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Spatiotemporal distribution and age of seizure onset in a pediatric epilepsy surgery cohort with cortical dysplasia

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ABSTRACT

Objective: Focal Cortical Dysplasias (CD) are a common etiology of refractory pediatric epilepsy and are amenable to epilepsy surgery. We investigated the association of lesion volume and location to age of seizure onset among children with CD who underwent epilepsy surgery.

Methods: A retrospective study of epilepsy surgery patients with pathologically-confirmed CD. Regions of interest (ROI) determined preoperative lesion volumes on 1.5 T and 3 T T2 and SPGR MRIs, and location in 7 distributed neural networks. Descriptive and inferential statistics were used.

Results: Fifty-five patients were identified: 35 girls (56.5 %). Median age of seizure onset: 19.0 months (range 0.02 months - 16.0 years). Median age of surgery: 7.8 years (range 2.89 months - 24.45 years). CD were frontal (n = 21, 38 %); temporal (n = 15, 27 %); parietal (n = 10, 18 %); occipital (n = 3, 5%); multilobar (n = 6, 11 %). Frontal FCD had seizure onset < 1-year-old ($P = 0.10$); temporal lobe CD seizure onset was more likely > 5-years-old (P= 0.06). Median lesion volume for CD was 23.23 cm^3 (range: 1.87-591.73 cm^3). Larger CD lesions were associated with earlier epilepsy ($P = 0.01$, r = -0.16). We did not find that lesions proximal to early maturing cortical regions were associated with earlier seizure onset. We found an association with CD location in the default mode network (DMN) and age onset < 5years old ($P = 0.03$). Age of seizure onset was negatively correlated with percent of CD overlapping motor cortex ($P = 0.001$, r =-0.794) but not with CD overlap of the visual cortex ($P = 0.35$). There was no effect of CD type on age of epilepsy onset.

Significance: Larger CD lesions are associated with earlier onset epilepsy. CD most commonly occurs within the DMN and Limbic network, and DMN is associated with seizure onset before 5-years-old. Percent of CD overlapping motor cortex correlates with earlier seizure onset. These observations may reflect patterns of brain maturation or regional differences in clinical expression of seizures.

1. Introduction

Malformations of cortical development (MCD), in particular focal cortical dysplasias (CD), are common causes of pharmacoresistant epilepsy in children. CD may be small with clear borders; or they may be diffuse, ill-defined, and may occur in one or more lobes (Guerrini et al., 1996). CDs are the most frequent etiology of surgically amendable epilepsy in children (Harvey et al., 2008). The age of seizure onset varies

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from infancy to adolescence (Kwon et al., 2016; Wyllie et al., 1998). There is a broad spectrum of associated seizures: focal seizures with or without impaired awareness, focal seizures with rapid propagation that mimic generalized epilepsy; and facilitated infantile spasms (Dulac et al., 1996; Lortie et al., 2002). High resolution epilepsy sequences improve CD detection, especially at 3 T (Di Rocco et al., 1994). Typical MRI findings include cortical thickening, blurring of the cortical-white matter junction, and increased signal on T2-weighted images. In children younger than 24 months, CD may be more difficult to identify due to immature myelination (Barkovich et al., 1988).

The CD classification system proposed by the ILAE categorizes CD into type I, II and III (Blumcke et al., 2011); however, they exhibit inconsistent clinical-histologic-radiologic correlation (Guerrini et al., 2015). There is limited understanding of factors that contribute to the timing of seizure onset in children with CD. CD types IB, IIA and IIB may have an earlier seizure onset age compared to the IA subtype (Elaine Wyllie et al., 1994; Widdess-Walsh et al., 2005). A few reports suggest that location of the CD may also play a key role in seizure onset. Children with extra-temporal lobe CD may present at a younger age than temporal lobe CD (Elaine Wyllie et al., 1994). However, this is not consistent, others report there is no correlation between seizure onset and location of CD (Dulac et al., 1996; Lortie et al., 2002). Factors such as location, extent, size, distribution and clinical onset are not well-established. Since the revised ILAE CD classification of 2011, several recent studies inform the growing understanding of molecular genetics in the formation of CD. For example CD type IIB may harbor a post-zygotic somatic mosaicism in the mTOR pathway (Lim et al., 2015; Rossini et al., 2017). If the mutation occurs in a late cycle, the lesion will be smaller and more restricted as an CD; but if it occurs in an earlier cycle, a larger lesion ensues and involves several adjacent gyri as a diffuse dysplasia. The earliest cell cycle mutations in this pathway may involve the entire hemisphere as occurs in hemimegalencephaly (Najm et al., 2018; Sasaki et al., 2005).

Brain maturation is an ongoing process into early adulthood. Myelination of the brain begins in mesio-caudal regions and extends rostro-laterally. Primary sensory (visual, auditory, sensory) and motor cortex are the first to mature. The myelination in ventral regions (in areas that support higher cognitive functions) matures later (Yakovlev et al., 1967). Gray-matter volume and thickness follows a similar pattern whereby frontal, parietal and temporal association cortex thins into adolescence whereas white matter volume increases. Brain maturation patterns in relation to CD location may be a factor that influences age of seizure onset.

We aimed to determine the association of clinical features, lesion volume, and location to the age of seizure onset among children with CD who underwent epilepsy surgery. We hypothesized that cortical regions with earlier myelination are important for expression of seizures. This was tested in two ways: we postulated that CD proximity to areas of earlier myelination maturation would lead to earlier age of epilepsy onset; and that CD might preferentially occur in one of seven distributed neural networks. Thus, CD located in or adjacent to earlier myelinated regions such as sensorimotor or visual cortex would lead to younger age of seizure onset, and that those that developed in association areas with later myelination and cortical thinning would cause seizure onset later in childhood and adolescence. We also hypothesized that larger lesion volume would correlate with earlier onset seizures.

2. Material and methods

2.1. Clinical characteristics

This is a retrospective cohort design of patients who underwent resective epilepsy surgery between January 1, 2009 – December 31, 2016 at Children's National Hospital in Washington, DC. All had pathological confirmation and categorization of CD. Patients with isolated mesial temporal sclerosis, hemimegalencephaly, stroke, tuberous sclerosis, and tumors were excluded. One patient had dual pathology-the ROI was drawn around the CD and not the hippocampal sclerosis. Baseline characteristics, clinical presentation, neuroimaging, anti-seizure medications, pathologic diagnosis and surgical outcome were collected. All patients had video EEG to confirm and characterize epilepsy prior to surgery. The study was approved by the Children's National Hospital Institutional Review Board (IRB).

All 55 patients had pathological confirmation and categorization of CD. CD subtypes were identified in 51 patients. Twenty-seven were reported in a previous study (Bartolini et al., 2017). Twelve specimens were re-reviewed by a pediatric neuropathologist (MAS) to classify subtype of CD according to 2011 ILAE classification and others were re-reviewed by pathology reports. Subclassification was not possible in four patients due to limited samples.

2.2. Imaging protocols and analysis

All patients had a high-resolution MRI with an epilepsy protocol, including specialized infant sequences for those younger than 24 months (Gaillard et al., 2009). MRI was obtained at 1.5 T until 2011 when 3 T magnets were then employed. CD 3D volumes were hand-drawn from either T2 or SPGR images. ROIs were selected in patients' native space using Mricrogl software (http://www.mccauslandcenter.sc.edu/mricrogl/). Selection was based on whichever MRI sequence best delineated the abnormality.

We computed the CD mask centroid location, calculated absolute volumes, and the proportion of lesion ROI to total brain volume. Specifically, we drew the lesion ROI in three dimensions (axial, coronal and sagittal). Then we normalized the T2 or SPGR images (whichever the CD volume was drawn on) to standard Montreal Neurological Institute (MNI) space in SPM (Crinion et al., 2007) and applied the deformation field to the CD 3D volume, to identify the lesion location based on the ROI center of mass and to evaluate the distribution of CD among different lobes. The CD volumes were hand drawn and all ROIs finalized by one rater NTC. We also computed the minimum distance and the amount of overlap between the lesion and the sensory-motor strip as well as the calcarine cortex as these areas myelinate first (from the AAL atlas in MNI space). For the normalization step, the MNI template is not validated for those younger than five years with expected margin of error less than 5 mm (Muzik et al., 2000) and therefore we assumed it would provide a reasonable estimate of distance and that it would not affect lobar localization. Insular CDs were analyzed as frontal lobe CDs.

We then plotted lesion locations against age of onset groups ($<$ 2 yr, $>$ 2–5 yr and $>$ 5 yr) on the standard MNI brain. These age groups were selected as $<$2 yr represents the imaging end of immature myelination, and the $>$ 2–5 yr group (31 % of study population) represents early childhood while $>$ 5 yr (19.6 % of study population) captures older children and adolescents. For the purpose of display, we flipped the right sided lesion to the left hemisphere, thus all lesions are shown and analyzed further in one hemisphere. We also computed the penetrance map, which is the percentage of patients in each age onset group that had lesion in each voxel in the MNI brain (with color spectrum of hot, brighter is higher percentage) to display distribution of CDs.

Given epilepsy is an apparent network disease, next we examined the pattern of each individual patient's CD in relation to seven distributed cortical networks (Schaefer et al., 2018; Yeo et al., 2011). Our model was based upon networks previously described in the resting-state literature, including four major networks: dorsal attention, ventral attention, frontoparietal control, and default networks; as well as somatomotor, visual, and limbic networks. This typical set of resting-state networks has now been reproduced in hundreds of studies that are consistent across different anatomical or functional parcellations (Fan et al., 2016; Glasser et al., 2016; Gordon et al., 2016; Yeo et al., 2011). Specifically, the 7 resting state networks from Yeo's low-dimensional parcellation based on data from one thousand healthy subjects' high spatial (2 mm^3) and temporal resolution (Time of

Repetition = 0.72 s). resting-state fMRI (56 min long), has been cited by over 1700 publications. One key feature of this parcellation is apparent complexity of cortical regions associated with higher order cognitive processing (association cortices). For example, in the middle temporal area, there are several bordering regions with very different patterns of connectivity (i.e., belonging to different large-scale networks), which will be totally missed if using conventional lobar or gyral boundaries. For each patient, we assigned each subject into one of the seven networks, based on their maximal extent of CD overlap with the networks, which is considered as their CD dominant residing network. We then tested within each network, whether the proportion/distribution of patients in each age onset group (<2 yr, > = 2 &<5 yr,> = 5 yr) that had dominant residing network in it or not is different across age onset groups.

2.3. Statistical analysis

The data were analyzed by descriptive statistics, Mann-Whitney U-test, Fisher's exact test, one-way ANOVA, and Spearman correlation as appropriate. We tested the relationship between age onset group and residing cortical network through Fisher's exact test. All statistical procedures were performed using the Statistical Package for Social Sciences (SPSS Version 23.0; IBM, NY).

3. Results

3.1. Clinical characteristics

The clinical data are summarized in Table 1. Fifty-five patients were identified: 27 girls; 28 boys. For seizure characteristics, most patients had focal onset seizures (87 %). Two had facilitated infantile spasms (3%). Five had generalized tonic clonic seizures (9%). One patient presented with epileptic ataxia. The median age of seizure onset was 19 months (range 0.02 months – 16 years). MRI abnormalities were identified at median age 5.9 years (range 1 month – 9.4 years) using an epilepsy protocol at 1.5 T (12 patients, 22 %) or 3 T (43 patients, 78 %) (Gaillard et al., 2009). The median age at epilepsy surgery was 94 months (range 2.9 months – 24.5 years).

3.2. Size, location and distribution of CD

45.5 % occurred in the left hemisphere. CD were located in the following regions (Table 1): frontal 20 (36.3 %), temporal 15 (27.2 %), parietal 11 (20.0 %), and occipital two (3.6 %) or multilobar seven (12.7 %). The multilobar locations are temporo-parietal three (42.8 %), parieto-occipital two (28.6 %), temporo-occipital one (14.2 %) and fronto-parieto-occipital one (14.2 %).

The size of CD ranged from 0.07 to 28.3% of the total brain volume. Median volume of lesions was 23.23 cm^3 (range 1.87 – 591.73 cm^3). For display and descriptive purposes only, varied ROI sizes were divided into two groups: small and large, defined as <100 cm^3 and ≥ 100 cm^3.

Table 1
Clinical characteristics, location and volume of the lesions.

	Focal Cortical Dysplasia (n = 55)
Sex (%male)	28 (50.9 %)
Age of seizure onset (median)	19 months
Range	0.02 months to 16 years
Left hemisphere lesion (%)	25 (45.5 %)
Age at surgery (median)	94 months
Range	2.9 months to 24.5 years
Volume of lesions	23.23 cm^3
Median (cm^3)	(range; 1.87 to 591.73 cm^3)
Proportion of CD to total brain volume Median (%)	13.7 %
Range	0.07–28.3%

Four patients had large CD (7.3 %). All of them were located in extra-temporal regions or multilobar regions that included temporal lobe (Fig. 1). Four patients had large CD (7.3 %). All of them were located in extratemporal regions or multilobar regions that included temporal lobe (Fig. 1). The whole brain penetrance map of all the subjects showed the temporal lobe CD to be preferentially located in the anterior temporal region.

3.3. Association between location of CD and seizure onset

Half of the patients with CD (44 %) developed seizures within the first 12 months of life. The mean age of seizure onset in the frontal lobe CD was 2.54 years (range 0.04–12.5 years), temporal lobe CD was 3.28 years (range 0.17–16 years), parietal lobe CD was 2.97 years (range 0.002–10 years), occipital lobe CD was 0.77 years (range 0.08–1.75 years) and multilobar CD was 2.3 years (range; 0.5–4 years).

Figs. 1 and 2 show the distribution of age of seizure onset by CD location. Extra-temporal lobe CD had seizure onset before one year of age in 50 % of the patients and 80 % have seizure onset before 5-years-old. Temporal lobe CD patients were more likely to have later seizure onset. There was a trend for frontal CD to have seizure onset before age 2 years old ($P = 0.10$) and temporal lobe CD to have seizure onset after 5 years old ($P = 0.06$) (Figs. 1,2).

27 children had CD overlap or proximity with the primary motor cortex and fourteen patients with the visual cortex. The volumes of CD are larger for the patients that had CD overlap or proximity with primary motor cortex (t = 3.7315, df = 26.104, p < .001 Welch two sample t test) and those with visual cortex (t = 5.4759, df = 12.025, p < .001). However, volumes of CD are only correlated with percentage of overlap with visual cortex (r=-.44, p < 0.001) but not primary motor (r=-0.06, p = 0.65). The mean of the percent overlapping area of CD in motor cortex compared to total CD volume was 7 % (range 0.00–84.7%). Four children had CD in motor area with more than 30 % of their total CD volume. All of them developed seizures before age 12 months. The mean of the percent overlapping area of CD in calcarine cortex compared to total CD volume was 6 % (range 0.00–66%). Four children had CD in calcarine cortex with more than 30 % of total CD volume. All of them had seizure onset before 36 months. Age of seizure onset was negatively correlated with percent of CD overlapping motor cortex ($P < 0.001$, r = -0.794) but not with CD overlap of the visual cortex ($P = 0.35$) (Fig. 3).

3.4. Association between dominant residing network and seizure onset

Overall, across all 55 patients, the proportion of CD occurred differently across the several networks (Chi-squared = 18.5, df = 6, $P = 0.005$), with a high proportion in the DMN (0.29, $P < 0.001$, 95 % Confidence Interval=[0.18, 0.43]) and the Limbic networks (0.22, $P < 0.001$, 95 % Confidence Interval =[0.11, 0.36]). The most dominant residing networks were equally represented across age onset groups (Table 2), except for the Default Mode, confirmed by Fisher's Exact test ($P = 0.04$) for crosstab of Network (7) by Age onset Group (>5year, <5year). Specifically, there were higher odds of having an CD in DMN when onset age was less than age 5 years ($P = 0.03$) compared to onset age after age 5 years. Somatosensory and Visual networks were not present in the oldest age onset group.

3.5. Association between size of CD and seizure onset

As continuous variables, larger lesions were associated with earlier age of seizure onset (Fig. 4) (r= -0.16, $P = 0.01$).

3.6. Association between pathology subtypes of CD and seizure onset

We can confidently identify the subtype of CD pathology in 51 patients (type I, n = 8; type II, n = 39; type III, n = 4). The CD subtypes were: type IIA, n = 19; type IIB, n = 18; type IB, n = 7; type IIIA, n = 2;

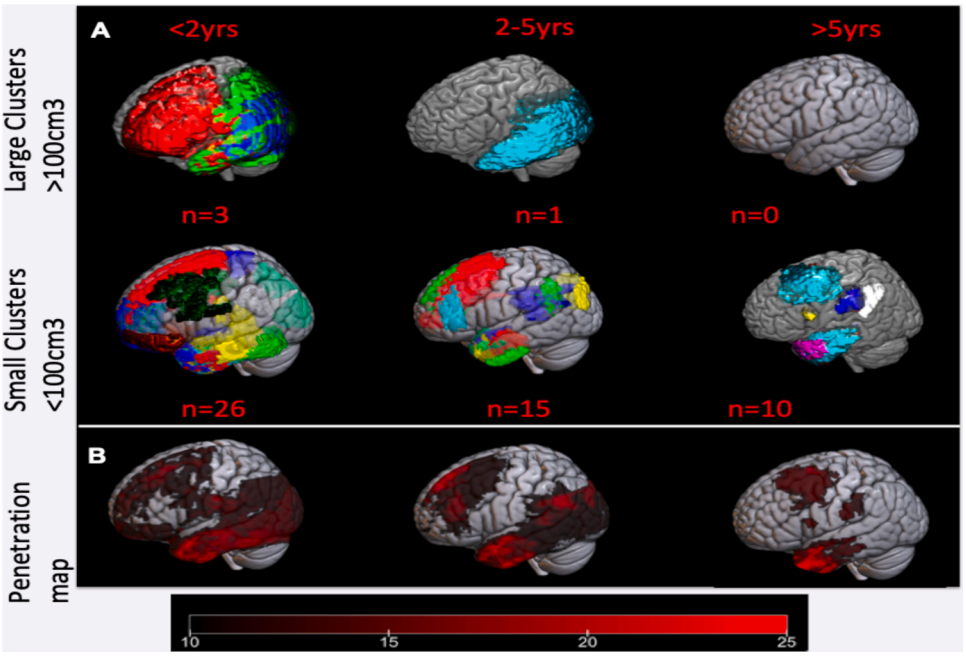


Fig. 1. (A-B) Location of the small and large sized CD group in each age of onset group. Each color represents a different patient **(A)**. Penetrance map distribution divided by age group **(B)**.

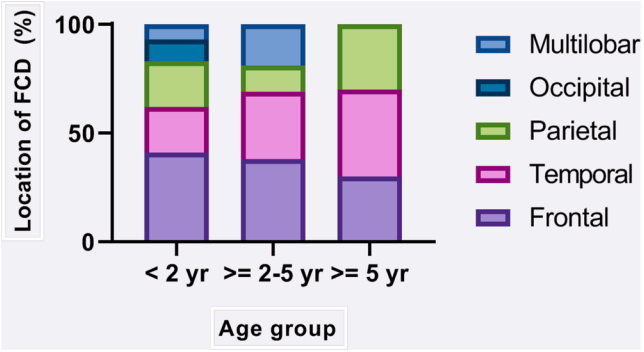


Fig. 2. Location of CD in relation to seizure onset.

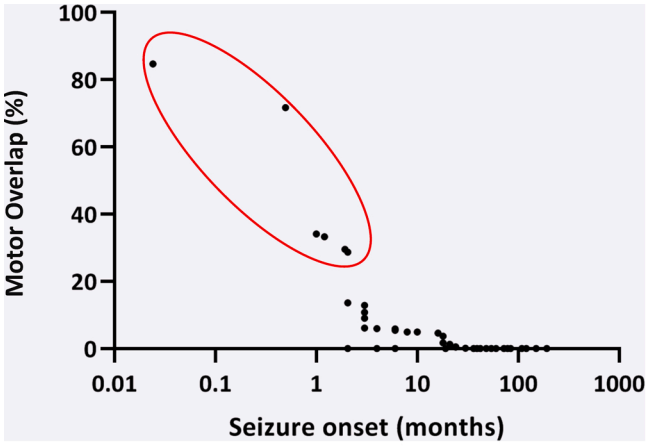
type IIIB, n = 2; and undetermined, n = 3. One was reported as CD type I without further specification and two as CD type II without further specification. CD Type II was more frequently encountered in extra-temporal areas, particularly in the frontal lobe.

There is no association between CD pathology type and seizure onset group ($P = 0.65$) (Fig. 4).

4. Discussion

Our study affirms that age of seizure onset is related to size of focal cortical dysplasia in children. Larger lesions presented earlier in life. We hypothesized that brain regions with early myelination would have earlier onset of seizures. Our data do not clearly demonstrate this as we found that the frontal lobe CD may present at a younger age, whereas temporal lobe CD may have later seizure onset. Age of seizure onset was negatively correlated with percent of CD overlapping motor cortex. Moreover, some neural networks may be more epileptogenic early in life which is supported by the observation that many earlier onset CDs reside within the DMN (Fig. 5).

The CD group with age of seizure onset under one year exhibited a trend for location in the frontal area, whereas the temporal lobe was the most prevalent focus in the patients with age of onset of seizures older



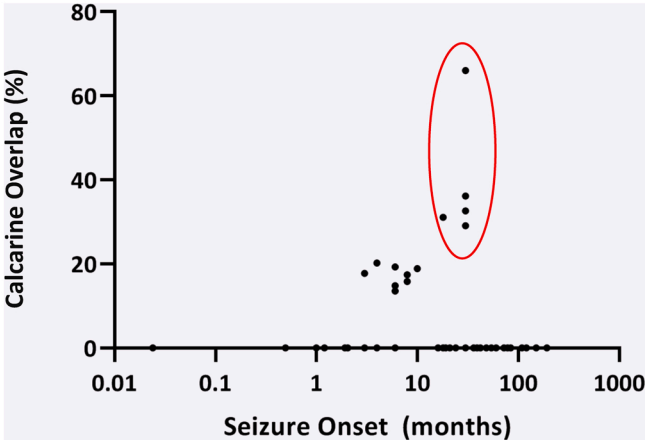


Fig. 3. **(A-B)** Percent of CD overlapping motor cortex **(A)** and visual cortex **(B)**, and age seizure. The red circle demonstrates CD in motor and calcarine cortex with more than 30 % of total CD volume overlap.

Table 2
Dominant residing network and seizure onset.

	CON	DOR	LIM	SAL	SOM	VIS	DMN
Age Onset Group 1 (<2 yr)	1	2	5	4	5	3	9
Age Onset Group 2 (2−5 yr)	2	0	3	1	1	2	7
Age Onset Group 3 (>5 yr)	1	2	4	3	0	0	0

*CON: Frontal Parietal Control Network. DMN: Default Mode Network. DOR: Dorsal Attention Network. LIM: Limbic Network. SAL: Salience Ventral Attentional Network. SOM: Somatosensory Motor Network. VIS: Visual Network.

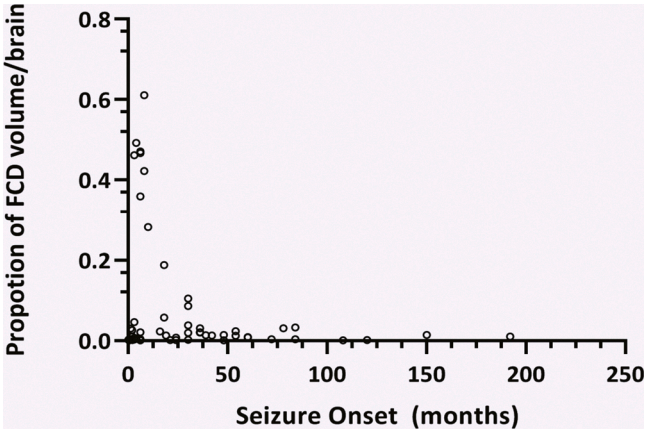


Fig. 4. Negative correlation (-0.16) between age of seizure onset and size of lesion ($P = 0.01$).

than five years. This is similar to a previous study that suggested that the age of seizure onset in extra-temporal CD is younger than in temporal lobe CD, and earlier seizures are associated with cognitive impairment or developmental delays (Wyllie et al., 1998). In a series of infantile CD, a subgroup of patients had seizure onset before the age of one month. This subgroup had CD located in the frontal, central and posterior areas. None of the patients had lesions in temporal areas (Lortie et al., 2002). In a study in adult onset epilepsy, most of the patients had CD located in the temporal region (Lerner et al., 2009). We posit that the sequence of myelination maturation might explain this observation. Brain maturation of myelination begins in the mesio-central and rostral areas, and spreads caudo-laterally (Sarnat and Flores-Sarnat, 2014). Cortical regions achieve maturation in cortical thickness and cerebral metabolism first in primary sensory and motor cortex, cingulate cortex, thalamus, brainstem, cerebellar vermis, and hippocampal regions. This is followed by maturation in the parietal, temporal and frontal association cortices (Barkovich, 1996). We hypothesized that focal seizures in children originate from regions of early cortical and white matter maturation. For example, sensorimotor and occipital (especially calcarine) cortex may have earlier seizure onset, with none occurring after age three years. Although there was no direct correlation between percent overlap of calcarine cortex and seizure onset, the patients with higher percentage overlap (>30 %) all had seizure onset less than three years. Conversely, seizures arising from association areas, including the temporal pole, parietal cortex and anterior frontal convexity would have later epilepsy onset (Chugani, 1998; Gaillard et al., 2009). White matter maturation may be important for propagation and thus the clinical manifestation of seizures (Dulac et al., 1996; Guerrini et al., 2015). Temporal white matter continues to myelinate until the second and third decades of life (Yakovlev et al., 1967).

While we found no clear relationship across all CD ages and proximity to primary motor and sensory areas, those with proximity to motor cortex but not calcarine cortex all had seizure onset in the first year of life and onset in sensorimotor networks not found after age three years. This supports the notion that for a subset of children, regional myelin maturation may be a factor in early expression of seizures. However, the relationship between location of CD and seizure onset is not consistent across studies. One large retrospective study showed no correlation between age of seizure onset and location of the CD (Fauser et al., 2006). This might suggest that other intrinsic epileptogenicity factors, such as pathology type, may influence seizure onset. Another possibility is that epileptogenicity may be related to alterations of distributed networks. We found a preponderance of CD in younger children located in the Default Mode Network; there may be electrophysiological, pharmacological, or developmental, properties of neurons within this network that predispose to seizure generation and expression (Lopes et al., 2014; Wylie et al., 2014). Studies have found DMN abnormalities associated with focal epilepsies. Using resting state MRI, Yang et al. demonstrated problems with node-wise temporal variability in patients with temporal lobe epilepsy.(Yang et al., 2020) Gonen et al. have summarized at least eight studies in a non-systematic review demonstrating alterations/aberrations in DMN in temporal lobe epilepsy.(Gonen et al., 2020)

The subtype of CD did not influence age of seizure onset. Some studies have noted that CD type IIB presents early in life while CD type IA has later seizure onset (Fauser et al., 2006). Recent studies have reported somatic mutations in different neuronal or glial subtypes in an effort to elucidate the pathogenesis of CD (Blumcke et al., 2017; D'Gama et al., 2015; Lim et al., 2015). Abnormalities of the mTOR pathway are widely described: tuberous sclerosis (TSC) shares the mTOR pathway mutation with hemimegalencephaly and CD type IIB (Blumcke et al., 2017; D'Gama et al., 2015; Lim et al., 2015). TSC is caused by loss-of-function mutations in TSC1 or TSC2, and results in abnormal activation in the mTOR pathway (Lipton and Sahin, 2014). There are reports of isolated CD or hemimegalencephaly that are associated with otherwise silent TSC mutations (D'Gama et al., 2015; Lim et al., 2017). The presence of mTOR pathway mutations may help to explain the earlier onset and larger lesions seen in CD type IIB, as TSC mutations often are also associated with earlier seizure onset. CD type IIB are also located more commonly in extra-temporal lobe areas which myelinate earlier, as compared to CD type I which are found more often in temporal regions that myelinate later (2526). CD type II may have more clinical severity and earlier onset (Tassi et al., 2002).

Advances in neuroimaging techniques have led to earlier identification of CD, but the diagnosis of CD by magnetic resonance imaging (MRI) in infants and young children (<24 months) remains challenging. Immature myelination may blur the gray-white differentiation necessary to identify CD, and this may result in falsely negative MRI interpretation. As with previous reports, most CD pathology subtypes (except some Type IIB) cannot be distinguished by MRI findings (Bartolini et al., 2017). The age of seizure onset and CD location may be key factors associated with pathological subtype.

4.1. Limitations

There are several limitations to this study. The volumes may not be precise as lesion edges are sometimes difficult to delineate, especially in younger patients. The normalization of children younger than four years, especially infants, to an older template may have caused measurement error up to several millimeters. However, these limitations are unlikely to influence the main observations regarding general distribution and size of CD. The same is likely for studies obtained at 1.5 T where lesions may appear less extensive than at 3 T. The CD may be proportionately larger in the youngest patients due to developmental brain growth. We also restricted our study to children who underwent surgery which may confer a referral bias for the more epileptogenic lesions.

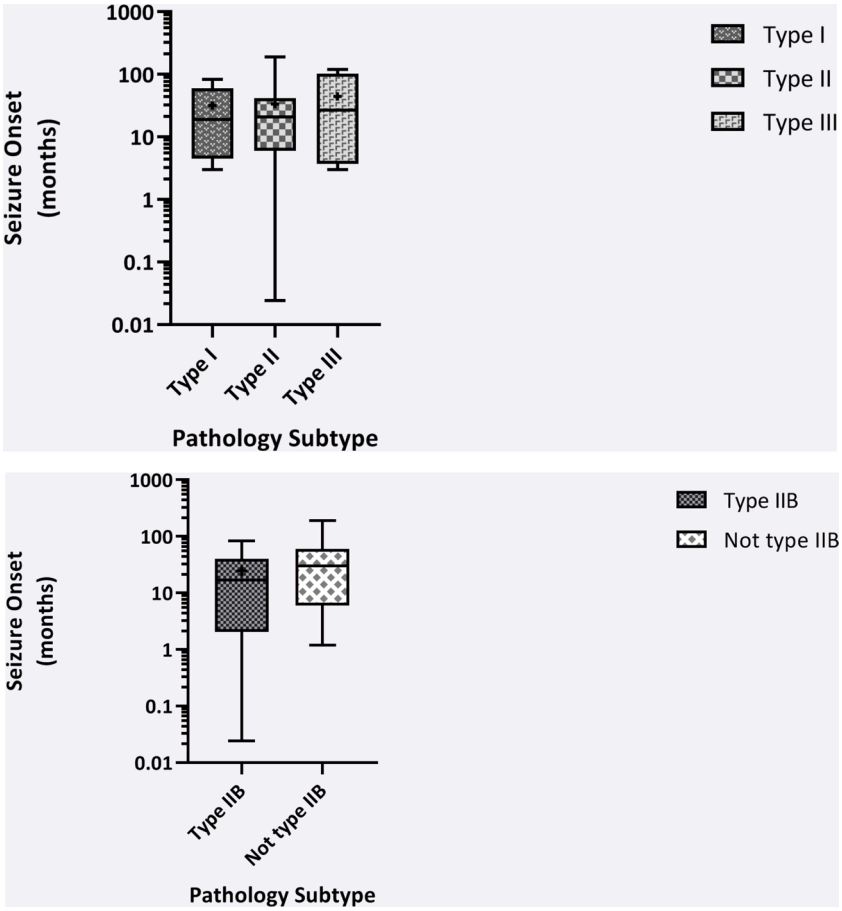


Fig. 5. **(A-B)** Pathology subtypes of CD and seizure onset **(A)**. Pathology subtype IIB and non-IIB and seizure onset **(B)**.

5. Conclusion

Our study suggests that larger CD lesions are associated with earlier onset epilepsy. Location and pathology subtype might be other factors that influence the age of seizure onset, including location within the Default Mode Network and location in sensorimotor cortex. Seizures that develop before one year of age may be more likely to arise from a frontal CD, while seizure onset after age five tends to occur in association with temporal CD. These observations may reflect patterns of brain maturation, or differences in network expression of clinical symptoms and epilepsy. Developmental network expression merits further investigation including the extent to which the network in which a given CD resides is disrupted. Further study is necessary to determine whether the type of somatic mutation is linked to epileptogenicity and seizure onset.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of Competing Interest

None.

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References

Barkovich, A.J., 1996. Normal development of the neonatal and infant brain, skull and spine. Pediatr. Neuroimaging 9–54.

Barkovich, A.J., Kjos, B.O., Jackson Jr, D.E., Norman, D., 1988. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. Radiology 166, 173–180.

Bartolini, L., Whitehead, M.T., Ho, C.Y., Sepeta, L.N., Oluigbo, C.O., Havens, K., Freilich, E.R., Schreiber, J.M., Gaillard, W.D., 2017. Temporal lobe epilepsy and focal cortical dysplasia in children: a tip to find the abnormality. Epilepsia 58, 113–122.

Blumcke, I., Thom, M., Aronica, E., Armstrong, D.D., Vinters, H.V., Palmini, A., Jacques, T.S., Avanzini, G., Barkovich, A.J., Battaglia, G., Becker, A., Cepeda, C., Cendes, F., Colombo, N., Crino, P., Cross, J.H., Delalande, O., Dubeau, F., Duncan, J., Guerrini, R., Kahane, P., Mathern, G., Najm, I., Ozkara, C., Raybaud, C., Represa, A., Roper, S.N., Salamon, N., Schulze-Bonhage, A., Tassi, L., Vezzani, A., Spreafico, R., 2011. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE diagnostic methods commission. Epilepsia 52, 158–174.

Blumcke, I., Spreafico, R., Haaker, G., Coras, R., Kobow, K., Bien, C.G., et al., 2017. Histopathological findings in brain tissue obtained during epilepsy surgery. N. Engl. J. Med. 377, 1648–1656.

Chugani, H.T., 1998. A critical period of brain development: studies of cerebral glucose utilization with PET. Prev. Med. 27, 184–188.

Crinion, J., Ashburner, J., Leff, A., Brett, M., Price, C., Friston, K., 2007. Spatial normalization of lesioned brains: performance evaluation and impact on fMRI analyses. NeuroImage 37, 866–875.

D'Gama, A.M., Geng, Y., Couto, J.A., Martin, B., Boyle, E.A., LaCoursiere, C.M., Hossain, A., Hatem, N.E., Barry, B.J., Kwiatkowski, D.J., Vinters, H.V., Barkovich, A. J., Shendure, J., Mathern, G.W., Walsh, C.A., Poduri, A., 2015. Mammalian target of rapamycin pathway mutations cause hemimegalencephaly and focal cortical dysplasia. Ann. Neurol. 77, 720–725.

Di Rocco, C., Iannelli, A., Marchese, E., Vigevano, F., Rossi, G.F., 1994. Surgical treatment of epileptogenic hemimegalencephaly. Minerva Pediatr. 46, 231–237.

Dulac, O., Pinard, J.M., Plouin, P., 1996. Infantile Spasms Associated With Cortical Dysplasia and Tuberous Sclerosis, Dysplasia of Cerebral Cortex and Epilepsy. Lippincott-Raven, Philadelphia, pp. 217–225.
Elaine Wyllie, C.B., Prayson, Richard, Estes, Melinda, Comair, Youssef, Kosalko, Joanne, Skibinski, Christine, 1994. The clinical Spectrum of focal cortical dysplasia and epilepsy. J. Epilepsy 7, 303–312.
Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The human brainnetome atlas: a new brain atlas based on connectional architecture. Cereb. cortex 26, 3508–3526.
Fauser, S., Huppertz, H.J., Bast, T., Strobl, K., Pantazis, G., Altenmueller, D.M., Feil, B., Rona, S., Kurth, C., Rating, D., Korinthenberg, R., Steinhoff, B.J., Volk, B., Schulze-Bonhage, A., 2006. Clinical characteristics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients. Brain 129, 1907–1916.
Gaillard, W.D., Chiron, C., Cross, J.H., Harvey, A.S., Kuzniecky, R., Hertz-Pannier, L., Vezina, L.G., 2009. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia 50, 2147–2153.
Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D. C., 2016. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178.
Gonen, O.M., Kwan, P., O'Brien, T.J., Lui, E., Desmond, P.M., 2020. Resting-state functional MRI of the default mode network in epilepsy. Epilepsy Behav. 111, 107308.
Gordon, E.M., Laumann, T.O., Adeyemo, B., Huckins, J.F., Kelley, W.M., Petersen, S.E., 2016. Generation and evaluation of a cortical area parcellation from resting-state correlations. Cereb. Cortex 26, 288–303.
Guerrini, R.D.C., Bureau, M., Mancini, J., Canapicchi, R., Livet, M.O., et al., 1996. Dysplasias of Cerebral Cortex and Epilepsy. Lippincott-Raven, Philadelphia.
Guerrini, R., Duchowny, M., Jayakar, P., Krsek, P., Kahane, P., Tassi, L., Melani, F., Polster, T., Andre, V.M., Cepeda, C., Krueger, D.A., Cross, J.H., Spreafico, R., Cosottini, M., Gotman, J., Chassoux, F., Ryvlin, P., Bartolomei, F., Bernasconi, A., Stefan, H., Miller, I., Devaux, B., Najm, I., Giordano, F., Vonck, K., Barba, C., Blumcke, I., 2015. Diagnostic methods and treatment options for focal cortical dysplasia. Epilepsia 56, 1669–1686.
Harvey, A.S., Cross, J.H., Shinnar, S., Mathern, G.W., 2008. Defining the spectrum of international practice in pediatric epilepsy surgery patients. Epilepsia 49, 146–155.
Kwon, H.E., Eom, S., Kang, H.C., Lee, J.S., Kim, S.H., Kim, D.S., Kim, H.D., 2016. Surgical treatment of pediatric focal cortical dysplasia: clinical spectrum and surgical outcome. Neurology 87, 945–951.
Lerner, J.T., Salamon, N., Hauptman, J.S., Velasco, T.R., Hemb, M., Wu, J.Y., Sankar, R., Donald Shields, W., Engel Jr, J., Fried, I., Cepeda, C., Andre, V.M., Levine, M.S., Miyata, H., Yong, W.H., Vinters, H.V., Mathern, G.W., 2009. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. Epilepsia 50, 1310–1335.
Lim, J.S., Kim, W.I., Kang, H.C., Kim, S.H., Park, A.H., Park, E.K., Cho, Y.W., Kim, S., Kim, H.M., Kim, J.A., Kim, J., Rhee, H., Kang, S.G., Kim, H.D., Kim, D., Kim, D.S., Lee, J.H., 2015. Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy. Nat. Med. 21, 395–400.
Lim, J.S., Gopalappa, R., Kim, S.H., Ramakrishna, S., Lee, M., Kim, W.I., Kim, J., Park, S. M., Lee, J., Oh, J.H., Kim, H.D., Park, C.H., Lee, J.S., Kim, S., Kim, D.S., Han, J.M., Kang, H.C., Kim, H.H., Lee, J.H., 2017. Somatic mutations in TSC1 and TSC2 cause focal cortical dysplasia. Am. J. Hum. Genet. 100, 454–472.
Lipton, J.O., Sahin, M., 2014. The neurology of mTOR. Neuron 84, 275–291.
Lopes, R., Moeller, F., Besson, P., Ogez, F., Szurhaj, W., Leclerc, X., Siniatchkin, M., Chipaux, M., Derambure, P., Tyvaert, L., 2014. Study on the relationships between intrinsic functional connectivity of the default mode network and transient epileptic activity. Front. Neurol. 5, 201.
Lortie, A., Plouin, P., Chiron, C., Delalande, O., Dulac, O., 2002. Characteristics of epilepsy in focal cortical dysplasia in infancy. Epilepsy Res. 51, 133–145.
Muzik, O., Chugani, D.C., Juhász, C., Shen, C., Chugani, H.T., 2000. Statistical parametric mapping: assessment of application in children. Neuroimage 12, 538–549.
Najm, I.M., Sarnat, H.B., Blumcke, I., 2018. Review: the international consensus classification of focal cortical dysplasia - a critical update 2018. Neuropathol. Appl. Neurobiol. 44, 18–31.
Rossini, L., Villani, F., Granata, T., Tassi, L., Tringali, G., Cardinale, F., Aronica, E., Spreafico, R., Garbelli, R., 2017. FCD Type II and mTOR pathway: evidence for different mechanisms involved in the pathogenesis of dysmorphic neurons. Epilepsy Res. 129, 146–156.
Sarnat, H.B., Flores-Sarnat, L., 2014. Morphogenesis timing of genetically programmed brain malformations in relation to epilepsy. Prog. Brain Res. 213, 181–198.
Sasaki, M., Hashimoto, T., Furushima, W., Okada, M., Kinoshita, S., Fujikawa, Y., Sugai, K., 2005. Clinical aspects of hemimegalencephaly by means of a nationwide survey. J. Child Neurol. 20, 337–341.
Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.N., Holmes, A.J., Eickhoff, S. B., Yeo, B.T.T., 2018. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb. Cortex 28, 3095–3114.
Tassi, L., Colombo, N., Garbelli, R., Francione, S., Lo Russo, G., Mai, R., Cardinale, F., Cossu, M., Ferrario, A., Galli, C., Bramerio, M., Citterio, A., Spreafico, R., 2002. Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain 125, 1719–1732.
Widdess-Walsh, P., Kellinghaus, C., Jeha, L., Kotagal, P., Prayson, R., Bingaman, W., Najm, I.M., 2005. Electro-clinical and imaging characteristics of focal cortical dysplasia: correlation with pathological subtypes. Epilepsy Res. 67, 25–33.
Wylie, K.P., Rojas, D.C., Ross, R.G., Hunter, S.K., Maharajh, K., Cornier, M.A., Tregellas, J.R., 2014. Reduced brain resting-state network specificity in infants compared with adults. Neuropsychiatr. Dis. Treat. 10, 1349–1359.
Wyllie, E., Comair, Y.G., Kotagal, P., Bulacio, J., Bingaman, W., Ruggieri, P., 1998. Seizure outcome after epilepsy surgery in children and adolescents. Ann. Neurol. 44, 740–748.
Yakovlev, P.I., Lecours, A.R., Minkowski, A., 1967. The myelogenetic cycles of regional maturation of the brain. In: A, M (Ed.), Regional Development of the Brain in Early Life. Blackwell Scientific, pp. 3–70.
Yang, S., Zhang, Z., Chen, H., Meng, Y., Li, J., Li, Z., Xu, Q., Zhang, Q., Fan, Y.S., Lu, G., Liao, W., 2020. Temporal variability profiling of the default mode across epilepsy subtypes. Epilepsia.
Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R. L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 1125–1165.