Published in final edited form as:

J Child Neurol. 2017 April ; 32(5): 467–474. doi:10.1177/0883073816685653.

Pediatric epilepsy surgery: The prognostic value of central nervous system comorbidities in patients and their families

Krista J Qualmann, MS, CGC¹, Christine G Spaeth, MS, LGC¹, Melanie F Myers, PhD, MS, LGC¹, Paul S Horn, PhD^{2,3}, Katherine Holland, MD, PhD², Francesco T Mangano, DO⁴, and Hansel M Greiner, MD²

¹Division of Human Genetics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, USA

²Division of Pediatric Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, USA

³Division of Biostatistics & Epidemiology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, USA

⁴Division of Pediatric Neurosurgery, Department of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, USA

Abstract

Central nervous system (CNS) comorbidities have been identified in patients with epilepsy. Several of these comorbidities have been correlated with poor surgery outcomes in patient cohorts. The authors sought to determine if prevalence of comorbidities in pediatric epilepsy surgery patients and their families correlate with long-term seizure outcome in a cross-sectional analysis. Three-generation pedigrees were elicited to compare family history of epilepsy, ADHD, anxiety, autism, bipolar disorder, cognitive disability, depression, migraine, and motor disability to surgery outcomes in 52 patients. Proportions of affected patients and relatives were compared to general population comorbidity rates and the patients' most recent seizure outcome classification. Patients and families had significantly higher rates of comorbidities than the general population. Poorer long-term seizure outcomes following resective surgery were associated with autism or cognitive

Corresponding author: Hansel M. Greiner, MD, Assistant Professor of Pediatrics and Neurology, Co-Director, Epilepsy Surgery Program, 3333 Burnet Ave. Cincinnati, OH 45229, P: (513) 636-4222 | F: (513) 636-0018, Hansel.Greiner@cchmc.org.

Author contributions

KJQ was involved in the study design, recruitment of patients, data collection, data analysis and interpretation, obtaining funding, writing the original draft and subsequent edits to this manuscript. CGS, MFM, and HMG were involved in the study design, data analysis and interpretation, editing of several drafts of this manuscript, and mentorship. PSH contributed to the study design, data analysis and interpretation, statistical analysis, and editing of several drafts of this manuscript. KH and FTM were involved in data collection, data analysis and interpretation, and editing of this manuscript.

Some of these findings were previously presented at the annual meeting of the National Society of Genetic Counselors in New Orleans, Louisiana, in 2014.

Declarations of conflicting interests

KH has received grant support from the National Institutes of Health [R01-NS062756]. KJQ, CGS, MFM, PSH, FTM, and HMG report no disclosures.

Ethical approval

Informed consent was obtained from families participating in the study. This study was approved by the Institutional Review Boards at Cincinnati Children's Hospital Medical Center and the University of Cincinnati (Study #2013-2590).

disability in patients. Together these data support evidence for a common pathophysiological mechanism between epilepsy and CNS comorbidities.

Keywords

Intractable epilepsy; resective surgery; family history; clinical outcomes; pathophysiological mechanism

Introduction

Patients with epilepsy have higher rates of comorbid central nervous system (CNS) conditions compared to the general population, including attention deficit hyperactivity disorder (ADHD)¹⁻³, anxiety disorder²⁻⁴, autism spectrum disorder^{2,3,5-7}, bipolar disorder^{2,4,8}, cognitive disability^{3,6,9}, depression²⁻⁴, migraine^{2,3,10}, and motor disability^{6,9}, supporting the argument for a shared pathophysiological mechanism^{10,11}. Family history of seizures has previously been associated with the presence of behavioral disorders¹¹ and migraines¹² in epilepsy patients, suggesting these comorbidities are heritable with epilepsy. However, studies to document whether or not there is also a higher prevalence of these comorbidities in patients' family members are lacking. While worse seizure outcomes following temporal lobectomy have been reported in adult patients with a personal history of psychiatric disorders¹³ and pediatric patients with cognitive dysfunction or learning disability¹⁴ and the Childhood Behavior Checklist has been used to report on the rates of behavioral, emotional, and social function in pediatric patients before and after epilepsy surgery¹⁵⁻¹⁷, little is known about the relationship between patient and family member CNS comorbidities and seizure outcome after epilepsy surgery. As there is no published literature describing the relationship between a family history of CNS comorbidities and resective surgery outcomes, the identification of such a relationship would suggest that family history may modify individual prognosis.

The primary aim of this study was to determine prevalence of CNS comorbidities (ADHD, anxiety disorder, autism spectrum disorder, bipolar disorder, cognitive disability, depression, migraine, motor disability) in pediatric patients undergoing epilepsy surgery at a single institution and their families, and correlate these findings with long-term seizure outcome. Identification of a correlation between patient comorbidities and their clinical outcomes will strengthen the evidence for a shared pathophysiological mechanism and further aid clinicians in tailoring prognostic predictions prior to surgery.

Methods

Cohort

This retrospective cross-sectional study compared family history of epilepsy and CNS comorbidities to surgery outcomes in pediatric patients who underwent resective brain surgery. Patients were identified through a clinical seizure database maintained by the CCHMC Division of Neurology. Patients qualified for surgery if they had failed to maintain good seizure control after at least two appropriately selected and trialed AEDs and a

localized seizure focus was identified. All patients who underwent resective surgery for epilepsy, including hemispherectomy, lobectomy, and/or corticectomy, at CCHMC between January 1, 2007- June 30, 2012 were contacted. Patients who underwent corpus callosotomy only or were over the age of 18 at time of initial surgery were excluded.

Family history information

Family history information was collected via questionnaire from the patients' parents or legal guardians, referred to as the "participants." Participants who were not able to recount family history information or who did not speak English were excluded.

Familial relationships were labeled in reference to the patient who received resective surgery. An online questionnaire was developed to collect family history information using the Research Electronic Database Capture (REDCap) program. Participants had the option to take the questionnaire online or via telephone. A brief follow-up telephone interview was conducted with online participants. The researcher was blind to patient surgery outcomes at the time of questionnaire completion.

A three-generation pedigree was obtained. Participants were asked if each family member had been diagnosed by a medical provider with epilepsy, seizures not diagnosed as epilepsy, and CNS comorbidities including ADHD, anxiety disorder, autism spectrum disorder, bipolar disorder, cognitive disability, depression, migraine, and motor disability. Comorbidities were defined for participants as stated in Table 1. Comorbidities reported in the patient were verified in the electronic medical record as occurring pre-surgery or post-surgery. Comorbidities diagnosed post-surgery were recoded as negative. Demographic information was also collected.

The proportion of affected individuals was calculated by the following formula: (# affected individuals)/(total # individuals). Proportions of affected patients, first-degree relatives (FDRs), and total relatives were calculated for each comorbidity. FDRs included the patient's parents and full siblings. Total relatives included the patient's FDRs, half siblings, nieces, nephews, grandparents, aunts, uncles, and first cousins.

A history of epilepsy or seizures in family members was collapsed into a single variable, "epilepsy/seizures." CNS comorbidities were also collapsed into bins for some analyses. The "psychiatric" bin included having a diagnosis of one or more of the following: ADHD, anxiety disorder, bipolar disorder, and depression. The "any" bin included having a diagnosis of one or more of any of the comorbidities included in this study.

The proportion of patients affected with each comorbidity prior to surgery was calculated. Patients with an un-verified comorbidity were treated as missing values and not included for these calculations. For comparison, general population rates of autism¹⁸ and motor disability^{6,19} were based on pediatric studies, rates of ADHD²⁰, anxiety disorder²⁰, depression²⁰, and migraine²¹ were based on children and adolescent studies, and rates of bipolar disorder²² were based on adolescent studies. The general population rate for cognitive disability²³⁻²⁵ was determined by adding the rates for developmental delay, intellectual disability, and learning disabilities in pediatric studies.

Treatment history

Treatment history and surgery outcome information was abstracted from the CCHMC Division of Neurology clinical seizure database. Abstracted variables included total number of trialed AEDs, history of tuberous sclerosis complex (TSC), whether or not grid placement was performed, frequency of seizures prior to surgery, duration of epilepsy prior to surgery, type of surgery, and completeness of resection. Type of surgery was dichotomized into temporal and extratemporal procedures. Temporal procedures included anterior temporal lobectomy and temporal lobectomy. Extratemporal procedures included corticectomy, extratemporal lobectomy, hemispherotomy, lesionectomy, and multi-lobar surgery. Completeness of resection was determined by either a) all of MRI abnormality resected in cases for which no invasive EEG performed or b) both MRI abnormality and seizure onset zone (determined by clinical team as the group of 5 electrodes with consistent earliest ictal change) resected in cases for which invasive EEG performed.

Surgery outcomes

Surgery outcome data were reported using the International League Against Epilepsy (ILAE) scale²⁶. Outcome data were reported at one year post-surgery and the patient's most recent evaluation. Seizure category was defined based on brain magnetic resonance imaging (MRI) and electroencephalography (EEG) concordance with the operated hemisphere. MRI, Ictal EEG, EEG and MRI/EEG concordance were defined as previously described²⁷.

Outcome data were collapsed into dichotomous variables. Patients who remained seizure-free after surgery were categorized as ILAE = 1 and patients who were not seizure-free after surgery were categorized as ILAE > 1. Seizure category data were reported as an ordinal variable where 1 (best expected outcome) was defined as lesional or multi-lesional concordant, 2 was defined as non-lesional concordant, 3 was defined as lesional or multi-lesional discordant, and 4 (worst expected outcome) was defined as non-lesional discordant.

Statistical analysis

Univariate analyses were performed to determine if the mean proportion of affected relatives across all patients was significantly greater than what would be expected based on prevalence rates in the general population. Fisher's exact tests were used to compare patient comorbidities to ILAE surgery outcomes and to compare seizure category across ILAE surgery outcomes. T-tests and Wilcoxon rank sum tests were used to compare the mean proportions of affected relatives to ILAE surgery outcomes. Logistic regression models were used to identify predictors of surgery outcome and seizure category. A stepwise variable selection procedure was used to find the most parsimonious model. Results were considered to be statistically significant if the p-values were less than 0.05. All statistical analyses were performed using SAS ® (version 9.3, SAS Institute Inc., Cary, NC).

Results

Response rate and demographics

One hundred and fifty-six individuals were contacted to participate in the study. Of these, eight individuals were excluded due to the inability to provide family history information (n

= 6) or the inability to speak English (n = 2). A total of 52 participants completed the questionnaire, a 35.1% response rate. One individual was lost to follow-up regarding seizure outcome and patient comorbidity data. This individual was only included in the analysis of affected family members and demographic information.

Mean follow-up time from initial surgery to most recent evaluation was 42.7 months for the entire cohort, with no significant difference between ILAE groups. There was an uneven distribution of males and females, with males making up 41.7% (10/24) of the ILAE = 1 group and 70.4% (19/27) of the ILAE > 1 group (p = 0.05) (Table 2). Grid placement was more common in the ILAE > 1 group than in the ILAE = 1 group (92.6% [25/27] v. 66.7% [16/24]; p = 0.03). Patients in the ILAE > 1 group also had tried a greater number of medications than patients in the ILAE = 1 group (5.04 v. 3.38; p = 0.04) (Table 3). Logistic regression models identified total number of trialed AEDs as a predictor of worse outcomes following surgery when it was the only variable included in the model, with the odds of having an ILAE > 1 post-surgery increasing by a factor of 1.3 for every additional medication trialed (OR = 1.3; 95% CIs 1.0, 1.6; AUC = 0.68; p = 0.04).

Comorbidities in patients

Patients had significantly higher rates of ADHD (p < 0.001), autism spectrum disorder (p < 0.001), cognitive disability (p < 0.001), and motor disability (p < 0.001) than the general population (Table 4).

Comorbidities in patients' families

FDRs had significantly higher rates of depression (p < 0.001) and decreased rates of cognitive disability (p < 0.001) than the general population (Table 5). Total relatives had significantly higher rates of depression (p < 0.001) and epilepsy/seizures (p = 0.03) and decreased rates of cognitive disability (p < 0.001) and migraine (p = 0.005) compared to the general population (Table 5).

Patient comorbidities as a predictor of surgery outcome

When examining comorbidities individually, a diagnosis of autism or cognitive disability was significantly associated with an ILAE > 1 (Table 6). Seven of 50 patients (14.0%) had autism. All seven individuals with autism had an ILAE > 1 at their most recent follow-up evaluation (26.9% [7/26 patients with ILAE > 1] v. 0% [0/24 patients with ILAE = 1]; p = 0.01). Thirty-seven of 50 patients (74.0%) had cognitive disability. Twenty-four of the 37 patients with cognitive disability had an ILAE > 1 at their most recent follow-up evaluation (88.9% [24/27 patients with ILAE > 1] v. 56.5% [13/23 patients with ILAE = 1]; p = 0.02). Cognitive disability was also a predictor of ILAE > 1 outcome in logistic regression models, with the odds of a poor outcome increasing by a factor of 6.2 in patients diagnosed with a cognitive disability prior to surgery (OR = 6.2; 95% CIs 1.6, 31.2; AUC = 0.66; p = 0.01). In this case the probability of ILAE > 1 outcome given a patient had cognitive disability was 0.65 with a 95% CI of 0.48, 0.78. Similarly, if a patient did not have cognitive disability the probability dropped to 0.23 with a 95% CI of 0.08, 0.52.

There was a significant association between patients affected with any of the examined comorbidities and an ILAE > 1 (Table 6). Forty-two of 51 patients (82.4%) were affected with one or more comorbidities. Twenty-six of these individuals had an ILAE > 1 at their most recent follow-up evaluation (96.3% [26/27 patients with ILAE > 1] v. 66.7% [16/24 patients with ILAE = 1]; $p = 0.009$). All but one of the unaffected patients in this bin had an ILAE = 1 at their most recent follow-up evaluation.

ILAE outcome scores at 12 months post-surgery were available for 44 patients. Twenty-one patients had an ILAE = 1 and 23 patients had an ILAE > 1. When the above analyses were repeated, there were no statistically significant associations between patient comorbidities and ILAE outcome at 12 months post-surgery (data not shown).

Family history of comorbidities as a predictor of surgery outcome

No significant associations were identified between mean proportion of affected FDRs or total relatives and ILAE outcome. Patients with ILAE > 1 had an increased mean proportion of total relatives affected with seizures/epilepsy (Mean = 0.037; SD = 0.064) than patients with ILAE = 1 (Mean = 0.012; SD = 0.02), which trended towards significance by t-test ($p = 0.057$; data not shown).

Comorbidities as a predictor of seizure category

There was a significant difference in distribution of seizure category across ILAE groups, with more individuals with “poorer” (more discordant, MRI non-lesional) seizure category variables having an ILAE > 1 ($p = 0.02$) (Table 3). Logistic regression models demonstrated an association between the number of trialed AEDs and “poorer” category, with the odds of having a “poorer” seizure category increasing by a factor of 1.4 for every additional medication trialed (OR = 1.4; 95% CIs 1.1, 1.7; AUC = 0.67; $p = 0.006$).

Discussion

This study is the first to comprehensively describe relationships between CNS comorbidities in intractable epilepsy patients, their families, and resective surgery outcomes. Higher rates of CNS comorbidities were identified in both patients and their families when compared to the general population. In addition, the presence of autism or cognitive disability in patients was associated with poorer long-term seizure outcome following resective surgery.

Comorbidities in patients

Patients had higher rates of ADHD, autism, cognitive disability, and motor disability compared to the general population, as expected based on current literature. Since rates of CNS comorbidities in patients with refractory epilepsy are not established, we were not able to compare the prevalence rates from our study to matched controls. When considering CNS comorbidity rates in the wider epilepsy population, the rates of ADHD^{1,3} in our population fell within the ranges previously reported. However, there were differences in our population's comorbidity rates compared to those reported in the literature, including lower rates of anxiety (2.2% v. 16%³), autism (14.0% v. 38.0%⁵), bipolar disorder (2.0% v. 12%⁸), depression (2.1% v. 26%³), and migraine (8.2% v. 20-24%³) and higher rates of cognitive

and motor disability (74.0% & 42.0%, respectively v. 15-30%⁶ for either comorbidity). The lower prevalence rates reported in our study are partially due to the fact that any comorbidities diagnosed post-surgery were recoded as negative. Multiple individuals in our cohort went on to be diagnosed with several CNS comorbidities, including anxiety, depression, and migraine post-surgery (data not shown). Alternatively, certain comorbidities may be under-diagnosed in children or pediatric patients have not yet developed them. In addition, since our sample population includes only patients with intractable epilepsy, disease progression or severity may partially account for the higher prevalence of cognitive impairment in our study²⁸. Similarly, McClellan et al.⁵ reported 47% of their pediatric cohort to have a learning disability following temporal lobe surgery for epilepsy, which would represent only a subset of the broadly defined cognitive disability category in our cohort.

Comorbidities in patients' families

Patients' family members had higher rates of some CNS comorbidities compared to the general population. FDRs had increased rates of depression. Total relatives had increased rates of depression and epilepsy/seizures. However, rates of cognitive disability in FDRs and cognitive disability and migraines in total relatives were significantly lower than the reported general population rates for these conditions. Higher rates of depression have previously been reported in mothers of children with epilepsy^{29, 30}. While self-reported data are known to be limited by recall bias³¹, studies have consistently found family history information to have a high specificity, meaning few relatives without disease are misclassified as having disease³². Further, previous studies have shown that the sensitivity of reported health information decreases as the degree of relatedness increases³³. Therefore, we suspect that the true prevalence rates of comorbidities in our study are higher than the rates that were reported by participants, particularly for more distant relatives.

Comorbidities and surgery outcome

Patients with a diagnosis of autism or cognitive disabilities were more likely to have poor long-term seizure outcomes. In our patient population, patients with poorer seizure outcomes trialed more AEDs than patients with better seizure outcomes. Total number of trialed AEDs was also a significant predictor of worse surgery outcomes, suggesting that providers were more likely to trial more AEDs prior to surgery in patients with a profile less likely to benefit from resective surgery. Number of AEDs did not predict the presence of autism or cognitive impairment in our cohort and there was no significant interaction between these terms in logistic regression models (data not shown). Therefore, our data suggest that AED usage does not contribute to the increased prevalence of autism or cognitive disability in our patient population and should not be considered a confounding factor.

Patients reported to be affected with any comorbidity were also more likely to have poor long-term seizure outcome. Strikingly, all but one of the patients unaffected by all of the examined comorbidities remained seizure-free at their most recent evaluation. Taken as a whole, these data imply that patient CNS comorbidities, most importantly, the presence of cognitive disability or autism, have negative prognostic value for seizure outcome following resective surgery.

Relationships between poorer surgery outcomes and the presence of autism⁵, cognitive dysfunction¹⁴ and lifetime history of psychiatric comorbidities¹³ have been reported. Our study supports that autism and cognitive disability are predictors of worse surgery outcomes in a pediatric population. However, we did not replicate the reported association with individual or pooled psychiatric comorbidities. This discrepancy may be explained via differences in study populations. Kanner et al.¹³ reported lifetime rates of psychiatric comorbidities in their adult patients, while we report pre-surgical diagnoses in pediatric patients. It is possible that as our population ages, the rate of psychiatric comorbidities may increase. Finally, an association between the proportion of total relatives with seizures/epilepsy and worse surgery outcomes trended towards significance, supporting the role of detailed family history gathering for prognosis³⁴.

Pathophysiological mechanism of epilepsy and CNS comorbidities

Two possible general hypotheses could be drawn. The first is that certain patients are more likely to have a widely distributed epileptic network that is difficult to completely localize and resect. The second is that patients with a genetic propensity to other brain disorders have localizable epilepsy which is resected completely, but a secondary area of epileptogenesis later develops, preventing long-term seizure freedom.

The relationship between autism, cognitive impairment, and the evolution of seizure outcomes over time supports the latter hypothesis. The fact that initial postoperative outcomes at one year were generally favorable in these patients and then deteriorated to significantly poorer outcomes suggests epileptogenesis at another site is responsible for their poor outcomes, rather than incomplete resection of the epileptic network at the time of surgery. Seizures resulting from incomplete resection of the epileptic network are generally present within 6 -12 months of epilepsy surgery^{35, 36}.

Prognostic factors identified in this study should be used to improve preoperative counseling rather than categorically rule out surgery. For instance, patients with MRI non-lesional and discordant evaluations are generally not good candidates for resective surgery, but in a small number (n = 6 in our series) there may be sufficient evidence for a “dominant” resectable epileptogenic zone to palliate seizure frequency and potentially reduce medication burden.

Study limitations

Although our study was limited to those who chose to participate, our study population was similar to the larger CCHMC epilepsy population in terms of the relative frequency of seizure-free outcome and the distribution between seizure category and outcome. The majority of patients had a histopathological diagnosis of cortical dysplasia as an etiology. While cortical dysplasia is the most common cause of pediatric intractable epilepsy leading to epilepsy surgery³⁷, it does limit generalizability to other etiologies. Likewise, findings of increased comorbidities in patients and families were observed in our study of intractable pediatric epilepsy, but may not be generalizable to a larger epilepsy population.

Conclusion

We found an increased prevalence of pre-surgical CNS comorbidities in epilepsy patients undergoing resective surgery. Increased prevalence of depression and epilepsy/seizures in other family members is consistent with the current literature. Cognitive disability and autism spectrum disorder in the patient appear to be important negative prognostic factors for postoperative seizure outcome. Identification of such factors and a detailed family history may provide information to better counsel families considering resective surgery. Our findings support the hypothesis of a common pathophysiological mechanism between epilepsy and its comorbidities and highlight the importance of these comorbidities in both the patient and other relatives.

Acknowledgments

This work was completed in the Divisions of Human Genetics and Pediatric Neurology at Cincinnati Children's Hospital Medical Center in Cincinnati, OH.

Funding

This work was supported by the Jane Engelberg Memorial Fellowship Student Research Award, provided by the Engelberg Foundation to the National Society of Genetic Counselors; and National Institute of Neurological Disorders and Stroke [R01-NS062756].

References

1. Dunn DW, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. *Dev Med Child Neurol.* 2003; 45:50–54. [PubMed: 12549755]
2. Hamiwka LD, Wirrell EC. Comorbidities in pediatric epilepsy: beyond “just” treating the seizures. *J Child Neurol.* 2009; 24:734–742. [PubMed: 19359255]
3. Pellock JM. Understanding co-morbidities affecting children with epilepsy. *Neurology.* 2004; 62:S17–23.
4. Novy J, Castelao E, Preisig M, et al. Psychiatric co-morbidities and cardiovascular risk factors in people with lifetime history of epilepsy of an urban community. *Clin Neurol Neurosurg.* 2012; 114:26–30. [PubMed: 21955581]
5. McClellan A, Davies S, Heyman I, et al. Psychopathology in children with epilepsy before and after temporal lobe resection. *Dev Med Child Neurol.* 2005; 47:666–672. [PubMed: 16174309]
6. Shinnar S, Pellock JM. Update on the epidemiology and prognosis of pediatric epilepsy. *J Child Neurol.* 2002; 17:S4–17. [PubMed: 11918462]
7. Tuchman RF, Rapin I, Shinnar S. Autistic and dysphasic children. II: Epilepsy. *Pediatrics.* 1991; 88:1219–1225. [PubMed: 1956740]
8. Mula M, Schmitz B, Jauch R, et al. On the prevalence of bipolar disorder in epilepsy. *Epilepsy Behav.* 2008; 13:658–661. [PubMed: 18723118]
9. Bailet LL, Turk WR. The impact of childhood epilepsy on neurocognitive and behavioral performance: a prospective longitudinal study. *Epilepsia.* 2000; 41:426–431. [PubMed: 10756408]
10. Leniger T, Von Den Driesch S, Isbruch K, et al. Clinical characteristics of patients with comorbidity of migraine and epilepsy. *Headache.* 2003; 43:672–677. [PubMed: 12786928]
11. Hesdorffer DC, Caplan R, Berg AT. Familial clustering of epilepsy and behavioral disorders: evidence for a shared genetic basis. *Epilepsia.* 2012; 53:301–307. [PubMed: 22191626]
12. Winawer MR, Connors R. Evidence for a shared genetic susceptibility to migraine and epilepsy. *Epilepsia.* 2013; 54:288–295. [PubMed: 23294289]
13. Kanner AM, Byrne R, Chicharro A, et al. A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. *Neurology.* 2009; 72:793–799. [PubMed: 19255406]

14. Hennessy MJ, Elwes RDC, Honavar M, et al. Predictors of outcome and pathological considerations in the surgical treatment of intractable epilepsy associated with temporal lobe lesions. *J Neurol Neurosurg Psychiatry*. 2001; 70:450–458. [PubMed: 11254766]
15. Elliott IM, Lach L, Kadis DS, Smith ML. Psychosocial outcomes in children two years after epilepsy surgery: Has anything changed? *Epilepsia*. 2008; 49:634–641. [PubMed: 18177356]
16. Lendt M, Helmstaedter C, Kuczaty S, et al. Behavioural disorders in children with epilepsy: early improvement after surgery. *J Neurol Neurosurg Psychiatry*. 2000; 69:739–744. [PubMed: 11080225]
17. Smith ML, Elliott IM, Lach L. Cognitive, psychosocial, and family function one year after pediatric epilepsy surgery. *Epilepsia*. 2004; 45:650–660. [PubMed: 15144430]
18. CDC, U.S. Department of Health and Human Services, editors. Prevalence of Autism Spectrum Disorders, in Surveillance Summaries. U.S. Department of Health and Human Services; 2012. p. 19
19. Rumeau-Rouquette C, Grandjean H, Cans C, et al. Prevalence and time trends of disabilities in school-age children. *Int J Epidemiol*. 1997; 26:137–145. [PubMed: 9126513]
20. Polanczyk GV, Salum GA, Sugaya LS, et al. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry*. 2015; 56:345–365. [PubMed: 25649325]
21. Wober-Bingol C. Epidemiology of migraine and headache in children and adolescents. *Curr Pain Headache Rep*. 2013; 17:1–11.
22. Khazanov GK, Cui L, Merikangas KR, Angst J. Treatment patterns of youth with bipolar disorder: Results from the National Comorbidity Survey—Adolescent Supplement (NCS-A). *J Abnorm Child Psychol*. 2015; 43:391–400. [PubMed: 24958307]
23. Boyle CA, Boulet S, Schieve LA, et al. Trends in the prevalence of developmental disabilities in US children 1997–2008. *Pediatrics*. 2011; 127:1034–1042. [PubMed: 21606152]
24. Maulik PK, Mascarenhas MN, Mathers CD, et al. Prevalence of intellectual disability: a meta-analysis of population-based studies. *Res Dev Disabil*. 2011; 32:419–436. [PubMed: 21236634]
25. Rosenberg SA, Zhang D, Robinson CC. Prevalence of developmental delays and participation in early intervention services for young children. *Pediatrics*. 2008; 121:e1503–1509. [PubMed: 18504295]
26. Wieser HG, Blume WT, Fish D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia*. 2001; 42:282–286. [PubMed: 11240604]
27. Greiner HM, Horn PS, Arya R, et al. Acute postoperative seizures and long-term outcome following pediatric epilepsy surgery. *Seizure*. 2014; 23:483–486. [PubMed: 24680553]
28. Jokeit H, Ebner A. Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. *J Neurol Neurosurg Psychiatry*. 1999; 67:44–50. [PubMed: 10369821]
29. Ferro MA, Avison WR, Campbell MK, Speechley KN. Prevalence and trajectories of depressive symptoms in mothers of children with newly diagnosed epilepsy. *Epilepsia*. 2011; 52:326–336. [PubMed: 21204823]
30. Rodenburg R, Meijer AM, Dekovi M, Aldenkamp AP. Family factors and psychopathology in children with epilepsy: a literature review. *Epilepsy & Behavior*. 2005; 6:488–503. [PubMed: 15907744]
31. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol*. 1990; 43:87–91. [PubMed: 2319285]
32. Qureshi N, Wilson B, Santaguida P, et al. Family history and improving health. *Evid Rep Technol Assess*. 2009; 186:1–135.
33. Ottman R, Barker-Cummings C, Leibson CL, et al. Accuracy of family history information on epilepsy and other seizure disorders. *Neurology*. 2011; 76:390–396. [PubMed: 21263140]
34. Vento JM. Family history: a guide for neurologists in the age of genomic medicine. *Semin Pediatr Neurol*. 2012; 19:160–166. [PubMed: 23245548]
35. Vale FL, Pollock G, Benbadis SR. Failed epilepsy surgery for mesial temporal lobe sclerosis: a review of the pathophysiology. *Neurosurg Focus*. 2012; 32:E9.

36. Najm I, Jehi L, Palmini A, et al. Temporal patterns and mechanisms of epilepsy surgery failure. *Epilepsia*. 2013; 54:772–782. [PubMed: 23586531]
37. Hauptman JS, Mathern GW. Surgical treatment of epilepsy associated with cortical dysplasia: 2012 update. *Epilepsia*. 2012; 53:98–104.
38. Fisher, R., Saul, M., editors. *Overview of Epilepsy*. Stanford: C.E.C. Stanford Neurology; 2010. p. 1-56.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Comorbidity definitions used in questionnaire

Comorbidity	Questionnaire Definition
ADD/ADHD	Problems with attention, hyperactivity or impulsiveness
Anxiety disorder	Feelings of worry, uneasiness or fear of uncertain events
Autism spectrum disorder	Problems with social interaction and communication skills
Bipolar disorder	Severe mood swings, often between an excited and depressed state
Cognitive disability	Problems with learning, language or social skills, including developmental delays and learning delays
Depression	Feelings of sadness, anxiety, hopelessness or worry
Migraine	Severe headaches that can include nausea and vision problems
Motor disability	Problems with muscle movements, muscle control or posture

Abbreviations: ADD/ADHD = attention deficit disorder/attention deficit hyperactivity disorder

Table 2

Patient & Participant Demographics

Patient outcome classification as of most recent follow-up						
	ILAE = 1		ILAE > 1		Total	
	Mean	SD	Mean	SD	Mean	SD
Patient Demographics						
Mean current age	13.1 years	6.0	13.9 years	5.2	13.6 years	5.6
Mean age at surgery ^a	8.2 years	5.4	9.6 years	5.0	9.0 years	5.2
Mean age at most recent evaluation ^{a,b}	11.7 years	5.5	12.9 years	5.0	12.4 years	5.2
Mean time from surgery to most recent evaluation ^{a,b}	44.7 months	18.6	41.0 months	17.5	42.7 months	17.9
Total number of CNS comorbidities ^b	1.3	1.0	2.0	1.1	1.6	1.1
	n (%)		n (%)		n (%)	
Gender^c						
Male	10 (41.7)		19 (70.4)		30 (57.7)	
Female	14 (58.3)		8 (29.6)		22 (42.3)	
Race^d						
White/Caucasian	23 (95.8)		26 (96.3)		49 (94.2)	
African American	1 (4.2)		1 (3.7)		2 (3.8)	
Asian	0 (0)		1 (3.7)		1 (1.9)	
Prefer not to answer	0 (0)		0 (0)		1 (1.9)	
Participant Demographics						
Mean Age	40.8 years	7.4	44.7 years	7.4	42.8 years	7.6
	n (%)		n (%)		n (%)	
Race						
White/Caucasian	23 (95.8)		25 (92.6)		48 (92.3)	
African American	1 (4.2)		1 (3.7)		2 (3.8)	
Asian	0 (0)		1 (3.7)		1 (1.9)	
Prefer not to answer	0 (0)		0 (0)		1 (1.9)	
Relationship to patient						
Father	1 (4.2)		4 (14.8)		5 (9.6)	

Patient outcome classification as of most recent follow-up						
Patient Demographics	ILAE = 1		ILAE > 1		Total	
	Mean	SD	Mean	SD	Mean	SD
	23 (95.8)		23 (85.2)		47 (90.4)	
Mother						

ILAE outcomes are based on most recent clinical evaluation

For ILAE = 1, n = 24; For ILAE > 1, n = 27; Total N = 52

Participant demographics describe the participating parent who completed the questionnaire and/or telephone interview

Data collected from questionnaire, unless otherwise specified

^aData collected from clinical database maintained by CCHMC Department of Neurology

$$b_N = 51$$
^cSignificant difference in distribution between ILAE groups by Fisher's exact test, p=0.05

^dNumbers may not total 100%, as one patient was identified as mixed race, White/Caucasian and Asian

Abbreviations: ILAE = International League Against Epilepsy

Table 3

Distribution of treatment history factors for patients

	ILAE = 1 (n = 24)		ILAE > 1 (n = 27)		Total ^a (N = 52)	
	Mean	SD	Mean	SD	Mean	SD
Total number of medications tried ^b	3.4	2.7	5.0	2.7	4.3	2.8
Seizure frequency prior to surgery (number per month) ^c	145	322	73.0	192	104	257
Duration of epilepsy prior to surgery (years)	3.9	4.7	3.1	3.3	3.6	4.0
Diagnosis of TSC	n (%)		n (%)		n (%)	
Grid placement ^d	4 (16.7)		7 (25.9)		11 (21.2)	
Seizure category ^e	16 (66.7)		25 (92.6)		42 (80.8)	
Lesional or multi-lesional concordant	16 (66.7)		12 (44.4)		29 (55.8)	
Non-lesional concordant	5 (20.8)		1 (3.7)		6 (11.5)	
Lesional or multi-lesional discordant	2 (8.3)		9 (33.3)		11 (21.2)	
Non-lesional discordant	1 (4.2)		5 (18.5)		6 (11.5)	
Surgery Type						
Temporal	4 (16.7)		6 (22.2)		10 (19.2)	
Extratemporal	20 (83.3)		21 (77.8)		42 (80.8)	
Resection Completeness						
Complete	18 (75.0)		19 (70.4)		38 (73.1)	
Partial	6 (25.0)		8 (29.6)		14 (26.9)	

ILAE outcomes are based on most recent clinical evaluation

Data collected from clinical database maintained by CCHMC Department of Neurology

^a One patient was lost to follow-up regarding ILAE outcomes. This individual is not represented in the ILAE = 1 or ILAE > 1 groups, but may be included in this column for some measures.^b Significant difference in distribution between ILAE groups by Fisher's exact test, p = 0.03^c n = 20 for ILAE = 1 group; n = 23 for ILAE > 1 group; N = 44^d Significant difference in distribution between ILAE groups by t-test and Wilcoxon rank sum test, p = 0.03, 0.04, respectively^e Significant difference in distribution between ILAE groups by Fisher's exact test, p = 0.02

Abbreviations: IL/AE = International League Against Epilepsy; TSC = tuberous sclerosis complex; SD = standard deviation

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4

Percentage of affected patients v. general population rates for individual comorbidities

Measure	n (%)	N	General population rates (%)	p Value
ADHD	11 (22.0)	50	3.4 ^{1,3}	< 0.001
Anxiety	1 (2.2)	45	6.5 ¹⁹	0.97
Autism	7 (14.0)	50	1.1 ¹⁴	< 0.001
Bipolar disorder	1 (2.0)	51	2.5 ⁷	0.73
Cognitive disability	37 (74.0)	50	22.4 ¹⁵⁻¹⁷	< 0.001
Depression	1 (2.1)	48	2.6 ²⁰	0.74
Migraine	4 (8.2)	49	9.1 ^{22,23}	0.69
Motor disability	21 (42.0)	50	0.8 ^{5,18}	< 0.001

p Values from exact one-sided binomial model

Percentages calculated by multiplying the proportion of affected patients by 100 General population rates were reported from the following sources: ADHD – [20]; anxiety – [20]; autism – [18]; bipolar disorder – [22]; cognitive disability (including rates for developmental delay, intellectual disability, and learning disability) – [23-25]; depression – [20]; migraine – [21]; motor disability – [6, 19];

Abbreviations: ADHD = attention deficit hyperactivity disorder

Table 5
Mean proportion of affected relatives v. general population rates for individual comorbidities

Measure	Relationship of relatives to patient					
	FDRs			Total relatives		General population rates
	Mean	SD	p Value	Mean	SD	p Value
ADHD	0.053	0.111	0.23	0.035	0.050	0.83
Anxiety	0.065	0.161	0.99	0.066	0.104	0.96
Autism	0.005	0.035	0.20	0.007	0.018	0.16
Bipolar disorder	0.026	0.097	0.92	0.031	0.063	0.50
Cognitive disability	0.013	0.074	<0.001	0.018	0.041	<0.001
Depression	0.166	0.262	<0.001	0.103	0.128	<0.001
Epilepsy/seizures	0.032	0.091	0.09	0.026	0.049	0.03
Migraine	0.150	0.224	0.06	0.058	0.080	0.005
Motor disability	0.00	0.00	-	0.008	0.023	0.88

p Values from univariate analyses; N = 52 families

General population rates were reported from the following sources: ADHD – [20]; anxiety – [20]; autism – [18]; bipolar disorder – [22]; cognitive disability (including rates for developmental delay, intellectual disability, and learning disability) – [23-25]; depression – [20]; epilepsy/seizures – [38] migraine – [21]; motor disability – [6, 19];

Abbreviation: FDRs = first-degree relatives, including the patient, the patient's parents, and full siblings. The patient was not included as a FDR when calculating the proportion of affected relatives with epilepsy/seizures; ADHD = attention deficit hyperactivity disorder; SD = standard deviation

Table 6

Percentage of affected patients v. ILAE outcomes at most recent follow-up

Measure	ILAE = 1		ILAE > 1		Total Affected		p Value
	n (%)	N	n (%)	N	n (%)	N	
PSC (bin)	3 (12.5)	24	8 (29.6)	27	11 (21.6)	51	0.18
ANY (bin)	16 (66.7)	24	26 (96.3)	27	42 (82.4)	51	0.009
ADHD	3 (13.0)	23	8 (29.6)	27	11 (22.0)	50	0.19
Anxiety	0 (0)	23	1 (4.5)	22	1 (2.2)	45	0.49
Autism	0 (0)	24	7 (26.9)	26	7 (14.0)	50	0.01
Bipolar	0 (0)	24	1 (3.7)	27	1 (2.0)	51	1.00
Cognitive disability	13 (56.5)	23	24 (88.9)	27	37 (74.0)	50	0.02
Depression	0 (0)	23	1 (4.0)	25	1 (2.1)	48	1.00
Migraine	2 (8.7)	23	2 (7.7)	26	4 (8.2)	49	1.00
Motor disability	12 (50.0)	24	8 (32.0)	25	20 (40.8)	49	0.25

p Values from Fisher's exact test;

ILAE outcomes are based on most recent clinical evaluation;

Percentages calculated by multiplying the proportion of affected patients by 100

Abbreviations: ILAE = International League Against Epilepsy; PSC = Psychiatric comorbidities (ADHD, anxiety, bipolar disorder, depression); ANY (bin) = any comorbidities (ADHD, anxiety, autism, bipolar disorder, cognitive disability, depression, migraine, motor disability); ADHD = attention deficit hyperactivity disorder