 (66)	35 (100)[a]	N/A
Coste[38]	30	0	N/A	1.5 T	10 (33)	22 (73)	N/A
Di Gennaro[11]	60	0	24 (2–48)	1.5 T	43 (72)	60 (100)[a]	37 (62)
Kuba[18]	55	0	26	1.5 T	21 (38)	55 (100)[a]	21 (38)
Mitchell[9]	50	N/A	32 (8–52)	1.5 T	29 (58)	36 (72)	29 (58)
Naves[17]	122	N/A	25 (3–57)	1.5 T	64 (52)	122 (100)[a]	64 (52)

pt, patients; y, years; MTS, mesial temporal sclerosis; G/W, gray–white; hypom, hypomyelination; T, Tesla; N/A, not available.
[a]The presence of MTS was an inclusion criterion for this study.

findings precede onset of epilepsy and that seizures induced by FCD result in secondary hippocampal injury. The lower frequency of hippocampal sclerosis in our paper compared to other studies[11,17,18] may be a consequence of patient selection by several previous investigators for inclusion based on the presence of MTS.

These studies are primarily adult cohorts with a longer seizure duration.

MRI sensitivity and correlation with location and focal cortical dysplasia subtypes: 3T versus 1.5T MRI

Our study had an overall sensitivity of 89% (100% for the temporal lobe tip and 83% when examining only patients with FCD I) in detecting areas of FCD in children with refractory epilepsy and showed associations between different types of FCD, 3T MRI findings, and location. We observed that the TLE population has a higher likelihood than ETLE of having more pronounced MRI abnormalities (blurring of the gray–white matter associated with regionally decreased myelination or marked signal prolongation versus isolated blurring of the gray–white matter or normal MRI). FCD II was more likely to be identified as isolated gray–white matter blurring on imaging, whereas FCD I was associated with an MRI finding of gray–white matter blurring with regionally decreased myelination.

Despite the existence of relevant literature on the radiologic, pathologic, and clinical features of FCD in adults, data in children are fewer, and are usually included in larger cohorts of adults[19] (Table 3). The MRI sensitivity for FCD rarely surpasses 80% and is lower when analyzing for FCD I.[19] Previous studies concentrate on a specific FCD subtype without evaluation based on the location or region of the FCD.[20]

We restricted our study to patients who had imaging at 3T with a high-resolution epilepsy protocol,[21] as imaging using 3T MRI improves sensitivity in detecting cortical malformations when compared to 1.5T.[22] A prospective comparison showed detection of new lesions in 65% of previously MRI-negative patients. FCD was found in almost two thirds of patients who had a normal 1.5T and abnormal 3T MRI. Because of findings of 3T MRI, the clinical management was changed in 38% of patients.[23] A study that included 25 patients with FCD II, showed that 3T compared with 1.5 T MRI improved characterization of the FCD, owing mainly to increased detection of subcortical white matter signal changes tapering toward the ventricles.[24] A study highlighted the improvement of seizure-free surgical outcome after implementation of 3T MRI and FDG-PET in selected cases.[25] Another study[26] analyzed 21 patients (including 4 children) with 7T MRI who had a prior nonlesional study at 1.5T or 3T. All four patients who underwent surgery as the result of this reanalysis had FCD. The authors attributed the increased diagnostic accuracy specifically to gradient echo (GRE) GRE and T_2-FLAIR images. We found that T_2-FLAIR had a higher sensitivity than T1WI, T2WI, MT, and DTI for all subtypes of FCD.

1.5 T studies do not find any pathognomonic MRI characteristics for FCD I. Investigations report the presence of blurring of the gray–white matter junction in 14–56% of patients and white matter hyperintensity in 56–80%.[27–31] Previous studies found no differences in the TLE group

Table 3. Studies that describe MRI abnormalities and pathologic findings following Palmini in patients with focal cortical dysplasia

Pathology	FCD I				FCD II					
Magnet strength	1.5 T		1.5 T–3 T	3T	1.5 T		1.5 T–3 T	3 T		7 T
	Study									
MRI finding (n, %)	Lerner[27]	Krsek[28]	Alshafai[29]	Bartolini (this study)	Colombo[6]	Lerner[27]	Krsek[28]	Alshafai[29]	Bartolini[b]	De Ciantis[26]
Blurring GW junction	4 (14)	44 (56)	2 (20)	5 (83)	76 (92)	46 (73)	51 (76)	7 (41)	16 (84)	1 (33)
Decreased myelination	3 (11)	N/A	1 (10)	4 (67)	71 (86)	26 (41)	N/A	0	4 (21)	0
Marked prolongation relative to gray matter	2 (7)	9 (11)	N/A	0	17 (20)	22 (35)	31 (60)	N/A	1 (5)	1 (33)
Transmantle sign	N/A	0	0	1 (17)	76 (92)	N/A	8 (15)	1 (5)	4 (21)	1 (33)
WM hyperintensity	18 (56)	44 (56)	8 (80)	4 (67)	80 (96)	37 (59)	31 (60)	11 (65)	9 (47)	N/A
N patients per FCD type (% of total patients)	33 (34)	79 (51)	10 (37)	6 (22)	118 (100)	64 (66)	51 (33)	17 (63)	19 (70)	3 (14)
Total n patients in study (% children)	97 (N/A)	154 (N/A)[a]	27 (100)	27 (100)	118 (0)	97 (N/A)	154 (N/A)[a]	27 (100)	27 (100)	21 (19)

GW, gray–white; N/A, not available; WM, white matter.
[a]The study included 200 patients (192 children) but only 154 patients (unknown n of children) were included in the MRI study.
[b]Includes one case of FCD II with associated mesial temporal sclerosis ("dual pathology," following the 2011 ILAE classification).

among different FCD types[30,31] and reported FCD I more in TLE patients than any other extratemporal location individually,[27] similar to our findings. In our study, gray–white blurring, usually associated with regionally decreased myelination, was present in 80% of children with TLE and FCD I, which is higher than in previous studies. This difference may arise from image sequences at 3T, interpretation of the pathologic specimens, and selection bias of those children on whom we operated.

Studies of FCD II with 1.5T also show mixed results. Gray–white blurring is reported in 33–92% of patients,[20,26–30] marked signal prolongation relative to normal gray matter in 33–59%,[26–28] and white matter hyperintensity in 60–96%.[20,27–29] A combination of cortical thickening, gray–white blurring, and transmantle sign was found in all 59% of patients with FCD II who had a positive MRI.[32] A specific aspect of the central sulcus appearance named "power button sign" was found in 62% of FCD II patients in a case-control study and was considered highly specific for this type of dysplasia.[33] Our results support a study[34] that analyzed pathologic specimens from 13 patients with FCD who had en bloc resection with a 7T magnet; 85% of patients had ETLE. The authors found isolated gray–white blurring in the four patients who had FCD IIa and hypothesized a less severe neuroradiologic feature when compared to FCD IIb, owing to the absence of edema, balloon cells, and myelin alteration. Our patients with FCD II were more likely to have isolated gray–white blurring, although we did not find a difference between FCD IIa and IIb.

Limitations

The retrospective nature has an intrinsic possibility of selection bias. We chose our patients based on the pathology results, but our patient selection is biased toward infants and children with identifiable MRI abnormalities, hence resulting in a higher sensitivity and lower number of negative MRI studies. All images were read by only one blinded pediatric neuroradiologist. The identification of FCD depends on the quality of MRI studies, the skill of those reading MRI, and the use of functional imaging and/or EEG/magnetoencephalography (MEG) linked to review of MRI data[35,36] and the skill of the neuropathologist. One third of our patients had FDG-PET, which may increase the detection rate of FCD when combined with 3T MRI. The sample size may limit the ability to draw conclusions on the efficacy of MRI in predicting a specific pathologic subtype and the relevance of location of FCD. This is particularly true when TLE and ETLE MRI characteristics are compared, as imaging may appear intrinsically different in different brain regions, potentially owing to the different myelination patterns as described previously. However, if we consider that only a minority of patients were younger than 5 years, it is unlikely that the difference observed in the imaging characteristics is the result of a different stage of myelination. We did not obtain MRI studies of the pathologic specimens to confirm the radiologic features of FCD that we found in vivo. Two- thirds of patients (n = 18) had intraoperative neuronavigation, half had intraoperative MRI, and all patients had postoperative MRI. Thus while we cannot pinpoint the specific location of the specimen, we can confidently claim that the tissue derives from the targeted abnormality. Decreased postoperative seizure frequency and pathologic tissue findings support the notion that the epileptogenic zone was correctly identified if not necessarily completely removed. The possibility of residual FCD is unlikely to alter our observations, including the FCD type.

Our study population is heterogeneous, with different FCD types and MRI findings, including three cases of associated MTS. Moreover, the neuroradiologic characteristics of our study population are shared among FCD subtypes. The lack of significance when comparing TLE and ETLE for certain MRI findings such as the transmantle sign may potentially be attributed to the sample size. The Engel outcome for patients with temporal tip findings was class I or II, supporting the relevance of our observations for clinical care. A minority of our patients (n = 5) had successful repeat surgery for residual FCD.

Conclusion

Our findings suggest the importance of conducting a meticulous analysis of the myelination patterns, especially of the temporal lobe tip, using 3T MRI in patients with medically refractory epilepsy to help guide the presurgical evaluation, and may suggest FCD subtype. T_2-FLAIR sequence is the most sensitive to identify the area of FCD. All of our patients with temporal tip involvement showed gray–white matter blurring with regionally decreased myelination and white matter hyperintense signal. Blurring was not confined to the area of focal cortical dysplasia, but extended to the whole temporal tip. MRI features are shared between FCD subtypes, but gray–white matter blurring with regionally decreased myelination is more often seen with FCD I, whereas isolated gray–white blurring is more often seen with FCD II. None of these changes can be considered pathognomonic for a specific FCD type, and larger series will be needed to confirm these observations.

Disclosure of Conflict of Interest

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