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Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy

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The epidemiology of lesions identified by magnetic resonance imaging (MRI), along with the use of pre-surgical evaluations and surgery in childhood-onset epilepsy patients has not previously been described. In a prospectively identified community-based cohort of children enrolled from 1993 to 1997, we examined (i) the frequency of lesions identified by MRI; (ii) clinical factors associated with 'positive' MRI scans; and (iii) the utilization of comprehensive epilepsy evaluations and neurosurgery. Of the original cohort of 613 children, 518 (85%) had usable MRI scans. Eighty-two (16%) had MRI abnormalities potentially relevant to epilepsy ('positive' scans). Idiopathic epilepsy syndromes were identified in 162 (31%) of whom 3% had positive scans. The remainder had non-idiopathic epilepsy syndromes of which 22% had positive MRI findings. Multiple logistic regression analysis identified non-idiopathic epilepsy and abnormal motor-sensory (neurological) examinations as predictors of a positive MRI scan. Of the non-idiopathic patients with normal neurological exams and who were not pharmacoresistant, 10% had positive MRI scans, including four patients with gliomas. Evaluations at comprehensive epilepsy centres occurred in 54 pharmacoresistant cases. To date 5% of the imaged cohort or 8% of non-idiopathic epilepsy patients have undergone surgical procedures (including vagal nerve stimulator implantation) to treat their epilepsy ($n = 22$) or for tumours ($n = 6$) without being drug resistant. Applying our findings to the general population of children in the USA, we estimate that there will be 127/1 000 000 new cases per year of pharmacoresistant epilepsy, and 52/1 000 000 childhood-onset epilepsy patients undergoing epilepsy evaluations. In addition, approximately 27/1 000 000 will have an epilepsy-related surgical procedure. These findings support recommendations for the use of MRI in evaluating newly diagnosed paediatric epilepsy patients, especially with non-idiopathic syndromes, and provide estimates on the utilization of comprehensive evaluations and surgery.

Keywords: epidemiology; mesial temporal sclerosis; cortical malformation; epilepsy surgery; pharmacoresistance

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Abbreviations: HA = hippocampal atrophy; ILAE = International League Against Epilepsy; MCD = malformations of cortical development; MTS = mesial temporal sclerosis; TLE = temporal lobe epilepsy; VNS = Vagal nerve stimulators

Introduction

Structural brain abnormalities are an important cause of epilepsy and are frequently associated with pharmacoresistance. With a few exceptions (Dlugos *et al.*, 2001; Spooner *et al.*, 2006), most of our understanding of these lesions comes from tertiary surgical centres where highly selected patients are thoroughly evaluated. Relatively little is known about the frequency of MRI positive lesions, their association with pharmacoresistance and the use of surgical evaluations and surgery from the community perspective. In its assessment of epilepsy care worldwide, the International League Against Epilepsy (ILAE), Subcommission for Paediatric Epilepsy Surgery noted that insufficient data were available to estimate the number of potential surgical candidates among children with refractory epilepsy and the type and nature of underlying structural lesions associated with new onset epilepsy (Cross *et al.*, 2006). Further, there was little information regarding the proportion of children with refractory epilepsy who were referred for evaluation at comprehensive epilepsy centres, and how many of these received surgery.

The Connecticut Study of Epilepsy is a community-based cohort followed for a median of over a decade in which considerable clinical and research neuroimaging has been performed. This cohort can provide some initial answers to the questions raised in the ILAE's report. In particular, (i) the overall frequency and type of structural abnormalities, identified by MRI, associated with newly diagnosed epilepsy in children; (ii) the clinical features associated with a higher yield of positive MRI findings; and (iii) patterns in the use of comprehensive epilepsy evaluations and surgery.

Methods

Recruitment

The Connecticut Study of Epilepsy is a community-based study that recruited children (1 month to 16 years of age) with newly diagnosed epilepsy from 16 of the 17 offices of practicing paediatric neurologists in the state between 1993 and 1997. Connecticut is a relatively small state with approximately 500 000 children (<16 years old) during the time of recruitment. The US healthcare system relies heavily on specialist care where available. Before recruitment began, paediatricians in the state (paediatricians are considered primary care physicians in the USA) were polled about their practices regarding referral of children with newly diagnosed epilepsy to a paediatric neurologist (a first-level specialist). All paediatricians surveyed responded that their usual practice was to refer to a paediatric neurologist for at least an initial evaluation.

Parents were interviewed at the time of entry to the study. Close contact was maintained with the families, by telephone, every 3–4 months. Permission was obtained to access relevant medical records at initial study entry and on an on-going basis, including records from evaluations at comprehensive epilepsy centres and neurosurgical and histopathology reports. Patients were considered to have had a comprehensive evaluation if they were admitted to an epilepsy centre for prolonged (at least overnight) video electroencephalography (EEG)-telemetry, often with other evaluations e.g. ictal single photon emission computed tomography (SPECT) and Fluorodeoxyglucose-Positron emission tomography (FDG-PET). Other details of the study's recruitment and follow-up methods have been published previously (Berg *et al.*, 1999, 2006). Information regarding sensory and motor neurological deficits (the 'neurological exam') was abstracted from the medical records of this examination performed by the neurologist. Cognitive and developmental status was assessed based on information in medical records, school records, special service providers, periodic interviews with parents and, for over half of the cohort, a neuropsychological exam performed for research purposes (Berg *et al.*, 2008).

Clinical characterization of cohort

Each child's seizure type and electro-clinical syndrome were classified according to ILAE criteria (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and relevant updates (Roger *et al.*, 2002; Panayiotopoulos, 2005). Underlying causes of the epilepsy were classified according to ILAE recommendations (Commission on Epidemiology and Prognosis and International League Against Epilepsy, 1993).

For this presentation, type of epilepsy was classified as 'idiopathic' if the epilepsy conformed to one of the well-described traditional idiopathic electro-clinical syndromes and 'non-idiopathic' for all other cases. Characterizations of epilepsy syndromes and aetiology were updated as new evidence became available from further EEGs, MRI scans, genetic testing, neurocognitive testing, as well as changes in seizure types. The characterizations of each patient's epilepsy were based on the most recent systematic reassessments done 9 years after initial diagnosis. In some instances, the relevance of what appeared to be a potentially epileptogenic lesion on MRI, to a particular individual's epilepsy, was unclear. Such cases were included in our analyses although it was probable that the MRI finding was coincidental in the context of the patient's specific forms of epilepsy. Pharmacoresistance was defined as the failure of two different appropriate anti-epileptic drugs (AEDs) to bring seizures under complete control when used as prescribed and pushed to the maximum tolerated levels (Berg *et al.*, 2006). This is essentially the definition proposed by the ILAE Task Force on Defining Refractory Epilepsy (French, 2009).

Imaging

More than half of the cohort had MRI scans as part of their initial diagnostic evaluation, from 1993 to 1997 (Berg *et al.*, 2000). The entire cohort was followed, on average, for over a decade and many have had additional clinical neuroimaging. Furthermore, many participated in a phase of the study in which a research MRI scan was performed under a uniform seizure protocol. All research scans and almost all clinical scans were performed on a 1.5 T magnet. Clinical scans used sequences and protocols for the scanners on which they were performed and these represent the standard of care for the local regions. The research scans were performed on either a 1.5 T Siemens Sonata or a 1.5 T General Electric Signa and were originally designed to evaluate mesial temporal anatomy. The sequences used were as

follows: sagittal localizer, T_1-weighted; coronal gradient echo 1.5 mm thick contiguous sections acquired in a 3D volume acquisition of the entire brain—to evaluate: (i) hippocampal atrophy (HA) and amygdala atrophy and (ii) malformations of cortical development (MCD); coronal 3-mm thick high resolution fast spin echo (FSE) T2W sections through the temporal lobe—to evalaute atrophy in the hippocampus and amygdala and signal change; coronal fluid attenuated inversion recovery (FLAIR) 5-mm thick sections through the brain—to evaluate: (i) anatomic or signal abnormality in the brain and (ii) hippocampal signal changes.

Interpretation of MRIs and classification of patients

All available research MRI and original clinical MRI scans were interpreted independently by two neuroradiologists with extensive epilepsy imaging experience (RB&RF). The MRI findings were considered as positive if a lesion was identified that could potentially be related to the underlying epilepsy. Minor MRI findings that were not potentially epileptogenic, such as a pineal cyst, were excluded. MRI findings for all subjects were further reviewed by a paediatric epilepsy neurosurgeon (G.W.M.) to characterize the type of MRI abnormality and determine if the lesions were potentially treatable with resective surgery. We defined those lesions involving portions of one cerebral hemisphere as 'potentially surgical'. In addition, cases of hypothalamic hamartomas, and tubers associated with tuberous sclerosis complex (TSC) were counted as potential surgical candidates (Weiner *et al.*, 2006).

Preferred source of imaging information

When multiple scan types were available, the following sources of imaging information were relied upon, in descending order of preference: (i) research MRI ($n = 299$); (ii) clinical MRI re-reviewed and interpreted by study neuroradiologists ($n = 107$); and (iii) clinical MRI for which only the written report was available ($n = 113$). When multiple scans from the same source were available (e.g. several re-interpreted clinical scans), one was selected based on the following preferred criteria: (i) a preoperative study; (ii) the best quality study; and (iii) a study done at an older age, particularly when the participant was an infant at the onset of epilepsy. In some instances, the research MRI was performed after a subject had already had surgery. In these cases, we included information from the pre-surgical scan regarding the imaging characterization of the lesion with that from the research scan, which also considered residual abnormalities. When possible, we compared the interpretation of definite abnormalities from clinical reports to those identified based on our own central review in order to identify any potential inadequacies in using clinical reports when original scans were not available.

This report focuses on the MRI abnormalities considered to be definitely or potentially relevant to epilepsy ('positive' scans). Incidental (e.g. a pineal cyst) and equivocal MRI abnormalities were considered as negative for this study. Because MRI is the preferred mode for neuroimaging in epilepsy evaluations (Hirtz *et al.*, 2000), subjects for whom only computed tomography (CT) results were available ($n = 42$) were not included in our analysis although we provide the information from this group in Table 1.

Analyses

Comparisons were tested with chi-squared and *t*-tests as appropriate for the data. Logistic regression was used for multivariable analysis to identify independent indicators of positive MRI findings.

Ethics

The procedures used throughout this study were approved by the Institutional Review Boards of all participating institutions. The initial procedures for obtaining the parents' informed permission and, when possible, the children's informed assent conformed to the provisions of the Declaration of Helsinki as did procedures for obtaining informed consent once study subjects reached 18 years of age.

Results

Imaging in the cohort

Of the 613 children with newly diagnosed epilepsy, 520 (84.8%) had at least one MRI scan. An additional 42 (6.9%) children had a CT scan without MRI and 51 (8.3%) had no imaging study performed. Two subjects with MRIs were excluded from our analysis. The first case was excluded because the original MRI and radiology report were not available and the description of the abnormalities obtained from the physician's notes was inadequate for classifying the lesion. The second case was excluded because of head trauma (with associated imaging abnormalities) that occured several years after the onset of epilepsy and just prior to the only available MRI scan. Hence, 84.5% (518/613) had usable MRI scans. There were some differences between those who had MRI scans, CT only, and no scans in terms of neurological and cognitive examination, pharmacoresistance and mortality (Table 1). Those without any neuroimaging were more likely to have idiopathic generalized electro-clinical syndromes than those with CT or MRI (41% versus 20%, $P = 0.0004$).

Source of positive MRI scans

There were differences in the frequency of positive scans and clinical characteristics between subjects who had research MRIs compared with those with only clinical scans (Table 1). Those who participated in the non-sedated research MRI were more likely to have a normal scan ($P < 0.001$), a normal neurological exam ($P < 0.0001$), an IQ score above 80 ($P < 0.0001$) and to still be alive ($P = 0.002$) compared with those with re-read and not re-read (combined) clinical scans. If research scans were positive, the MRI findings were more likely to be uni-hemispheric and focal than findings from clinical scans ($P = 0.01$). In addition, because the research scans were performed 8–9 years after study entry, the research scan group was older at the time of their imaging than the participants for whom we used clinical scans (15.5 years $\pm$ 4.1 versus 6.1 years $\pm$ 4.6). Subjects with re-read versus non-re-read scans were similar in terms of age when scanned (5.6 years for re-read and 6.6 years for non-re-read scans), other patient characteristics and MRI findings.

Table 1 Comparisons of study subjects with research MRIs, clinical MRI scans that were re-read, and clinical MRI scans that were not-re-read (radiology report only)

Feature	Research MRI ($n=298$[a]) *n* (%)	Re-read clinical MRI ($n=107$) *n* (%)	Not re-read clinical MRI ($n=113$[a]) *n* (%)	CT scan only ($n=42$) *n* (%)	No imaging ($n=51$) *n* (%)
Overall interpretation of scan					
MRI negative	267 (89.6)	84 (78.5)	85 (75.2)	32 (76.2)	
MRI positive	31 (10.4)	23 (21.5)	28 (24.8)	10 (23.8)[b]	
Extent of lesion for abnormal scans					
Uni-hemispheric	22 (71.0)	9 (39.1)	13 (46.4)	2 (33)[c]	
Bi-hemispheric	9 (29.0)	14 (60.9)	15 (53.6)	4 (67)	
Pharmacoresistance					
Absent	237 (79.5)	73 (68.2)	76 (67.3)	37 (88.1)	48 (94.1)
Present	61 (20.5)	34 (31.8)	37 (32.7)	5 (11.9)	3 (5.9)
Cognitive status					
IQ $\geqslant$ 80	254 (85.2)	62 (57.9)	66 (58.4)	27 (64.3)	41 (80.4)
IQ $<$ 80	44 (14.8)	45 (42.1)	47 (41.6)	15 (35.7)	10 (19.6)
Neurological exam					
Normal	285 (95.6)	78 (72.9)	89 (78.8)	31 (73.8)	47 (92.2)
Abnormal	13 (4.4)	29 (27.1)	24 (21.2)	11 (26.2)	4 (7.8)
Deceased					
No	296 (99.3)	102 (95.3)	107 (94.7)	39 (92.9)	51 (100)
Yes	2 (0.7)	5 (4.7)	6 (5.3)	3 (7.1)	0

a Two subjects who did have MRIs were excluded, one because the original scan and report were unavailable, and the information provided in the records was inadequate to characterize the findings beyond being abnormal; the other because of a severe head injury that occurred just prior to the only scan (research MRI) that was done, but several years after the onset of epilepsy.
b Three treated hydrocephalus, five pre-perinatal strokes, one lissencephaly and one Pfeiffer syndrome.
c Extent of lesion could not be determined from the CT report in four cases.

The identification of definite abnormalities obtained from the original radiological report was comparable with the results obtained when the original MRI images were re-interpreted for the study purposes. Kappa for the agreement over whether the findings were normal (including equivocal and incidental abnormalities) versus definitely abnormal was 0.85 [95% confidence interval (CI) 0.73–0.98]. The specific interpretations of the MRI abnormalities (location and nature of lesion) were also very similar when we compared the clinical with the research interpretations for each positive scan. The excellent agreement between research and original clinical interpretations for definite MRI abnormalities indicates that our reliance on clinical reports for a proportion of study subjects did not introduce major error in the identification of obvious structural abnormalities.

Neuroimaging findings

Of the 518 subjects included in the analyses, 82 (15.8%, 95% CI = 12.7–19.0) had evidence of structural lesions that were considered potentially relevant to epilepsy (Table 2). Thirty (37%) were considered acquired (mostly pre- and perinatal cerebral injuries), 22 (27%) MCD, 18 (22%) discrete lesions (e.g. tumours) and 12 (15%) lesions associated with a variety of genetic conditions.

Five subjects (#26, #40, #67, #68 and #70) had structural lesions that were difficult to reconcile with their idiopathic electroclinical syndromes (Table 2) and which, under other circumstances, might be considered relevant to the cause of a patient's epilepsy. These included two with evidence of HA (Table 2, #68 and #70). In these five cases, however, the findings were ultimately deemed as probably coincidental. Two more patients had clinical histories consistent with acquired insults. The structural abnormalities visible on the MRI, however, did not correspond to their seizures (small thalamic lacunar infarct and a subependymal cyst contralateral to the EEG interictal focus; Table 2, Cases #18 and #66). Examples of some of the MRI findings, including those considered to be coincidental, are provided in Fig. 1.

Positive MRI scans were found in 21.6% (77/356) of patients with non-idiopathic epilepsy compared with 3% (5/162) for those in the idiopathic group. Compared with those with negative MRI scans, patients with positive imaging findings had a younger age at onset, and a higher frequency of abnormalities in both their motor-sensory neurological exams and cognitive status (Table 3). Drug resistance and mortality were also higher in the MRI positive group compared with the negative group. In a multiple logistic regression analysis of all imaged patients, the type of epilepsy (idiopathic versus non-idiopathic) and abnormal neurological exam were the strongest predictors of having a positive MRI scan (Table 4). In a multiple logistic regression analysis limited to study subjects with non-idiopathic forms of epilepsy ($n=356$), an abnormal neurological exam ($P<0.0001$) and pharmacoresistance ($P=0.04$) were independent correlates of a positive MRI. In children with an abnormal neurological exam, 65.7% (23/35) who were pharmacoresistant versus 53.3% (16/30) that were not pharmacoresistant had a positive MRI ($P=0.31$). In those with a normal neurological exam, however, 20.7% (17/82) who were pharmacoresistant versus 10.1% (21/209) who were not pharmacoresistant had a positive MRI ($P=0.02$). This last group

Table 2 All positive MRI findings in MRI-imaged cohort ($n = 82$)

Case #	Lesion type[a]	MRI finding	MTS/HA	Additional clinical notes	Extent of lesion	Lobe	Post-surg. candidate	Pharmaco-resistant	Evaluation	Surgery
1	Acquired	Atrophy—bilateral focal		Hypoglycemic encephalopathy; west syndrome	Bi-hemispheric	Parietal–occipital		Yes	EEG Tele and PET/SPECT	VNS
2	Acquired	Atrophy—bilateral-focal		Prenatal ischaemia and cerebral palsy	Bi-hemispheric	Occipital				
3	Acquired	Atrophy—diffuse		Prenatal ischaemia-deceased	Bi-hemispheric	All				
4	Acquired	Atrophy—diffuse		HIE	Bi-hemispheric	All		Yes		
5	Acquired	Atrophy—diffuse		Prenatal ischaemia; west syndrome	Bi-hemispheric	All		Yes		
6	Acquired	Atrophy—diffuse		Post-infection; west syndrome	Bi-hemispheric	All		Yes		
7	Acquired	Atrophy—diffuse	Yes	HIE	Bi-hemispheric	All				
8	Acquired	Atrophy—diffuse and plagiocephaly		Prenatal ischaemia-deceased	Bi-hemispheric	All		Yes	EEG Tele	
9	Acquired	Atrophy—diffuse and ventriculomegaly	Yes	HIE	Bi-hemispheric	All				
10	Acquired	Atrophy—focal		Prenatal ischaemia	Uni-hemispheric	Parietal-right	Yes	Yes	EEG Tele and PET/SPECT	VNS
11	Acquired	Atrophy—focal		Postnatal CVA	Uni-hemispheric	Occipital-right	Yes			
12	Acquired	Atrophy—focal		Postnatal CVA	Uni-hemispheric	Parietal–occiptial-right	Yes	Yes		
13	Acquired	Atrophy—focal		IVH	Uni-hemispheric	Parietal-left	Yes	Yes		
14	Acquired	Atrophy—focal		Prenatal ischaemia	Uni-hemispheric	Frontal-right	Yes	Yes	EEG Tele and PET/SPECT	Surgery
15	Acquired	Atrophy—focal		Neonatal CVA	Uni-hemispheric	Parietal-left	Yes			
16	Acquired	Atrophy—focal			Uni-hemispheric	Parietal-right	Yes			
17	Acquired	Atrophy—focal		Prenatal ischaemia	Uni-hemispheric	Temporal-left	Yes			
18	Acquired	Atrophy—lacunar infarct		*Strep*. pneumonia	Uni-hemispheric	Thalamus-right		Yes		
19	Acquired	Atrophy—multilobar		R-MCA stroke	Uni-hemispheric	Frontal–parietal-right	Yes	Yes	EEG Tele and PET/SPECT	Surgery
20	Acquired	Atrophy—multilobar and ventriculomegaly	Yes	Prenatal ischaemia	Uni-hemispheric	Temporal–parietal–occipital-right	Yes	Yes		
21	Acquired	Congenital Toxoplasmosis Hydrocephalus			Uni-hemispheric	Temporal	Yes			
22	Acquired	Microcephaly and Ventriculomegaly		HIE	Bi-hemispheric	All				
23	Acquired	Porencephaly and Ventriculomegaly			Uni-hemispheric	Hemisphere-left	Yes			
24	Acquired	PVL		H/O Trauma	Bi-hemispheric	Frontal				
25	Acquired	PVL		Spastic deplegia	Bi-hemispheric	Parietal				
26	Acquired	PVL		IVH/absence epilepsy	Uni-hemispheric	Frontal-left	Yes			
27	Acquired	PVL		H/O IVH	Bi-hemispheric	All		Yes		
28	Acquired	PVL	Yes	H/O IVH	Bi-hemispheric	All		Yes	EEG Tele	
29	Acquired	PVL		H/O IVH	Bi-hemispheric	All				
30	Acquired	PVL and Porencephaly		H/O IVH; west syndrome	Uni-hemispheric	Frontal–temporal–parietal-right	Yes	Yes	EEG Tele and PET/SPECT	VNS
31	MCD	Cortical dysplasia		West syndrome	Bi-hemispheric	Frontal		Yes		VNS
32	MCD	Cortical dysplasia	Yes-Path only	SUDEP	Bi-hemispheric	Parietal		Yes	EEG Tele and PET/SPECT	Surgery and VNS
33	MCD	Cortical dysplasia			Uni-hemispheric	Frontal-right	Yes			
34	MCD	Cortical dysplasia			Uni-hemispheric	Temporal-right	Yes			
35	MCD	Cortical dysplasia			Uni-hemispheric	Frontal–parietal-left	Yes			
36	MCD	Cortical dysplasia			Uni-hemispheric	Parietal-left	Yes			

(continued)

Table 2 Continued

Case #	Lesion type[a]	MRI finding	MTS/HA	Additional clinical notes	Extent of lesion	Lobe	Post-surg. candidate	Pharmaco-resistant	Evaluation	Surgery
37	MCD	Cortical dysplasia	Yes		Uni-hemispheric	Temporal-left	Yes	Yes	EEG Tele and PET/SPECT	Surgery and VNS
38	MCD	Cortical dysplasia		West syndrome	Uni-hemispheric	Temporal-left	Yes	Yes	EEG Tele	
39	MCD	Hemimegalencephaly			Uni-hemispheric	Hemisphere-left	Yes	Yes	EEG Tele and PET/SPECT	
40	MCD	Heterotopia		JAE/JME	Bi-hemispheric	Frontal				
41	MCD	Heterotopia, Chiari-II			Bi-hemispheric	Temporal–occipital				
42	MCD	Hetertopia	Yes		Uni-hemispheric	Temporal-right	Yes	Yes		
43	MCD	Hetertopia			Uni-hemispheric	Occipital-left	Yes	Yes	EEG Tele and PET/SPECT	
44	MCD	Holoprosencephaly		Deceased	Bi-hemispheric	All				
45	MCD	Lissencephaly		West syndrome	Bi-hemispheric	All		Yes		
46	MCD	Pachygyria		Deceased	Bi-hemispheric	All		Yes		
47	MCD	Pachygyria			Bi-hemispheric	All		Yes	EEG Tele	
48	MCD	Pachygyria and colpocephaly			Bi-hemispheric	All				
49	MCD	Polymicorgyria and colpocephaly			Bi-hemispheric	Frontal–parietal		Yes		
50	MCD	Polymicrogyria			Bi-hemispheric	Frontal–parietal		Yes	EEG Tele and PET/SPECT	VNS
51	MCD	Schizencephaly			Uni-hemispheric	Frontal–parietal-right	Yes			
52	MCD	Schizencephaly			Uni-hemispheric	Frontal-left	Yes			
53	Genetic	Degenerative	Yes	Complex IV deficiency-deceased	Bi-hemispheric	All		Yes	EEG Tele and PET/SPECT	
54	Genetic	Degenerative		Batten disease-deceased	Bi-hemispheric	All		Yes		
55	Genetic	Degenerative		Menkes/west syndrome-deceased	Bi-hemispheric	All		Yes		
56	Genetic	Neurofibromatosis			Bi-hemispheric	All				
57	Genetic	Neurofibromatosis	Yes		Bi-hemispheric	Temporal				
58	Genetic	Tuberous sclerosis complex		West syndrome	Bi-hemispheric	Multiple Tubers	Yes	Yes		
59	Genetic	Tuberous sclerosis complex			Bi-hemispheric	Multiple Tubers	Yes	Yes	EEG Tele and PET/SPECT	
60	Genetic	Tuberous sclerosis complex			Bi-hemispheric	Multiple Tubers	Yes			
61	Genetic	Tuberous sclerosis complex		West syndrome	Bi-hemispheric	Multiple Tubers	Yes	Yes		
62	Genetic	Tuberous sclerosis complex			Bi-hemispheric	Multiple Tubers	Yes			
63	Genetic	Tuberous sclerosis complex			Bi-hemispheric	Multiple Tubers	Yes	Yes	EEG Tele	Surgery and VNS
64	Genetic	Tuberous sclerosis complex			Bi-hemispheric	Multiple Tubers	Yes	Yes	EEG Tele	
65	Discrete Lesion	Cavernous angioma			Uni-hemispheric	Tempora–Parietal-left	Yes	Yes	EEG Tele and PET/SPECT	Surgery and VNS
66	Discrete Lesion	Cyst		EEG focus contralateral	Uni-hemispheric	Parietal-right	Yes			
67	Discrete Lesion	Cyst		BRE	Uni-hemispheric	Temporal-right				
68	Discrete Lesion	HA/Sclerosis	Yes	IGE	Bi-hemispheric	Temporal				
69	Discrete Lesion	HA/Sclerosis	Yes		Uni-hemispheric	Temporal-left	Yes			
70	Discrete Lesion	HA/Sclerosis	Yes	BRE	Uni-hemispheric	Temporal-left				

71	Discrete Lesion	HA/Sclerosis	Yes		Uni-hemispheric	Temporal-right	Yes				
72	Discrete Lesion	HA/Sclerosis	Yes	Prenatal ischaemia	Uni-hemispheric	Temporal-right	Yes				
73	Discrete Lesion	HA/Sclerosis	Yes		Uni-hemispheric	Temporal-right	Yes	Yes	EEG Tele		
74	Discrete Lesion	Hypothalamic Hamartoma			Uni-hemispheric	Hypothalamus-right	Yes	Yes	EEG Tele and PET/SPECT	Surgery and VNS	
75	Discrete Lesion	Hypothalamic Hamartoma			Uni-hemispheric	Hypothalamus-right	Yes	Yes	EEG Tele and PET/SPECT	Surgery	
76	Discrete Lesion	Tumour—Grade II Astrocytoma			Uni-hemispheric	Temporal-left	Yes	Yes	EEG Tele	Surgery	
77	Discrete Lesion	Tumour—low grade Glioma			Uni-hemispheric	Parietal–occipital-left	Yes			Surgery	
78	Discrete Lesion	Tumour—Anaplastic Astrocytoma			Uni-hemispheric	Occipital-right	Yes			Surgery	
79	Discrete Lesion	Tumour—DNET			Uni-hemispheric	Frontal-right	Yes			Surgery	
80	Discrete Lesion	Tumour—DNET			Uni-hemispheric	Frontal–parietal-left	Yes			Surgery	
81	Discrete Lesion	Tumour—Ganglioglioma			Uni-hemispheric	Temporal-right	Yes			Surgery	
82	Discrete Lesion	Tumour—Oligodendroglioma	Yes-Post Op		Uni-hemispheric	Temporal-right	Yes			Surgery	

a Based on the MRI finding and clinical information, lesions were classified as 'Acquired' if there was evidence of destructive cortical process and atrophy from an insult (e.g. ischaemia, stroke), as malformation of cortical development (MCD; e.g. cortical dysplasia, lissencephaly), a 'Discrete Lesion' for uni-hemispheric, focal lesions of the type often treated surgically (e.g. tumours, cavernous malformations) and 'Genetic' for MRI findings characteristic of and associated with specific identified genetic disorders (e.g. Batten's Disease, tuberous sclerosis) although we recognize that some lesions could have been classified in more than one category (e.g. lissencephaly; MCD and genetic).

BRE = benign rolandic epilepsy; CVA = cerebrovascular accident; DNET = dysembryoplastic neuroepithelial tumour; HIE = hypoxic-ischemic encephalopathy; IGE = idiopathic generalized epilepsy; IVH = intraventricular hemorrhage; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; MCD = malformation of cortical development; PVL = periventricular leucomalacia; R-MCA = right middle cerebral artery; SUDEP = sudden unexpected death in epilepsy; VNS = vagal nerve stimulator

contained four patients with gliomas. A total of 24 patients with normal neurological and cognitive exams and no history suggesting a previous insult or condition (e.g. head trauma, bacterial meningitis) had positive MRI findings. This represents almost a third of all positive MRI scans among patients with non-idiopathic epilepsies.

In addition to being associated with pharmacoresistance, patients with positive MRI findings were less likely to experience remission periods after second drug failure. Of those with non-idiopathic epilepsies who had tried at least a second drug and been followed at least 3 years after second drug failure ($n = 104$), 19/68 (27.9%) with negative scans and 1/36 (2.8%) with positive scans were seizure-free for >3 years at last contact ($P = 0.002$). None of the cases with idiopathic syndromes and positive MRI scans was pharmacoresistant.

Uni- versus bi-hemispheric MRI abnormalities

Forty-four (54%) of the subjects had uni-hemispheric (including subcortical) and 38 (46%) had bi-hemispheric lesions. Compared with patients with uni-hemispheric lesions, those with bi-hemispheric lesions had a younger age at seizure onset, and a higher proportion had an abnormal cognitive or neurological status, as well as higher mortality (Table 5). Pharmacoresistant epilepsy was slightly, but not significantly, more frequent in patients with bi- versus uni-hemispheric lesions (57.9% versus 40.9%, $P = 0.12$). This was true even after excluding five individuals with idiopathic forms of epilepsy and positive MRI scans.

Of those with refractory non-idiopathic epilepsy and positive MRI scans, we identified 22 (55.0%) as potential surgical candidates. Thus, 4.2% (95% CI 2.5%, 6.0%) of the MRI-imaged cohort had pharmacoresistant epilepsy associated with potentially resectable structural abnormalities. This represents 6.2% (95% CI 3.7–8.9%) of patients with non-idiopathic epilepsy.

Mesial temporal sclerosis/HA

Sixteen subjects had mesial temporal sclerosis (MTS) or HA. In one patient with bi-hemispheric MRI abnormalities, MTS was found on histopathology only (Table 2, #32). In another patient MTS/HA was interpreted from the MRI as being secondary to postoperative changes (Table 2; #82). In 14 others, MTS was diagnosed based on visual assessment of hippocampal volumetric loss, increased FLAIR or T2 signal change, or both. Information came from five research, eight re-read clinical and one not re-read clinical scans. Of the 14 patients with MRI identified MTS/HA, seven had evidence of other structural abnormalities on their scans. One patient, with a negative MRI, had subtle cortical dysplasia identified at histopathology, and the last patient also had neurofibromatosis. Only five patients had isolated MTS/HA on their MRI scans. As previously mentioned, two of these patients had idiopathic electro-clinical syndromes and well-controlled seizures. Of the other three cases, two were in remission on AEDs and the third was pharmacoresistant with an interictal EEG focus consistent with mesial temporal lobe origin ipsilateral to the imaging findings (Fig. 1A).

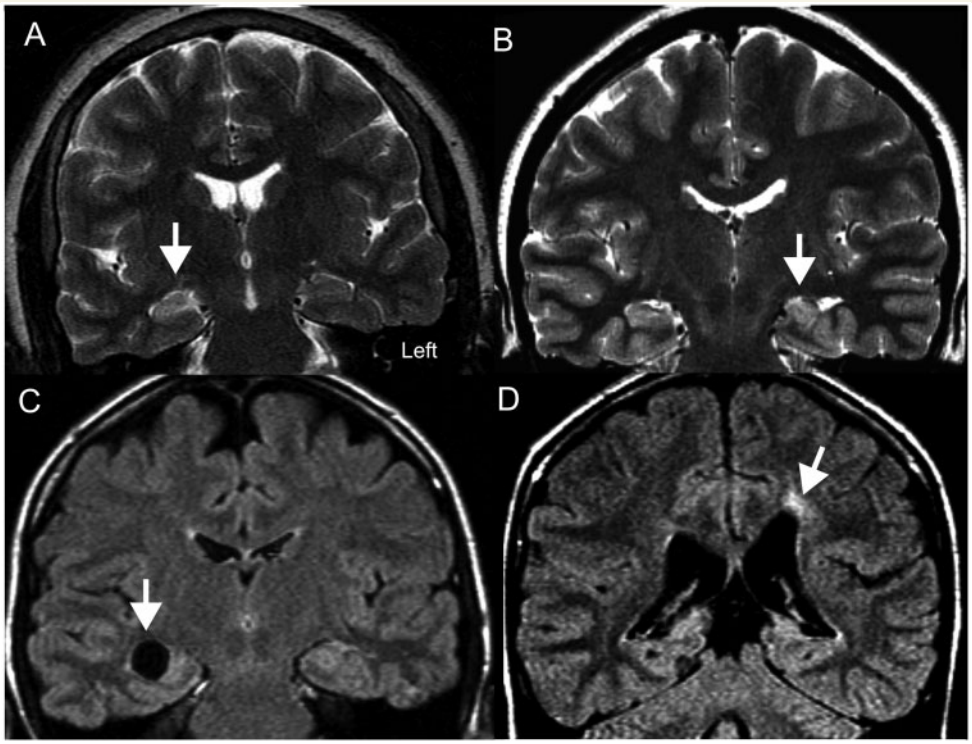

Figure 1 (A) Example of a patient with pharmacoresistant epilepsy with EEG suggesting a right temporal focus. MRI shows increased T2 signal in the right hippocampus (arrow). This is the only case so far of a patient with MRI MTS whose seizures are not controlled by drugs and with a concordant EEG. (Table 2; Case #73). (**B**) Example of another patient with TLE whose seizures are controlled by drugs. Interictal EEG shows greater left than right abnormalities. MRI discloses left HA with some T2 signal changes (arrow; Table 2; Case #69). (**C**) This patient has electro-clinical findings most consistent with benign rolandic epilepsy including characteristic epileptiform discharges activated during sleep. MRI revealed a cyst in the right mesial temporal lobe (arrow). The MRI finding was considered coincidental in this particular clinical context (Table 2; Case #67). (**D**) This patient has childhood absence epilepsy, a diagnosis based on the characteristic 3 Hz generalized spike and wave on EEG associated with absence spells induced with hyperventilation. MRI disclosed evidence of an old left intraventricular haemorrhage (arrow) and this patient also has a mild right hemiparesis. The MRI lesion was considered coincidental in the clinical context (Table 2; Case #26).

Table 3 Comparisons of subjects with negative and positive MRI scans with respect to clinical variables

		MRI		
	Total ($n=518$) *n* (%)	Negative ($n=436$, 84.2%) *n* (%)	Positive ($n=82$, 15.8%) *n* (%)	*P*-value
Traditional idiopathic syndromes	162 (31.3)	157 (36.0)	5[a] (6.1)	<0.0001
Age at onset <2 years	113 (21.8)	83 (19.0)	30 (36.6)	0.0004
Pharmacoresistant	132 (25.5)	92 (21.1)	40 (48.8)	<0.0001
Deceased	13 (2.5)	5 (1.2)	8 (9.8)	<0.0001
FSIQ <80 or equivalent	136 (26.3)	92 (21.1)	44 (53.7)	<0.0001
Abnormal neurological exam	66 (12.7)	26 (6.0)	40 (48.8)	<0.0001
Length of follow-up (years, SD)		11.7 (2.9)	10.5 (3.9)	0.009
Time to second AED failure ($n=92$, years, SD)		2.7 (3.1)	1.8 (2.4)	0.08

a Five cases with idiopathic electro-clinical syndromes and probably incidental structural abnormalities as described in the text. AED = anti-epileptic drug; FSIQ = full scale intelligence quotient.

Comprehensive evaluations and surgery

Evaluations at comprehensive epilepsy centres were conducted in 54/132 (40.9%) of pharmacoresistant patients and in 53/117 (45.3%) of non-idiopathic, pharmacoresistant patients. In the non-idiopathic group, 30/77 (39%) patients with negative MRI scans and 23/40 (58%) with positive MRI scans were evaluated (Table 6). This last group included 16/22 (72.7%) of those with potential surgical lesions. Of these 16, the median time from

failure of second drug to first in-hospital monitoring was 2 years (five were within 1 year, three within 1–2 years, four within 2–3 years and four after >3 years). For the remaining six potential surgery cases with pharmacoresistant epilepsy, two had less than one seizure per month and another was followed for <1 year. Comprehensive evaluations were also performed in 7/18 (38.8%) with abnormal scans, but who were not considered likely surgical candidates and in 30/76 (28.8%) with normal MRI scans. Their median time from failure of the second drug to evaluation was 1.3 years (14 within 1 year, nine within 1–2 years, five within 2–3 years and six after >3 years).

Of 61 patients with normal MRI scans who were pharmacoresistant and who did not have comprehensive evaluations, 14 (23.0%) had idiopathic electro-clinical syndromes and 34 (55.6%) were seizure-free for at least 1 year at last contact. Of the 11 pharmacoresistant patients with abnormal MRI scans, but who were not considered likely surgical candidates and who did not have comprehensive evaluations, eight (72.7%) had other generalized electro-clinical syndromes including three with neurodegenerative conditions.

During a median follow-up period of 11.5 years, 28 (5.4%) patients in the MRI cohort have undergone some surgical procedure. Surgery was performed in 16.7% (22/132) of those with pharmacoresistant epilepsy. This represents 4.2% (22/518) of our imaged cohort, 18.8% (22/117) of non-idiopathic pharmacoresistant patients and 41.5% (22/53) of non-idiopathic patients who underwent an evaluation. Resective or disconnection epilepsy

Table 4 Multivariable logistic regression model of predictors of positive MRI scan for all patients and for patients with non-idiopathic forms of epilepsy

Predictor	Relative risk	95% CI	*P*-value
Predictors of positive MRIs			
Idiopathic syndrome	0.26	0.10–0.65	0.004
Abnormal neurological exam	4.24	2.89–6.22	<0.0001
Pharmacoresistant	1.42	0.99–2.02	0.06
IQ <80[a]	1.08	0.68–1.70	0.74
Age at onset <2 years[a]	0.88	0.63–1.23	0.45
Patients with non-idiopathic forms of epilepsy			
Abnormal neurological exam	4.05	2.76–5.93	<0.0001
Pharmacoresistant	1.47	1.02–2.12	0.04
IQ <80[a]	1.14	0.70–1.85	0.60
Age at onset <2 years[a]	0.88	0.63–1.24	0.48

Death is not considered a predictor of the MRI findings but as an outcome.
a Estimates for IQ<80 and for age at onset were obtained after adjustment for ineurological exam and pharmacoresistance as well as, in the first half of the table, idiopathic syndromes. These three factors were adjusted for each other but not for IQ or age at onset.

Table 5 Comparison of patients with uni-hemispheric versus bi-hemispheric structural abnormalities on MRI

	Uni-hemispheric abnormalities[a] (*n* = 44) Years (SD)	Bi-hemispheric abnormalities (*n* = 38) Years (SD)	*P*-value
Average age at onset	6.1 (4.5)	3.6 (3.8)	0.008
Average time to second drug failure	1.9 (2.5)	1.7 (2.4)	0.73
Average follow-up[a]	11.6 (2.8)	9.3 (4.5)	0.008
	N (%)	*N* (%)	
Pharmacoresistant	18 (40.9)	22 (57.9)	0.12
Deceased	0 (0)	8 (21.1)	0.001
FSIQ <80	15 (34.1)	29 (76.3)	0.0001
Abnormal neurological exam	15 (34.1)	25 (65.8)	0.004
Type of epilepsy			
Focal	38 (86.4)	21 (55.3)	0.0002
Other generalized	2 (4.6)	16 (42.1)	
Idiopathic	4 (9.1)	1 (2.6)	

Of the uni-hemispheric lesions, 39 were focal, 4 multi-lobar and 1 involved the entire hemisphere. In the bi-hemispheric group, 12 involved bilateral homologous regions (e.g. bi-temporal), 2 were multi-lobar, 9 multifocal and 15 involved both hemispheres diffusely.
The *P*-value is driven by the differences in the focal and other generalized group.
a Most (although not quite all) of the difference in follow-up is due to the higher mortality in the bilateral MRI positive group.

Table 6 Comprehensive epilepsy evaluations, epilepsy surgery and lesion surgery

	Refractory (*n* = 132)			Not refractory MRI positive (*n* = 42)
	MRI positive (*n* = 40)		MRI negative (*n* = 92 including 15 idiopathic cases)	
	Not potential surgical (*n* = 18)	Potential surgical (*n* = 22)		
Comprehensive evaluation (including PET/SPECT)[a]	7 (4)	16 (11)	31[b] (16)	NA
No comprehensive evaluation	11	6	61	NA
Resective surgery	1	7	3	6
Repeat surgeries	1	2	0	0
Multiple subpial transections	0	0	1	0
Corpus callosotomy	0	2[c]	0	0
Vagal nerve stimulator	4 (1[d])	6 (4[d])	5 (1[d])	0

a Numbers within parenthesis represents a subset of those evaluated.
b One case with an idiopathic form of epilepsy underwent inpatient video monitoring.
c One of these two is also counted above with repeated focal resection before corpus callosotomy.
d Indicates the number who also had some other kind of surgery.

Table 7 Details of 19 surgical cases

Case # from Table 2	Primary MRI abnormality	Lesion/histopathology	Type of surgery	⩾1 year seizure-free at last contact
Uni-hemispheric Lesion on MRI and pharmacoresistant ($n=7$)				
#74	Hypothalamic hamartoma	Hypothalamic hamartoma	Focal resection	No
#75	Hypothalamic hamartoma	Hypothalamic hamartoma	Focal resection	Yes
#37	HA	Cortical dysplasia + HA	Two focal resections + callosotomy	No
#19	MCA infarct	MCA infarct	Multilobar resection	Yes
#14	Cystic encephalomalacia	Non-specific gliois	Focal resection	No
#76	Neoplasm	Grade II astrocytoma	Focal resection	Yes
#65	Cavernous angioma	Cavernous angioma	Two focal resections[a]	Yes
Uni-hemispheric lesions and not pharmacoresistant ($n=6$)				
#81	Neoplasm	Ganglioma	Focal resection	Yes
#79	DNET	DNET	Focal resection (prior to seizure onset)	Yes
#80	DNET	DNET	Focal resection	Yes
#77	Neoplasm	Low grade glioma	Focal resection	Yes
#78	Neoplasm	Anaplastic astrocytoma	Focal resection	Yes
#82	Neoplasm	Oligodendroglioma	Focal resection	Yes
Bi-hemispheric lesions on MRI and pharmacoresistant ($n=2$)				
#32	Bi-parietal atrophy + generalized atrophy	MMCD + MTS[b]	Two focal resections	No[c]
#63	TSC	—	Callosotomy	No
Negative MRI and pharmacoresistant ($n=4$)				
Neg1	Equivocal MCD	Normal	Focal resection	No[c]
Neg2	Normal	Polymicrogyria	Focal resection	Yes
Neg3	Normal	No Pathology	Mutiple subpial transection	No
Neg4	Normal	Dysplasia	Focal resection	No

a Surgery was done immediately for the initial lesion. Some years later, seizures recurred and were refractory to pharmacologic treatment and VNS. A second resective procedure was performed and the patient has been seizure-free since surgery.
b MMCD = minimal or microscopic cortical dysplasia (Palmini *et al*., 2004). MTS was found only on pathology, not on presurgical MRI.
c Deceased, sudden unexpected death.

surgery (for seizure control) was performed on 13 patients, one of whom first had a lesion resected (i.e. was not pharmacoresistant at the time of the first procedure), but then later required epilepsy surgery (Table 7). Four patients with negative MRI scans and cryptogenic epilepsy had surgery. Abnormal histopathology was documented in two of these cases. Vagal nerve stimulators (VNS) were used in 15 patients (11.4% of those with refractory seizures), and included six patients who underwent other procedures either before or after VNS implantation. Following resective procedures, five pharmacoresistant patients became seizure-free. The other six lesion resection-only patients are also seizure-free. Two patients who were not seizure-free after surgery have died.

Estimates for comprehensive evaluation and surgery for the general population

Our findings provide some preliminary estimates of the use of comprehensive evaluations and surgery at a national level, based on 10 years of follow-up. Canadian and Icelandic studies estimate the annual incidence rate of epilepsy in children, under 15 or 16 years of age, at between 410 (Camfield *et al*., 1996) and 637/1 000 000 (Olafsson *et al*., 2005) per year. Using an approximate average of 500/1 000 000 newly diagnosed paediatric cases of epilepsy per year and assuming clinical practice comparable to what we observed in this study, there will be approximately 127/1 000 000 new cases of childhood-onset pharmacoresistant epilepsy per year. Further, about 52/1 000 000 children will undergo comprehensive epilepsy evaluations. Approximately 27/1 000 000 from this age group will have surgical procedures, 21/1 000 000 for treatment of seizures and 6/1 000 000 for lesion resection only.

Discussion

We can provide some preliminary answers to questions raised in the ILAE Sub-Commission report (Cross *et al*., 2006) based upon our representative study of children with newly diagnosed epilepsy in whom 85% had MRI scans. MRI scans were positive with structural abnormalities possibly related to epilepsy in 15.8% of this cohort and in one of five of those who had non-idiopathic syndromes. A proportion of abnormalities found on MRI scans

were probably coincidental and likely not to be related to those patients' specific types of epilepsy.

While the yield of MRI was high (~25%) in the <2 year onset group, in fact, the strongest correlate of having a positive scan was the type of epilepsy (non-idiopathic) and an abnormal neurological exam. Among those with non-idiopathic epilepsies, the neurological exam was the single strongest predictor of a positive MRI, followed by pharmacoresistance. However, even if the neurological exam was normal and seizures were not pharmacoresistant, one in 10 had a positive MRI. These included four children with gliomas which, at the very least, warrant periodic monitoring although the standard of practice in the USA is to offer surgery. We note that a recent study of surgery for low-grade gliomas indicated that seizure control was much more likely if surgery occurred within 1 year of seizure onset (Chang *et al.*, 2008). Our finding supports the recommendations that MRI be used in evaluating children with new seizures unless a traditional idiopathic electro-clinical syndrome can be identified with confidence (Hirtz *et al.*, 2000, Gaillard *et al*., 2009). In addition, we previously showed that many individuals who failed trials of two drugs may still experience subsequent remissions (Berg *et al.*, 2009). The current analysis demonstrates that those with positive MRI scans are very unlikely to be in remission at last contact. This finding further supports the recommendations of the ILAE's Commission on Paediatrics that children who are pharmacoresistant be evaluated at a comprehensive centre, which should include a higher quality MRI. In essence, for any child whose seizures are not fully controlled by medication, a reason should be sought, and an MRI scan is an important tool in those with non-idiopathic epilepsy.

Connecticut is a small state in the north east of the USA. There is one well-established comprehensive epilepsy centre in the state and several others in neighbouring states (New York City, NY and Boston, MA). Other areas of the country and regions of the world may not have similar access to comprehensive epilepsy services. Our study reflects the current use of these resources as practiced in the community when there is good geographic access.

Earlier epidemiological studies of patients with epilepsy were performed before modern imaging was readily available and provided information about presumed structural brain abnormalities based on clinical history and evidence of functional impairment. Even the more recent epidemiological studies did not have widespread use of MRI (Camfield and Camfield, 2003; Jallon *et al.*, 2001; Arts *et al.*, 2004). There is also a large hospital-based series of new-onset seizure patients, mostly (~80%) adults who were all evaluated with MRI (King *et al.*, 1998). Thirteen percent of the scans were abnormal, and the MRI findings reflected the older age of the group (45% tumours, 16% trauma). There are, however, two paediatric series of patients with temporal lobe epilepsy (TLE) in which all children were evaluated with MRI and drug resistance (failure of two drugs) was assessed. One study found positive MRI scans in 32% of patients with TLE. Pharmacoresistance was present in 70% of the children with positive and 24% of those with negative scans (Dlugos *et al.*, 2001). The other study reported that 48% of children with TLE had a positive scan. All cases with a positive scan were pharmacoresistant compared with 44% with negative scans (Spooner *et al.*, 2006). Certain methodological differences make direct comparison difficult; however, these figures are within a range that correlates with our findings and collectively they emphasize the importance of MRI in evaluating all patients with newly diagnosed childhood-onset epilepsy.

To provide estimates that reflect comprehensive epilepsy care for a population, it is necessary to have a population-based or representative study group and sufficient clinical detail about imaging and current practice. There are several large epidemiological studies, which are purportedly population based or highly representative; however, MRI utilization was sparse, selective or not reported. Our study is reasonably representative of the population and has the highest MRI coverage of any such study reported to date. Our findings also indicate that the lack of MRI neuroimaging in most prior epidemiological probably results in an underestimate of the proportion of cases who have brain lesions, many of whom are probably classified as 'cryptogenic'. Future epidemiological studies should be designed to incorporate MRI imaging as a routine part of the epilepsy assessment for all study subjects, particularly those with non-idiopathic forms of epilepsy.

There are two large series of paediatric epilepsy surgery cases, one from the USA (Mathern *et al.*, 1999) and an international survey sponsored by the ILAE (Harvey *et al.*, 2008). For the more common types of surgical substrates (lesions associated with cerebral atrophy, MCD and tumours) the proportion of surgical candidates is comparable in these two series and within a range that correlates with our findings. These two large surveys also contained patients with lesions that were so rare that they were not represented in our community-based series (e.g. Rasmussen and Sturge-Weber). To be reasonably sure of ascertaining even one or two such rare events, future epidemiological studies would have to be on the order of at least two to three times as large as ours.

There was also a group of clinical MRI scans for which we relied on the written reports. While imperfect, our comparison between the clinical reports and our own interpretation of the original scans, when we could obtain them, indicated excellent agreement. Such findings enhance our confidence that this study captured the most obvious structural MRI abnormalities present in the clinical MRI scans. Furthermore, inclusion of cases for which we relied on clinical reports was essential in maintaining the representativeness of our cohort. As shown, those with clinical scans only (half of which were not re-read) were more likely to have IQ < 80, abnormal neurological exams, pharmacoresistant epilepsy and ultimately a higher proportion with structural brain abnormalities. Their exclusion would have systematically biased the composition of the cohort.

Both research and clinical MRI scans may have missed subtle abnormalities (Spooner *et al.*, 2006; Lerner *et al.*, 2009). For example, at least two patients with negative MRI scans in this cohort had positive histopathology for MCD (including one MCD, Type I) after resective neurosurgery. Thus, consistent with previous reports, standard structural MRI scans will not detect all pathologies in patients with refractory epilepsy (Salamon *et al*., 2006). Such findings are consistent with the ILAE's Subcommission recommendation that most if not all children with

refractory epilepsy should be referred to a specialty centre for comprehensive evaluation, as advanced neuroimaging protocols may detect subtle cortical lesions responsible for the intractable seizures (Cross *et al.*, 2006).

Although the Connecticut study has perhaps the highest coverage for MRI reported in a representative, epidemiological cohort to date, 15% of study participants did not have scans. Of the 93 who did not have an MRI scan, eight met criteria for pharmacoresistance. Thus, we have captured the great majority of pharmacoresistant patients (94.3%) who might qualify for comprehensive evaluations and possibly epilepsy surgery. We report the frequency of pharmacoresistance with mean follow-up of 10 years. While this interval should capture the most aggressive epilepsy syndromes, some patients may not yet have progressed to pharmacoresistance.

Our cohort is not, strictly speaking, population based because we recruited children from paediatric neurologists. However, because all participants were evaluated by paediatric neurologists, we are confident about the accuracy of the diagnosis of epilepsy and of the MRI lesions. This is not necessarily the case in studies that recruit from primary care physicians, as many disorders can be mistaken for epilepsy (Benbadis, 2006; Pellock, 2006). The potential error caused by this lack of diagnostic specificity in epidemiological studies has been reported (Gallitto *et al.*, 2005; Christensen *et al.*, 2007). The results of our study are highly comparable to another study from North America, which is considered population based, in terms of age at onset, gender and proportion with specific well-recognized epilepsy syndromes (Camfield *et al.*, 1996; Berg *et al.*, 1999; Camfield and Camfield, 2003), the proportion with mental retardation (Camfield and Camfield, 2007; Berg *et al.*, 2008) and mortality (Camfield *et al.*, 2002; Berg *et al.*, 2004). Furthermore, the ethnic composition of our cohort was highly comparable to the State of Connecticut, based on the 1990 census. These findings strongly suggest that it is likely that our results are representative of the population in which the study was performed. As such they provide a first estimate of the frequency of new cases of pharmacoresistant epilepsy per year arising from the age group studied, the expected types and frequency of MRI positive lesions in that group, and an assessment of the current utilization of epilepsy evaluations and neurosurgery for pharmacoresistant epilepsy of childhood onset from the perspective of practice in the community.

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