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Cortical thickness asymmetries and surgical outcome in neocortical epilepsy

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ABSTRACT

Purpose: We evaluated if cortical thickness measures were associated with surgical outcome in patients with non-lesional neocortical epilepsy.
Methods: Twenty-one young patients (age: 2.4–19.7 years) with epilepsy of neocortical origin and normal MRI underwent two-stage epilepsy surgery with subdural EEG monitoring. Cortical thickness was measured on presurgical volumetric MRI using the FreeSurfer software. The prognostic value of hemispheric and lobar/regional cortical thickness measures for 1-year and 2-year post-surgical seizure outcome has been analyzed.
Results: At one-year follow-up, 14 patients (67%) were seizure-free. Hemispheric and frontal lobe cortical thickness showed no/minimal asymmetry in seizure-free patients but thinner cortex ipsilateral to the seizure focus in those with recurrent seizures ($p = 0.02$). More robust differences were found in patients ≥ 6 years of age ($p = 0.006$ for frontal asymmetries), whose cortical thickness asymmetries remained prognostic for 2-year post-surgical outcome ($p = 0.007$). By using an optimal cutoff threshold based on a receiver operating characteristic analysis, mean hemispheric asymmetry predicted one-year seizure freedom with 93% sensitivity and 71% specificity in the whole group, and with 100% sensitivity and 92% specificity in patients ≥ 6 years of age.
Conclusion: In patients with neocortical epilepsy and normal MRI, neocortical thinning in the epileptic hemisphere, particularly in frontal cortex, is associated with poor surgical outcome. Although these results require validation in a larger cohort prospectively, these data suggest that presurgical evaluation of cortical thickness may assist in identification of patients at high risk for surgical failure.

1. Introduction

Epilepsy surgery is a well-established treatment modality with a relatively high success rate for medically intractable epilepsy. Presence of a focal cortical abnormality on MRI is a good prognostic indicator for epilepsy surgery in such patients: a systematic review and meta-analysis found that the odds of seizure freedom are almost three times higher in the presence of a focal lesion [1]. However, patients who have normal findings on conventional imaging compose a challenging group with a higher rate of surgical failure. In such patients, advanced image acquisition and processing techniques may provide additional localizing and prognostic information during presurgical evaluation [2–5]. Recent software developments, such as FreeSurfer, allow for automated analysis of brain structural features including the measurement of cortical thickness on clinical MRI sequences [6–8]. This approach has previously revealed neocortical thinning in both temporal and extratemporal lobe epilepsy [9–13]. An earlier study of patients with temporal lobe epilepsy demonstrated that cortical thinning in distinct brain regions, even outside the presumed epileptogenic zone, is associated with poor surgical outcome [11]. In a recent study of adults with frontal lobe epilepsy, frontal cortical thinning was associated with poor surgical outcome in those with type I dysplasia [14]. However, the relationship between cortical thickness and surgical outcome has not been evaluated in patients with pediatric neocortical epilepsy and non-localizing conventional MRI. Therefore, in the present study we evaluated the association between cortical thickness and surgical outcome in young patients with

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neocortical epilepsy associated with non-localizing MRI. The overall goal of this study was to assess the feasibility of cortical thickness as an imaging marker of post-operative seizure risk in this very challenging patient population with no focal abnormalities on clinical MRI. Accurate prognostic markers in such patients could have a strong clinical impact during the presurgical evaluation.

2. Material and methods

2.1. Subjects

We included 21 young patients (mean age: 9.9 years; range: 2.4–19.7 years) in the study, who fulfilled the following inclusion criteria: (i) medically refractory neocortical epilepsy based on electro-clinical studies; (ii) normal (non-localizing) clinical MRI, (iii) two-stage epilepsy surgery with chronic subdural EEG monitoring at the Children's Hospital of Michigan (Detroit); (iv) at least 2-year postsurgical follow-up. Detailed clinical, EEG and imaging data of all subjects are presented in Table 1. Comorbidities included clinically significant cognitive/developmental delay (n = 8), ADHD/hyperactivity (n = 3) and depression (n = 1). Five patients had a family history of epilepsy, and none of the patients had a history of febrile seizures or neonatal epilepsy. All patients were on antiepileptic medication in mono- or polytherapy (see details in Table 1). Before surgery, all patients underwent standard presurgical evaluation, as described recently [15]. In brief, all patients were evaluated with scalp ictal/interictal video-EEG, MRI, glucose metabolism positron emission tomography (PET) scans, and neuropsychological assessment. Subsequently, all cases were discussed in a weekly multidisciplinary epilepsy surgery conference where all these modalities were reviewed. Areas showing hypometabolism on PET (present in 18 patients, see details in Table 1) were inspected and no definite MRI abnormalities were found in those areas. At the end of the conference, a consensus was reached pertaining to candidacy for surgery and optimal surgical approach. The actual extent of resection was based on the results from chronic subdural EEG, with electrode coverage including at least some portions of all lobes in the affected hemisphere utilizing up to 128 subdural electrodes. Clinical data and clinically acquired images for these studies were used based on a protocol approved by the Wayne State University Institutional Review Board, and written informed consent was obtained from the patients (if >18 years of age) or from the parents or guardians (for children).

2.2. MRI acquisition

For the clinical epilepsy MR scanning protocol, a 3 T GE-Signa scanner (GE Healthcare, Milwaukee, WI) equipped with an 8-channel head coil was utilized to acquire multiple sequences, including axial T1- and T2-weighted, as well as coronal fluid attenuation inversion recovery (FLAIR) images. In addition, a three-dimensional fast-spoiled gradient recalled-echo sequence (FSPGR) was acquired at TR/TE/TI of 9.12/3.66/400 ms, with slice thickness of 1.2 mm, and planar resolution of 0.94×0.94 mm^2. MRI acquired within 6 months before the surgery was utilized for cortical thickness measurements. Young children (below age 12 years) were sedated and monitored during the MRI scanning using the pediatric sedation protocol of the Children's Hospital of Michigan.

2.3. MR image analysis

First, the scans were inspected to exclude significant motion or other artifacts. Cortical reconstruction and segmentation (area and volume) were performed using FreeSurfer (Version 5.3, http://surfer.nmr.mgh.

Table 1
Detailed clinical data of the 21 patients, listed from the youngest to the oldest.

Pt	Sex	Age at		Seizure type	AED	Scalp EEG focus localization[a]		FDG-PET focus	Resection		Histo-pathology	Seizure freedom 1 year	Seizure freedom 2 years
		Onset	MRI			Localization	Localized ictal onset?		Side	Lobe(s)			
1	M	1.5y	2.4y	ES	CLO, VPA	hemi	No	Multilobar	R	ftpo	Gliosis	Yes	Yes
2	M	0.5y	2.5y	CPS, ATON	OXC, LEV, ZON	tpo	Yes	Multilobar	L	fto	Gliosis	Yes	Yes
3	F	0.4y	3.8y	CPS	TPX, VPA	hemi	No	Multilobar	L	tpo	Gliosis	No	No
4	M	2.4y	4.9y	CPS	VPA, ZON	Frontal	Yes	Single	L	f	fcd IIA	Yes	Yes
5	M	2.5y	5.3y	SPS	OXC	Parietal	n/a	Multilobar	R	p	Gliosis	Yes	Yes
6	F	5.3y	5.7y	CPS, GTCS	TPX	hemi	n/a	Single	R	tpo	fcd IA	Yes	Yes
7	M	1.8y	5.9y	CPS	ZON, FEB, VPA	hemi	No	None	L	fto	Gliosis	Yes	No
8	F	1.8y	6.0y	ES	LAM	Frontal	n/a	None	R	f	Gliosis	Yes	Yes
9	M	2.0y	6.7y	CPS	OXC, LEV, VPA	fp	Yes	Single	R	fp	Gliosis	Yes	Yes
10	F	5.0y	6.9y	CPS, GTCS	OXC, ZON	tpo	Yes	Multilobar	L	ftpo	Gliosis	No	No
11	M	7.6y	8.1y	SPS	LAM, ZON	Normal EEG	n/a	Multilobar	R	f	fcd IA	Yes	No
12	F	6.6y	8.9y	SPS	OXC, CLR	ft	Yes	Multilobar	L	f	fcd IA	Yes	Yes
13	F	4.0y	10.9y	CPS	LAM, LEV	ft	Yes	Multilobar	R	fto	mMCD	Yes	Yes
14	F	6.0y	11.7y	CPS	OXC, LEV	ft	Yes	Multilobar	R	ft	fcd(t) IB gliosis(f)	Yes	Yes
15	M	7.5y	13.6y	CPS	LAM, OXC	Temporal	Yes	Multilobar	L	t	mMCD	No	No
16	F	0.3y	13.8y	CPS	LEV, LAM, OXC	tpo	Yes	Single	R	tpo	Gliosis	No	No
17	F	9.2y	15.2y	CPS	OXC	hemi	No	Multilobar	R	p	Gliosis	No	No
18	F	14.0y	15.5y	SPS	OXC	Temporal	Yes	Single	R	t	Gliosis	No	No
19	F	2.0y	16.2y	CPS	KLO, TPX, PHT	hemi	No	Single	R	f	Gliosis	No	No
20	F	0.9y	17.0y	CPS	LAM, KLO	FRONTAL	Yes	None	L	f	Gliosis	Yes	Yes
21	F	4.0y	19.7y	CPS	OXC, LAM, TPX	FRONTAL	Yes	Multilobar	R	p	Gliosis	Yes	No

Abbreviations: Pt: patient; y: year(s); M: male; F: female; hemi: hemispheric; R: right; L: left; f: frontal; t: temporal; p: parietal; o: occipital; fcd: focal cortical dysplasia; mMCD: mild malformation of cortical development; ES: epileptic spams; ATON: atonic seizures; CPS: complex partial seizures; SPS: simple partial seizures; GTCS: generalized tonic-clonic seizures; AED: anti-epileptic drugs; CLO: clobazam; VPA: valproic acid; OXC: oxcarbazepine; LEV: levetiracetam; ZON: zonisamide; TPX: topiramate; FEB: felbamate; LAM: lamotrigine; CLR: clorazepate; KLO: klonopin; PHT: phenytoin. n/a: no ictal EEG could be obtained, scalp EEG localization was based on interictal data.

[a] Scalp EEG findings (if localized) and resection were always localized on the same side.