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Brain magnetic resonance imaging findings and brain volumetric differences in a large series of benign rolandic epilepsy

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Abstract

Background: Several studies with a small sample size have investigated the relationship between structural and functional changes on MRI and the clinical and natural history of BRE. We aim to assess the frequency of incidental epileptogenic lesions on brain MRI in a large cohort of patients diagnosed with BRE and to assess the difference in volumetric brain measurements in BRE patients compared to healthy controls.

Methods: The case–control study includes 214 typical BRE cases and 197 control children with non-epileptic spells. Brain MRIs were evaluated for abnormalities which were classified into normal and abnormal with or without epileptogenic lesions with categorization of epileptogenic lesions. Brain segmentation was also performed for a smaller group of BRE patients and another healthy control group. Pearson's chi-squared test and two-tailed independent samples t-test were used.

Results: In patients with BRE, 7% had an epileptogenic lesion on their MRI. The frequency of epileptogenic lesion in the control group was 10.2% and not significantly different from those with BRE ($p = 0.2$). Significantly higher intracranial and white matter volumes were found in BRE patients compared to the healthy group while lower gray matter volume was found in BRE patients. Cortical and subcortical regions showed either higher or lower volumes with BRE. Interestingly, altered subcallosal cortex development which has a known association with depression was also found in BRE.

Conclusions: Our findings confirm the absence of any association between specific brain MRI abnormalities and BRE. However, the altered cortical and subcortical development in BRE patients suggests a microstructural-functional correlation.

Keywords

benign rolandic epilepsy, BRE, pediatric, brain MRI, brain volume

Introduction

Benign rolandic epilepsy (BRE) is a well-defined electro-clinical epilepsy syndrome mostly seen in children and recognized as benign, with remission noted by mid-adolescence.[1] It is one of the most common epileptic syndromes with an incidence reaching up to 15% in North America and Europe.[2] It usually starts in the first decade of life and manifests as simple partial motor seizures proceeded by a somatosensory aura. The seizures tend to occur when the patients are asleep as well as around the time they wake up. It is not uncommon for them to evolve into more generalized tonic-clonic types of seizures.[1]

The diagnosis of BRE relies completely on EEG and clinical findings. The use of imaging has been deemed unnecessary due to the natural history of the disease and the low rate of MR pathological findings in children with BRE.[1,3] On EEG, BRE shows a focal surface negative spike or sharp wave of high amplitude that is often preceded by a low amplitude surface positive spike that is seen to be sharper. Similarly, the negative spike is also commonly followed by a slow wave. Both the Rolandic and the frontal region are often affected by the aforementioned complex and can show different potential field, which relates to the prognosis of the disease and its clinical presentation.[4]

In recent years, several studies have investigated the relationship between structural and functional changes on MRI and the clinical and natural history of BRE.[5,6] Other studies have correlated cortical morphology with the natural history of the disease, thereby suggesting the possibility of significant MRI findings in patients with BRE.[7–9] However, the reported findings of microstructural alterations in the brain

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were contradictory among these studies.[5–9] Additionally, few studies have questioned the classification of BRE as a benign entity and have attempted to identify specific MRI findings that could be pathognomonic of it.[1] However, the largest study sample studied so far comprises of 25 patients.[8] Furthermore, very little data is available regarding the neuroimaging findings of Lebanese patients diagnosed with epilepsy and more specifically BRE.

Our study aims at assessing the frequency of incidental epileptogenic lesions on brain MRI in patients diagnosed with BRE based on EEG and clinical presentation in a large sample in Lebanon. We also aim to assess the difference in volumetric measurement of different brain regions between patients diagnosed with BRE as compared to healthy controls.

Methods

Study design/patients

Twenty-five adult and pediatric neurologists from all over Lebanon including several districts like Beirut, the North, the South, the Bekaa valley, and Mount Lebanon referred patients with newly diagnosed seizures or epilepsy to take part in this centralized study at our institution in partnership with the Lebanese Chapter of the International League against Epilepsy (ILAE). A full medical history was reviewed by two epileptologists in which a detailed description of the spells and a physical/neurological examination was performed. The work-up on each patient consisted of a 3-h sleep deprived video-EEG and an epilepsy protocol brain MRI. Follow-up by phone calls to inquire on adverse events from antiepileptic drugs (in case treatment was initiated) and follow-up visits as well as repeat EEGs if clinically indicated were ensured as per protocol. Based on the results, the patients were stratified into those with paroxysmal non-epileptic spells (first control group (CC1)) and patients with a single unprovoked seizure or epilepsy and this study focuses on patients with BRE. A second control group (CC2) for whom brain MRI was used for volumetric brain segmentation, included healthy control subjects with no familial and personal history of neurological or psychiatric diseases, and no head trauma, from our hospital's MRI database.

Inclusion/exclusion criteria

Patients were considered eligible if (1) they were between 1 and 14 years at the time of the first unprovoked seizure of the simple partial type with opercular semiology and/or (2) generalized tonic type with an EEG showing epileptiform discharges with typical morphology, location, and activation during sleep from maturational discharge.

Patients were excluded if (1) their seizure resulted from acute (e.g., cephalosporin and tramadol) or chronic (alcohol or addiction) drug use; (2) the seizure occurred in the setting of an acute metabolic abnormality (e.g., severe hyponatremia or hypocalcemia), or within 4 weeks of an acute cerebral insult; (3) they have a severe psychiatric illness, or pseudoseizures that might affect their behavior and cognition; and (4) they did not have an MRI study. For volumetric measurements, patients were excluded if there is lack of 3DT1-weighted images or due to bad quality of the images, which limit the segmentation process.

Before being enrolled in the study, all patients were informed about the nature of data collection, the next of kin or legal guardian was asked to sign an informed consent.

Data collection

A detailed description of the episodes as well as a full physical and neurological exam with appropriate laboratory tests and a sleep deprived 3-h video EEG study were performed for the determination of seizure type and etiology for all children. For this observational study, all imaging studies were ordered for clinical purposes by treating physicians at their respective hospitals throughout Lebanon.

For the sake of homogeneity regarding quality and accuracy of interpretation, all physical, neurological, and laboratory examination was repeated at our institution. MR imaging performed at our institution or on outside basis was also reviewed. Standard Picture Archiving Communication System (PACS) workstations were used to review all images, and all imaging done on outside basis were reviewed by the same neuroradiologist with expertise in epilepsy for 20 years who was also blinded to all clinical and non-imaging results. All video/EEGs were recorded on a Nicolet machine at a sampling rate of 250 Hz using the International 10–20 system for electrode placement and were interpreted by an experienced board certified neurophysiologist.

Neuroimaging data/magnetic resonance imaging scoring system

The 30-min epilepsy brain MRI protocol was performed on either 1.5 or 3 Tesla MRI systems and included a 3D T1, 3D fast fluid-attenuated inversion recovery (FLAIR), and axial and coronal Inversion Recovery, to detect migration anomaly, subtle gray–white matter blurring. The 3D volumetric acquisitions were used to detect subtle cortical malformations. Axial diffusion-weighted images (DWI), and axial T2FFE sequences were also obtained. MRI reports were classified as normal, abnormal, and epileptogenic, or abnormal and non-epileptogenic based on previously published criteria.[10–12] For the purpose of this study, only cortically-based lesions likely relevant to the cause of the seizure and concordant with the seizure semiology were considered epileptogenic. Epileptogenic lesions were subsequently categorized under disorders of cortical malformations (focal cortical dysplasia, hippocampal malformation, polymicrogyria, and heterotopia), mesial temporal sclerosis (MTS), neurocutaneous syndromes (phakomatosis), vascular lesions (stroke, intracerebral hemorrhage, amyloid angiopathy, arteriovenous malformation, cavernoma, etc.), traumatic (subdural hematoma, subarachnoid hemorrhage, intracerebral hematoma), tumor (glioma, metastasis, etc.), infectious causes, immunologic (limbic or Rasmussen encephalitis), or others (vasculitis, post-radiation gliosis, periventricular leukomalacia, and arachnoid cyst). MRI abnormalities consisting of isolated subcortical lesions of high FLAIR signal, leukoaraiosis (white matter hyperintensity consistent with small vessel ischemic disease), and brain atrophy (irrespective of the severity of the atrophy) were not considered epileptogenic,

Locations are classified by lobe, hemisphere, periventricular region, cerebellum, brainstem, or diffuse. Opercular involvement was also mentioned when present.

Magnetic resonance imaging acquisition and image processing for volumetric measurements

To limit the biases from using different machines with different sequence parameters, this section of the study was only performed on 50 out of the 214 patients. BRE patients and age and sex matched healthy control subjects had their brain MRI performed either at the radiology department of our institution on a 3T Philips Ingenia System (Philips Healthcare, Best, The Netherlands), or at an external imaging center on a 3T Siemens Verio System (Siemens Healthcare, Erlangen, Germany). For the volumetric assessment, only the 3D sagittal T1-weighted image was used (our institution: TR = 8.3 ms; TE = 3.8 ms; flip angle = 8°; field of view = 240 × 240 ×170 mm; spatial resolution =1 × 0.94 × 0.94 mm^3; external imaging center: TR = 1900 ms; TE = 32.48 ms; TI = 900 ms; flip angle = 9°; field of view = 512 × 512 × 150 mm; spatial resolution = 1 × 0.49 × 0.49 mm^3).

MRI images were manually checked by an experienced operator with more than fifteen years of experience (SH) for any major artifacts that could implicate errors or biases during image segmentation. Images first underwent a bias field correction using the N4-algorithm in 3DSlicer (https://www.slicer.org/), followed by a whole-brain extraction using the Brain Extraction Tool of the FMRIB Software Library (FSL5.0) to measure the intracranial volume (ICV).[13] Gray (GM) and white matter (WM), and cerebrospinal fluid (CSF) volumes were then estimated using SIENAX.[14] Subcortical left and right GM volume of the accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus were then measured using FIRST which is a model-based segmentation/registration tool that uses manually segmented models.[13]

An atlas-based segmentation was also performed to extract the volumes of specific GM cortical areas (anterior cingulate gyrus, superior, inferior, and middle frontal gyri, precentral gyrus, precuneus, frontal medial cortex, superior frontal cortex, and thalamic nucleus related to both posterior parietal lobe and temporal lobe) as well as the genu, body, and splenium of the corpus callosum (CC). The Harvard-Oxford cortical structural atlas and the JHU-ICBM WM atlas were non-linearly registered to each subject's T1 images using the Nifty-Reg software (http://cmictig.cs.ucl.ac.uk/wiki/index.php/NiftyReg). The resulting transformations were then applied to the atlas cortical GM and CC masks. All extracted cortical and subcortical GM and CC masks were checked for accuracy, and manually corrected when needed by a neuroradiology research student (Z.M.) and later verified and confirmed by an experienced neuroradiologist with more than 20 years of experience (R.H.). The volumes were subsequently extracted and normalized by the ICV.

Statistical analysis

Statistical analysis was completed using SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Pearson's chi-squared test was applied to test the association between the overall abnormalities and BRE. Two-tailed independent samples t-test was used to compare for statistical significance of differences in means of each volumetric variable between BRE and control groups. Statistical significance was defined as $p \leq .05$.

Results

Four hundred and eleven patients (215 male and 196 female patients) with a mean age of seven years (SD = 4.3 years) were included in this study. Two-hundred and fourteen (52.1%) were diagnosed with BRE and 197 (47.9%) CC1. The most common diagnosis in patients with non-epileptic spells 19.8% had syncope, 19.33% had psychogenic non-epileptic spells, and 14.7% had behavioral events. The mean age in patients with BRE was not significantly different from that of the control group (BRE = 6.8 ± 2.9 years; CC1= 7.2 ± 5.4 years; $p = .4$). There was also no statistically significant difference between the two groups with respect to sex ($p = .7$). Epileptogenic lesions were identified on MRIs in 6.5% (14/214) of BRE patients (CI = 4.3–11.2%) versus 10.2% (20/197) of the CC1 (CI = 7.1–15.7%). However, lesions frequency between both groups was not significantly different ($p = .2$). The frequency of each epileptogenic lesion in both groups is detailed in Table 1. Note that one case in the control group had focal cortical dysplasia and polymicrogyria. The BRE child with polymicrogyria was the only case to have opercular involvement. The EEG findings of 14 BRE children who have epileptogenic lesions were correlated to the location of these lesions on MRI (Table 2). Figure 1 illustrates four cases with different epileptogenic lesions on MRI.

For the volumetric measurements, 135 BRE patients and CC2 were identified from our institution's neuroimaging database. However, segmentations were performed for only 96 cases (59 males and 37 females); 50 children with BRE, and 46 healthy controls after excluding 39 cases (33 BRE and 6 controls) due to the lack of the 3DT1 image or due to bad image quality. No significant age difference was observed between both groups (BRE = 8.8 ± 3.4 years; healthy controls = 8 ± 5.3 years; $p = .5$). Table 3 details the volumetric differences between the two groups. Figure 2 illustrates a case segmentation in the subcortical regions.

For whole brain volume analysis, ICV and WM were significantly higher in BRE patients compared to healthy controls ($p = .001$ and 0.005, respectively), whereas GM was significantly lower in BRE ($p = .04$). Significantly higher volumes were found in BRE for the amygdala, medial frontal cortex (in particular on the left), orbitofrontal cortex, precuneus (in particular on the left), and left subcallosal cortex. Significantly lower volumes were found in BRE for the caudate nucleus (in particular on the left), cingulate gyrus, pars triangularis, middle temporal gyrus, precentral gyrus, right subcallosal cortex, and superior temporal gyrus. No significant differences were noted with volumetric measurements of the corpus callosum, accumbens, hippocampus, thalamus, pars opercularis, and superior and middle frontal gyri.

Table 1. Comparison of abnormalities in 34 (out of the 411) (8.3%) patients that were found to have epileptogenic lesions.

		BRE		Control			
Type of epileptogenic lesion				Frequency	Total (%)	Frequency	Total (%)
Disorders of cortical malformation	FCD[a]	4	**7 (50%)**	2	**5 (25.0%)**		
	Polymicrogyria	1		2			
	Heterotopia	1		0			
	Lissencephaly	0		1			
	HM[b]	1		0			
Vascular	Ischemic disease	1	**1 (7.1%)**	5	**5 (25.0%)**		
MTS[c]	MTS[c]	0	**0**	1	**1 (5.0%)**		
Tumor	Tumor	0	**0**	0	**0**		
NS[d]	Tuberous sclerosis	0	**0**	1	**1 (5.0%)**		
Traumatic	Trauma	0	**0**	0	**0**		
Infectious	Old encephalitis	1	**1 (7.1%)**	0	**0**		
Immunologic	Immunologic	0	**0**	0	**0**		
Other	PVL[e]	2	**5 (35.7%)**	6	**8 (40.0%)**		
	DWMD[f]	1		1			
	Joubert syndrome	0		1			
	Arachnoid cyst	1		0			
	IW[g]	1		0			
Total		**14**		**20**			

[a] FCD: Focal cortical dysplasia.
[b] HM: Hippocampal malformation.
[c] MTS: Mesial temporal sclerosis.
[d] NS: Neurocutaneous syndromes.
[e] PVL: Periventricular leukomalacia.
[f] DWMD: Diffuse white matter disease.
[g] IW: increased white matter FLAIR signal touching the cortex.

Table 2. EEG and MRI findings in BRE patients who had epileptogenic lesions.

Patient	Location of sharp waves on EEG	MRI abnormality
1	Left centro-parieto-midtemporal, right centro-midtemporal, left occipital-posterior temporal and right occipital	Periventricular leukomalacia
2	Bilateral mid-temporal and frontal	Hypoxic ischemic encephalopathy
3	Right centro-midtemporal	Right frontal focal cortical dysplasia
4	Right midtemporal	Left hemispheric polymicrogyria
5	Right parieto-midtemporal and left centro-parieto-midtemporal	Right trigone nodular heterotopia
6	Right centro-midtemporal	Periventricular white matter abnormality
7	Right and left parieto-midtemporal	Old encephalitis (putamen and hippocampi atrophic with abnormal signal)
8	Left parietal	Diffuse white matter abnormality
9	Bi-posterior (T5-O1 and T6-O2)	Right cingulate focal cortical dysplasia
10	Left parietal	Left temporal arachnoid cyst
11	Normal	Left focal cortical dysplasia
12	Right central, right occipital and left parietal	Periventricular leukomalacia
13	Left parieto-posterior temporal	Left hippocampal abnormality
14	Right central temporal	Right cingulate focal cortical dysplasia

Discussion

This is one of the largest reported cohorts of pediatric population with BRE with evaluation of epileptogenic lesions frequency on brain MRI and brain volumetric measurements. Our sample size consists of 214 patients, a much larger cohort compared to the second largest study of only 25 patients.[8] Our sample was unmatched but was split almost equally between cases and controls (52% vs 48%, respectively) and was similar in sex and age distribution.

Out of our total sample, only 34 patients (8.3% overall) showed epileptogenic lesions on brain MRI with no significant difference in frequency (p= 0.2) between the BRE cases (14/214 patients) and controls (20/197 patients). These results suggest the absence of any association between MRI abnormalities and BRE. The study of Boxerman et al. reported MRI abnormalities in 68% (17/25) of BRE patients including hippocampal abnormalities (peri-hippocampal cysts and hippocampus or temporal horn size asymmetry), congenital malformations (arachnoid cysts, mega cisterna

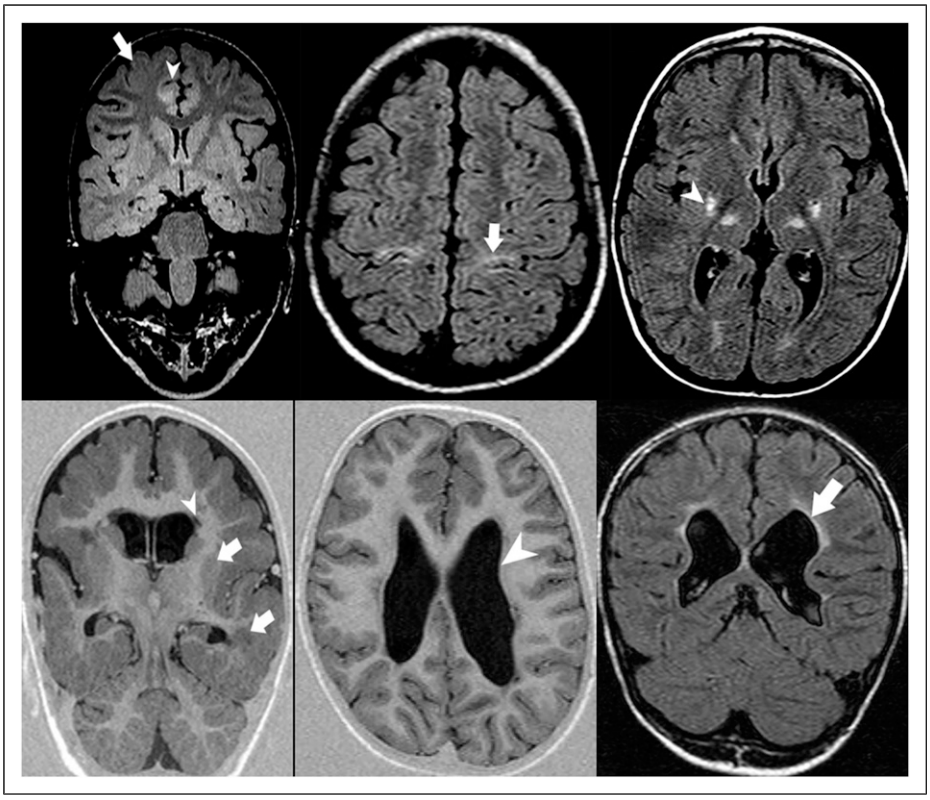

Figure 1. (a) 6-year-old girl with right cingulate focal cortical dysplasia. Coronal FLAIR image, showing cortical thickening (arrow) and high signal intensity along the right cingulate gyrus (arrowhead) with blurring of the white-matter gray-matter junction consistent with focal cortical dysplasia. (b and c) 5-year-old boy with hypoxic ischemic injury. Axial FLAIR images of the brain demonstrate abnormal T2 signal in the motor cortices (arrow) and in the basal ganglia (arrowhead), sequelae of hypoxic ischemic brain injury. (d) 3-year-old boy with polymicrogyria. Coronal phase-sensitive inversion recovery image of the brain demonstrates diffuse cortical thickening, polymicrogyria in the frontal, insula and temporal lobes (arrows) with dystrophic white matter lesions (arrowhead). (e and f) 5-year-old boy with periventricular leukomalacia. Axial phase-sensitive inversion recovery (e) and Coronal FLAIR (f) images of the brain show thinning of the white matter with abnormal signal in the periventricular white matter (arrow) and ex-vacuo enlargement of the lateral ventricles (arrowhead).

magna, Chiari I malformations, pineal cysts, and neuroepithelial cysts) and dilated perivascular spaces.[8] Most of the previously described lesions cannot be classified as epileptogenic; therefore, the high incidence of MRI abnormalities is irrelevant in this study.[10–12]

On the other hand, our study focused on different categories of epileptogenic lesions typically associated with epileptic seizures which were thoroughly detailed in Table 1. The most frequent epileptogenic lesion was focal cortical dysplasia (CD) (four cases in BRE versus two cases in control) followed by periventricular leukomalacia (two cases in BRE versus six cases in control). The spike-wave discharge in the four BRE cases with CD did not emanate from the region of focal cortical dysplasia, suggesting that the radiographic abnormalities might not be the cause of the seizure. Similarly, Sheth et al. presented a case report of an eight-year-old girl showing left hemisphere centrotemporal spikes with features of BRE and left hemisphere focal cortical dysplasia on MRI. They did further investigation using MRI-assisted EEG dipole analysis of the spikes to prove that the Rolandic fissure rather than the focal cortical dysplasia was the epileptogenic source of the spike-wave discharge.[15]

PVL was the second most common MRI abnormality seen in our study. Ekici et al. studied the incidence of epilepsy in 108 children with PVL and found that epilepsy developed in a third of included patients.[16] When investigating the factors correlated with epilepsy, they found a significant correlation with history of neonatal seizures, severe loss of WM, periventricular T2 hyperintensity, and corpus callosum involvement. Generalized tonic-clonic seizures and complex partial seizures were the most common types of seizure. They concluded that PVL might increase the risk of epilepsy; however, that risk was not assessed specifically in BRE. In our series, two children (Cases 1 and 12) with typical clinical presentation and progression supporting a diagnosis of BRE had PVL changes on MRI. These two cases had previous brain insult which is not necessarily the source of epileptic discharges, especially that they had classic clinical BRE presentation.

Our data showed a low frequency (2.9%) of hippocampal abnormality similar to what was reported by Boxerman et al. (4%) and much lower than previously reported (60%).[6,8] Lundberg et al. found hippocampal asymmetries and WM abnormalities in 10 out of 18 BRE cases.[6] Six children had a follow-up brain MRI after two years and three of them showed stable hippocampal asymmetry. However, the detection of hippocampal abnormalities can be biased by the radiologist perception and not based on objective measurements, which may explain the high incidence of hippocampal abnormalities in previous studies. In addition, high-resolution technique and 3D volumetric sequences are specifically needed for hippocampal evaluation with volumetric

Table 3. Whole brain, cortical and subcortical volumetric differences between 50 BRE and 46 control patients. Statistically significant results (*p*-value ≤ .05) are in bold.

Mean volume +/− standard deviation	Benign rolandic epilepsy	< or >	Control	*p*-value
Intracranial	**1375805 +/− 135866.08**	**>**	**1272352.43 +/−170461.52**	**0.001**
Cerebrospinal fluid	14.99 +/− 2.98	<	15.89 +/− 3.31	0.36
Gray-matter	**47.88 +/− 2.25**	**<**	**49.29 +/− 4.13**	**0.04**
White-matter	**37.13 +/− 2.35**	**>**	**35.13 +/− 4.22**	**0.005**
Genu of the corpus callosum	0.43 +/− 0.06	>	0.42 +/− 0.08	0.63
Body of the corpus callosum	0.56 +/− 0.06	>	0.55 +/− 0.08	0.31
Splenium of the corpus callosum	0.587 +/− 0.09	<	0.592 +/−0.11	0.78
Left accumbens	0.037 +/− 0.007	>	0.035 +/− 0.009	0.36
Right accumbens	0.031 +/− 0.006	>	0.029 +/− 0.008	0.26
Accumbens	0.07 +/− 0.01	>	0.06 +/− 0.01	0.27
Left amygdala	**0.09 +/− 0.01**	**>**	**0.08 +/− 0.01**	**0**
Right amygdala	**0.09 +/− 0.01**	**>**	**0.08 +/− 0.02**	**0.002**
Amygdala	**0.19 +/− 0.02**	**>**	**0.17 +/− 0.03**	**0**
Left caudate nucleus	**0.26 +/− 0.03**	**<**	**0.27 +/− 0.03**	**0.02**
Right caudate nucleus	0.27 +/− 0.03	<	0.28 +/− 0.04	0.07
Caudate nucleus	**0.53 +/− 0.05**	**<**	**0.55 +/− 0.07**	**0.03**
Left hippocampus	0.249 +/− 0.03	<	0.252 +/− 0.03	0.59
Right hippocampus	0.25 +/− 0.03	<	0.26 +/− 0.03	0.1
Hippocampus	0.50 +/− 0.05	<	0.51 +/− 0.05	0.24
Left pallidum	0.1163 +/− 0.009	<	0.1165 +/− 0.01	0.91
Right pallidum	0.1172 +/− 0.009	<	0.1178 +/− 0.01	0.78
Pallidum	0.2335 +/− 0.018	<	0.2343 +/− 0.019	0.85
Left putamen	0.3509 +/− 0.03	<	0.3543 +/− 0.04	0.62
Right putamen	0.3462 +/− 0.04	<	0.3516 +/− 0.04	0.47
Putamen	0.70 +/− 0.07	<	0.71 +/− 0.07	0.53
Left thalamus	0.57 +/− 0.04	>	0.56 +/− 0.03	0.73
Right thalamus	0.5533 +/− 0.04	>	0.5508 +/− 0.03	0.74
Thalamus	1.12 +/− 0.08	>	1.11 +/− 0.06	0.73
Left cingulate gyrus	**0.27 +/− 0.05**	**<**	**0.39 +/− 0.19**	**0**
Right cingulate gyrus	**0.45 +/− 0.1**	**<**	**0.6 +/− 0.25**	**0**
Cingulate gyrus	**0.72 +/− 0.15**	**<**	**0.99 +/− 0.44**	**0**
Left medial frontal cortex	**0.39 +/− 0.05**	**>**	**0.34 +/− 0.06**	**0**
Right medial frontal cortex	0.63 +/− 0.09	>	0.61 +/− 0.09	0.34
Medial frontal cortex	**1.02 +/− 0.11**	**>**	**0.95 +/− 0.13**	**0.004**
Left orbitofrontal cortex	**1.01 +/− 0.12**	**>**	**0.72 +/− 0.08**	**0**
Right orbitofrontal cortex	**0.98 +/− 0.11**	**>**	**0.66 +/− 0.08**	**0**
Orbitofrontal cortex	**1.99 +/− 0.21**	**>**	**1.38 +/− 0.14**	**0**
Left pars opercularis	0.25 +/− 0.06	>	0.24 +/− 0.07	0.55
Right pars opercularis	0.2385 +/− 0.05	<	0.2423 +/− 0.07	0.78
Pars opercularis	0.4848 +/− 0.09	>	0.4810 +/− 0.12	0.87
Left pars triangularis	**0.45 +/− 0.1**	**<**	**0.52 +/− 0.14**	**0.003**
Right pars triangularis	**0.43 +/− 0.09**	**<**	**0.51 +/− 0.1**	**0**
Pars triangularis	**0.88 +/− 0.16**	**<**	**1.04 +/− 0.19**	**0**
Left middle frontal gyrus	1.39 +/− 0.17	<	1.43 +/− 0.23	0.37
Right middle frontal gyrus	1.3940 +/− 0.19	>	1.3925 +/− 0.27	0.98
Middle frontal gyrus	2.79 +/− 0.33	<	2.82 +/− 0.44	0.65
Left middle temporal gyrus	**0.94 +/− 0.11**	**<**	**1.25 +/− 0.19**	**0**
Right middle temporal gyrus	**1.05 +/− 0.12**	**<**	**1.38 +/− 0.17**	**0**
Middle temporal gyrus	**1.99 +/− 0.21**	**<**	**2.62 +/− 0.31**	**0**
Left precentral gyrus	**1.29 +/− 0.15**	**<**	**1.48 +/− 0.32**	**0**
Right precentral gyrus	**1.25 +/− 0.14**	**<**	**1.43 +/− 0.25**	**0**
Precentral gyrus	**2.54 +/− 0.26**	**<**	**2.91 +/− 0.55**	**0**
Left precuneus cortex	**1.24 +/− 0.15**	**>**	**1.08 +/− 0.32**	**0.001**
Right precuneus cortex	1.37 +/− 0.16	>	1.28 +/− 0.29	0.08
Precuneus cortex	**2.6 +/− 0.28**	**>**	**2.4 +/− 0.59**	**0.01**
Left subcallosal cortex	**0.05 +/− 0.008**	**>**	**0.04 +/− 0.016**	**0.047**
Right subcallosal cortex	**0.06 +/− 0.01**	**<**	**0.07 +/− 0.02**	**0.02**

(continued)

Table 3. (continued)

Mean volume +/− standard deviation	Benign rolandic epilepsy	< or >	Control	*p*-value
Subcallosal cortex	0.111 +/− 0.02	<	0.113 +/− 0.03	0.69
Left superior frontal gyrus	1.88 +/− 0.21	<	1.95 +/− 0.32	0.24
Right superior frontal gyrus	1.94 +/− 0.27	<	2 +/− 0.31	0.19
Superior frontal gyrus	3.82 +/− 0.45	<	3.95 +/− 0.6	0.19
Left superior temporal gyrus	**1.09 +/− 0.09**	**<**	**1.21 +/− 0.25**	**0.003**
Right superior temporal gyrus	**0.98 +/− 0.12**	**<**	**1.17 +/− 0.21**	**0**
Superior temporal gyrus	**2.08 +/− 0.19**	**<**	**2.38 +/− 0.45**	**0**

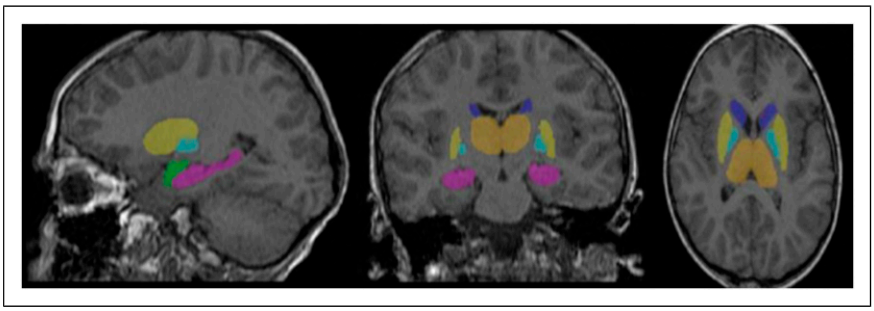

Figure 2. Example of a case segmentation in subcortical regions (dark blue = caudate, yellow = putamen, Orange = thalamus, cyan = pallidum, purple = hippocampus, green = amygdala).

measurements. The asymmetry in hippocampal size without abnormal signal cannot be diagnostic of mesial temporal sclerosis and can be a normal variation.[17] Pedraza et al. conducted a meta-analysis on the volumetric asymmetry of the hippocampus and amygdala in the normal population which revealed larger right hippocampal and amygdala volumes and also demonstrated that differences in slice thickness and MRI magnet field strength might cause volumetric asymmetry.[17]

Boxerman et al. showed no evidence of lateralization of abnormalities in BRE cases towards the side of EEG discharges, almost similar to our results (Table 2).[8] In our series, only one BRE patient (Case 9) had bilateral posterior discharges on EEG which could have originated from the right cingulate focal cortical dysplasia that was found on MRI. However, he had typical BRE presentation, and the disease course goes with BRE.

BRE is known to be not related to any structural lesion, namely at the level of the operculum.[8] This was confirmed in our series since only one of BRE patients had left hemispheric polymicrogyria involving the operculum while the EEG focal abnormalities emanate from the right mid-temporal region.

Structural MRI is known to be limited in detecting microscopic pathological abnormalities-like changes in cortical thickness and GM volumetric variability which can explain the higher incidence of developmental disturbances in BRE cases.[7,9] Pardoe et al. showed the affected cortical GM regions are related to neurocognitive dysfunction in 35 patients with BRE and these changes tend to normalize with age which goes with the natural history of disease.[7] Our volumetric findings in 50 BRE patients showed lower total GM volumes and higher total WM volume in BRE patients compared to healthy children. Similar findings of cortical thinning were described by other studies.[18,19] Garcia-Ramos et al. described cortical thinning in BRE at the time of diagnosis with sparse regions of both cortical thinning and thickening that developed over time.[19] However, these findings are discordant with another study that showed children with BRE have thicker or larger gray matters in the cortico-striatal pathway when comparing the cortical thickness and GM volume of 20 BRE patients to 20 healthy children.[9] Another study demonstrated no significant difference in the global cortical thickness between BRE and controls.[20]

We found thicker medial frontal and orbitofrontal cortices, precuneus gyrus, and amygdala, similar to Kim et al.[9] This can explain the presence of behavioral and learning difficulties, attention deficits, language delay, and hyperactive impulsive symptoms in BRE patients since these regions are involved in adaptive learning and speech-language production as well as executive function, self-processing, and visuospatial imagery.[9]

On the other hand, we found decreased thickness in the pars triangularis gyri which can explain the poor executive and cognitive functions in BRE as well as decreased thickness of the superior and middle temporal gyri and cingulate gyrus which correlates with attention deficit. We also found decreased volume of the precentral gyrus which explains the motor deficit in BRE, whereas Kim et al. found the opposite in these regions.[9] Overvliet et al. showed impaired language indices and cortical thinning in left-lateralized frontal, perisylvian, centro-parietal, and temporal regions in 24 BRE children between the age of 8 and 14 years with no association between cortical thickness and language indices in the regions of aberrant cortex.[21]

In addition, we found lower volume of the caudate nucleus, in particular on the left which also plays a role in executive functioning.[22] Our study also shows no statistically significant difference in the putamen volume between the two

groups, unlike Garcia-Ramos et al. who described larger volumes of putamen in BRE which persisted over two years but found not to be related to seizure-remission status.[19] Lin et al. also described hypertrophy of the putamen and left caudate nucleus which was found to be associated with improved cognitive performances and considered to be likely adaptive.[22]

In our cohort, subcallosal cortex shows variable thickness with higher volume on the left and lower volume on the right. This region was not evaluated in any of the previous studies. Subcallosal cortex abnormalities were associated with depression that can be reversed by various antidepressant therapies.[23] Increased likelihood of depression and anxiety was also described in children with BRE and found to be correlated with age, seizure frequency, spike wave index, and disease course.[24] Our finding can explain the increased incidence of depression in BRE patients and might help tailoring the appropriate antidepressant regimen.

In concordance with the above-mentioned studies, our findings suggest that Rolandic epilepsy should not be considered benign since many BRE patients showed some developmental delay associated with the described microscopic brain changes. The term "benign" should only be limited to the global neurological status and seizure prognosis in BRE.

Possible sources of limitations in our findings include observer bias which could affect the initial diagnosis of BRE when the physician is analyzing the EEG. However, the radiologist was blinded for the initial diagnosis. Selection bias of controls do exist since the control patients are not normal healthy subjects and MRI of the brain is only performed under specific medical indication, so our choice of control came from patients with clinical indication for imaging which might cause a Berkson bias. We addressed the confounding effect of age and sex since there was no significant statistical difference between the two groups concerning these two variables. There was also no significant difference in the technical quality between the exams of cases and controls.

In addition, inter-subject variability which contributes to the differences in brain anatomy and functionality across patients as well as lack of longitudinal analysis of neurocognitive measurements are other limitations in this retrospective study with a small sample size (n=50) for volumetric measurements. Prospective longitudinal studies with a larger sample of patients would help us understanding the unusual trajectories of BRE patients and their association with behavioral and cognitive functions.

In conclusion, our findings confirm the absence of any association between specific brain abnormalities on structural MRI and BRE which were not more common in BRE than in controls. However, the advanced analysis of brain volumetry shows altered cortical development in BRE patients, correlating with functional abnormalities seen in this category of patients.

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Ethical approval

This study was approved by the Institutional Review Board of our institution and all patients enrolled in the study gave written informed consent.

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