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Predictors of drug-resistant epilepsy in tuberous sclerosis complex

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Abstract

Utilizing the multicenter Tuberous Sclerosis Complex (TSC) Natural History Database including 2034 subjects, this study aimed to identify predictors of drug-resistant epilepsy in TSC. Basic epilepsy data were available for 1965 individuals in the database. Supplemental data were further collected from 1546 of these subjects through directed site queries, addressing additional epilepsy characteristics including the presence of drug-resistant epilepsy, therapies trialed, and outcomes of specific therapies. Epilepsy was reported in 86.4% of individuals with TSC. Infantile spasms were reported in 45.2% of individuals and focal seizures were reported in 84.4% of individuals. In those with focal epilepsy, drug-resistance was reported in 59.6%, with focal seizure onset prior to age 1 year (OR 1.9, CI 1.4–2.5, $p < 0.001$), infantile spasms (OR 2.0, CI 1.5–2.5, $p < 0.001$), and infantile spasms incompletely responsive to therapy (OR 47.6, CI 6.7–333.3, $p < 0.001$) being associated with an increased likelihood of drug-resistance.

Keywords

epilepsy; tuberous sclerosis complex; refractory; infantile spasms; seizures

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Author Contributions

AJ and MW conceived of the idea for the study. JN assisted with the collection of core and supplemental data in the TSC Natural History Database. AJ analyzed the data and wrote the first draft of the manuscript. All authors contributed to review of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the Washington University Institutional Review Board (IRB # 201505109).

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the opinion of the Tuberous Sclerosis Alliance or the Tuberous Sclerosis Complex Natural History Database Consortium.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant, multisystem disease characterized by hamartomatous growths affecting various organ systems, including the brain, kidneys, skin, eyes, heart, and lungs.¹ The disease exhibits widely variable expression ranging from asymptomatic or mild cases to severely affected individuals with multi-organ disease. Incidence is estimated to be approximately 1 in 6000 live births.² Two causative genes, *TSC1* on 9q34 and *TSC2* on 16p13, have been identified via linkage analysis.^{3,4}

Neurological symptoms including epilepsy, cognitive disability, and autism spectrum disorder, confer significant morbidity amongst affected individuals with TSC.⁵ Epilepsy affects greater than 80% of individuals with TSC, of whom nearly two-thirds suffer from drug-resistant epilepsy.⁶ Infantile spasms have been reported to occur in approximately one-third of individuals with TSC.⁶ A history of infantile spasms, younger age at seizure onset, and refractory epilepsy have previously been shown to be associated with poor cognitive outcomes.⁶ However, the underlying mechanisms of epilepsy in TSC are complex, and prognostication is difficult as early risk factors and reliable biomarkers have not been established. Furthermore, relatively little information is available about the characteristics and predictors of drug-resistant epilepsy in TSC.

Early, potentially preventative, epilepsy treatment has been postulated to improve epilepsy and cognitive outcomes,⁷ but this has yet to become standard in clinical practice. Medical therapy is first-line in epilepsy treatment. Everolimus has recently been studied as a targeted therapy for manifestations of TSC including epilepsy,⁸ but has not been studied in humans as a preventative epilepsy intervention. Epilepsy surgery has proven to be effective in the treatment of drug-resistant epilepsy in TSC, with the rate of seizure freedom after surgery approaching 60% in carefully-selected patients.⁹

Drug-resistant epilepsy in TSC confers increased morbidity and has been associated with poor neurological outcomes. As epilepsy treatment advances, we must also gain a better understanding of which patients stand to benefit the most from such treatments. Utilizing a large multicenter TSC database, we explored patient characteristics and potential risk factors associated with drug-resistant epilepsy. The identification of such risk factors could ultimately assist in the identification of individuals best suited for early and aggressive therapies.

Methods

Data from the multicenter TSC Natural History Database Project including 2034 patients were obtained from the Tuberous Sclerosis Alliance in August 2016. The patients were enrolled from 19 participating TSC clinics in the United States and Belgium, with enrollment beginning in 2006 and updated information being added to the database on a regular basis based on new data from follow-up visits, telephone calls, hospitalizations, and diagnostic tests or procedures. The participants were coded by unique identifiers and remained anonymous. Institutional review board approval was obtained at all sites.

The database contained information on demographics (age, gender, race), age at TSC diagnosis, epilepsy history (presence of infantile spasms or other seizure types, date of seizure onset, treatments utilized, and outcome of treatment), and the presence or absence of systemic disease manifestations. Neuropsychiatric data were collected, including the presence or absence of autism spectrum disorder, attention deficit hyperactivity, depression, and anxiety. Cognitive ability was reported, with standardized testing results provided if available, and a clinical assessment given otherwise. Normal cognitive ability was defined as an intellectual quotient (IQ) greater than 70, mild to moderate intellectual disability was defined as an IQ between 36 and 70, and severe to profound intellectual disability was defined as an IQ less than 35. The database also contained information pertaining to genetic testing of the *TSC1* and *TSC2* genes. If available, the specific genetic mutation, deletion, duplication, or insertion was reported.

As the original dataset from the TSC Natural History Database Project contained limited information about drug-resistant epilepsy and outcomes related to specific treatments, supplemental data were collected from the participating sites specifically for the purposes of this study, constituting the first “Subproject” of the TSC Natural History Database. The supplemental data were obtained by identifying all subjects with a history of epilepsy and querying the sites for more detailed information regarding the presence or absence of drug-resistant epilepsy (defined as adequate trials of two appropriately chosen and administered antiseizure medications, whether as monotherapy or in combination), medical and surgical treatments utilized, and outcomes of specific treatments. Outcomes were defined as controlled versus uncontrolled seizures, with control indicating seizure freedom. If the seizures were controlled, the sites were queried as to the treatment leading to control. If the individual was receiving multiple concurrent therapies, sites were queried as to the treatment thought to have led to seizure control. Time to seizure remission and duration of seizure remission was not ascertained. Clinical information was not available for every data field for every patient, thus accounting for different denominators for various data points.

The age of onset of a specific variable such as infantile spasms or focal seizures was calculated based on the recorded date of symptom onset or symptom diagnosis. For patients with symptom remission, the duration of symptoms was calculated based on the recorded date of symptom remission. For both the age of onset and duration of symptoms calculations, in cases where an exact date of symptom onset or remission could not be identified, either the reported year or the month and year were utilized. In the case of missing date fields, age of onset and symptom duration could not be calculated, thus these patients were excluded from the analysis.

Statistical analysis

Statistical analyses were performed using logistic regression for categorical variables and the nonparametric Mann-Whitney *U* test for continuous variables. All reported p-values used two-tailed tests of significance, with the level of significance being set at $\alpha < 0.05$. All statistical analyses were performed using SPSS Version 23 (IBM). All statistical methods and analyses were reviewed and verified by a statistician from the Division of Biostatistics at Washington University.

Results

A total of 2034 subjects were enrolled in the TSC Natural History Database Project as of August 2016. Epilepsy data (presence or absence of epilepsy) were available for 1965 subjects, with 86.4% (1699/1965) of individuals having a reported history of epilepsy. Epilepsy consisted of a history of infantile spasms, focal seizures, and/or other seizure types. Of 1699 individuals with epilepsy, the response rate for supplemental epilepsy data collection was nearly 92% (1556/1699). Ten individuals were excluded from the epilepsy analysis, as these individuals only had a single seizure and did not meet the traditional definition of epilepsy (defined as two or more unprovoked seizures), leaving 1546 subjects in the group analyzed further in this study.

As seen in Table 1, 803 (51.9%) of 1546 individuals were male. The median age was 16.0 years (IQR 9.6 years to 25.5 years). Race was available for 1308 individuals, of whom 1151 (88.0%) identified as Caucasian, 99 (7.6%) identified as black or African-American, and 58 (4.4%) identified as Asian, Pacific Islander, or Native-American. Of the 711 individuals with available genetic testing, 152 (21.4%) had a *TSC1* mutation, 483 (67.9%) had a *TSC2* mutation, and 76 (10.7%) had no mutation identified (NMI).

As seen in Table 2, a history of infantile spasms was reported in 656/1450 (45.2%) of individuals. Age of onset data was available for 522 subjects with infantile spasms, who had a median age of onset of 5.0 months (IQR 3.0 months to 7.2 months). Treatment outcome data was available for 560 individuals, of whom 458/560 (81.2%) individuals were successfully treated and experienced remission of infantile spasms. For those individuals who were successfully treated, duration of infantile spasms was able to be calculated for 231 individuals, who had a median exposure of 4.0 months (IQR 1.0 months to 12.0 months).

A history of focal seizures was reported in 1244/1474 (84.4%) of individuals. Age of onset data was available for 943 individuals with focal seizures, who had a median age of onset of 1.1 years (IQR 5.2 months to 3.5 years). Treatment outcome data was available for 1091 individuals, of whom 650/1091 (59.6%) met criteria for drug-resistant epilepsy. For those individuals with focal seizures who experienced remission, duration of focal seizures was able to be calculated for 126 individuals, who had a median exposure of 4.9 years (IQR 2.2 years to 10.4 years). For those individuals with focal epilepsy diagnosed prior to age one year, 207/413 (50.1%) individuals had a history of infantile spasms. For those individuals with drug-resistant focal epilepsy who were diagnosed with focal epilepsy under age one year, 123/223 (55.2%) had a history of infantile spasms.

Treatments leading to remission of infantile spasms or focal seizures

For those individuals with infantile spasms responsive to therapy, remission of infantile spasms was the result of medical therapy in 92.8% (387/458) of individuals, with therapies including vigabatrin (245/387), ACTH (49/387), topiramate (18/387) and other (75/387). Surgical therapy accounted for remission of infantile spasms in 5.0% (21/458) of individuals, with procedures including tuberectomy (13/21), lobectomy (4/21), and other various therapies (4/21) including corpus callosotomy and hemispherotomy. The ketogenic diet accounted for remission of infantile spasms in 1.2% (5/458) of individuals.

For those individuals with focal seizures responsive to therapy, medical therapy accounted for focal seizure control in 83.1% (438/540) of individuals, with the most frequently reported therapies including levetiracetam (73/438), lamotrigine (69/438), oxcarbazepine (65/438), carbamazepine (55/438), and valproic acid (30/438). Surgical therapy accounted for focal seizure control in 15.4% (81/438) of individuals, with the most frequently reported surgeries including tubectomy (37/81), lobectomy (19/81), hemispherotomy (4/81), and various other procedures (21/81) including multilobar resection and corpus callosotomy. The ketogenic diet accounted for focal seizure control in 0.6% (3/540) of individuals. See Table 3 for details. For those individuals with focal seizures refractory to treatment, 188 individuals had undergone surgical therapies (specifically hemispherotomy, lobectomy, or tubectomy).

Relationship of drug-resistant focal epilepsy to patient characteristics

Drug-resistant focal epilepsy was reported in 59.6% (650/1091) of individuals. Univariate logistic regression was performed to identify patient characteristics associated with an increased likelihood of drug-resistant focal epilepsy. As seen in Table 4, those individuals who presented with focal seizures at younger than 1 year of age had an increased likelihood (OR 1.9, CI 1.4–2.5, $p < 0.001$) of drug-resistant focal epilepsy as compared to individuals who presented with focal seizures at older than 1 year of age. Adjusting for TSC mutation status, age using the cut-off of 1 year remained significantly associated with an increased likelihood of drug-resistant epilepsy (OR 1.6, CI 1.1–2.3, $p = 0.02$). Gender ($p = 0.94$) and race ($p = 0.40$) were not associated with the likelihood of drug-resistant epilepsy.

TSC mutation testing was available for 568 individuals with focal seizures. TSC mutation status was associated with the presence versus absence of drug-resistant epilepsy ($p = 0.04$). Individuals with a *TSC2* mutation had a higher odds of drug-resistant epilepsy as compared to those with a *TSC1* mutation (OR 1.7, CI 1.1–2.5, $p < 0.001$). In contrast, comparisons between *TSC2* versus NMI ($p = 0.84$) and *TSC1* versus NMI ($p = 0.12$) did not reach statistical significance.

Relationship of drug-resistant focal epilepsy to infantile spasms

Of those individuals with focal epilepsy, data regarding the presence or absence of infantile spasms was available for 1047 individuals. In individuals with focal epilepsy, a history of infantile spasms (OR 2.0, CI 1.5–2.5, $p < 0.001$) was significantly associated with an increased likelihood of drug-resistant epilepsy. The outcome of infantile spasms was available for 389 individuals, and infantile spasms unable to be controlled by therapy (medical, surgical, or dietary) was strongly associated (OR 47.6, CI 6.7–333.3, $p < 0.001$) with an increased odds of drug-resistant epilepsy. Upon adjusting for TSC mutation status, a history of infantile spasms (OR 1.6, CI 1.1–2.3, $p = 0.01$) and failed treatment of infantile spasms (OR 25.0, CI 3.3–200.0) remained significantly associated with an increased likelihood of drug-resistant focal epilepsy. Duration of infantile spasms for those individuals with treatment-responsive spasms was only able to be calculated for 63 individuals, and the relationship between duration of infantile spasms and likelihood of drug-resistant epilepsy did not reach statistical significance ($p = 0.90$).

Relationship of drug-resistant focal epilepsy to neuropsychiatric disorders and cognition

Data regarding the presence or absence of neuropsychiatric comorbidities such as autism spectrum disorder, attention deficit hyperactivity disorder, anxiety, and depression was reported. Autism spectrum disorder (OR 1.9, CI 1.4–2.6, $p<0.001$) was associated with an increased odds of drug-resistant focal epilepsy. Attention deficit hyperactivity disorder (OR 0.5, CI 0.4–0.8) and anxiety (OR 0.6, CI 0.4–0.9, $p=0.02$) were associated with a decreased odds of drug-resistant epilepsy. Depression ($p=0.08$) did not demonstrate a statistically significant relationship with drug-resistant epilepsy. After adjusting for TSC mutation status, autism spectrum disorder (OR 1.7, CI 1.1–2.6, $p=0.017$) remained significantly associated with an increased likelihood of drug-resistant focal epilepsy, whereas attention deficit hyperactivity disorder (OR 0.4, CI 0.2–0.6, $p<0.001$) remained significantly associated with a decreased likelihood of drug-resistant focal epilepsy. Anxiety was no longer statistically significant ($p=0.69$) after adjusting for TSC mutation status.

Clinical assessment of intelligence quotient (IQ) was available for 437 individuals with focal seizures, specifically 251 individuals with drug-resistant focal epilepsy and 186 individuals with treatment-responsive focal epilepsy. Of those individuals with drug-resistant focal epilepsy, 19.9% (50/251) were reportedly of normal intelligence, 55.8% (140/251) reportedly had mild to moderate disability, and 24.3% (61/251) reportedly had severe disability. Of those individuals with focal epilepsy responsive to therapy, 39.8% (74/186) were reportedly of normal intelligence, 48.9% (91/186) reportedly had mild to moderate disability, and 11.3% (21/186) reportedly had severe disability. Clinical assessment of IQ ($p<0.001$) demonstrated a significant relationship with the odds of drug-resistant epilepsy. In comparison with individuals considered to be of normal intelligence, mild to moderate disability (OR 2.3, CI 1.4–3.6, $p<0.001$) and severe disability (OR 4.3, CI 2.3–7.9, $p<0.001$) were significantly associated with a higher likelihood of drug-resistant epilepsy.

In comparing focal seizures only versus a combination of infantile spasms and focal seizures, for those with focal seizures only, 14.9% (40/269) had severe disability, 47.6% (128/269) had mild to moderate disability, and 37.5% (101/269) were considered to be of normal intelligence. For those with a combination of infantile spasms and focal seizures, 22.5% (45/200) had severe disability, 61.5% (123/200) had mild to moderate disability, and 16.0% (32/200) were considered to be of normal intelligence. In comparison, those with focal seizures only had a higher likelihood of having normal intelligence versus those with focal seizures and infantile spasms ($p<0.01$).

Drug-resistant focal epilepsy in relationship to systemic and structural neurologic disease manifestations

We explored systemic and neurologic disease manifestations in relationship to the likelihood of drug-resistant focal epilepsy. Specifically, the presence of systemic findings including cardiac rhabdomyomas, retinal hamartomas, angiomyolipomas, lymphangioleiomyomatosis, and liver hamartomas, and skin findings including facial angiofibromas, hypomelanotic macules, shagreen patches, fibrous plaques, and confetti lesions, did not demonstrate a statistically significant relationship to the presence of drug-resistant epilepsy. The presence of periungual fibromas (OR 0.7, CI 0.5–0.9, $p=0.02$) was associated with a lower odds of

drug-resistant epilepsy, a finding which was of uncertain clinical significance. Additionally, the presence of neurologic findings including subependymal giant cell astrocytomas, subependymal nodules, cortical tubers, and cerebral white matter migration lines, did not demonstrate a statistically significant relationship to the presence of drug-resistant epilepsy (data not shown).

Discussion

This multicenter database including 2034 individuals provides unique insight into the risk factors associated with drug-resistant focal epilepsy in TSC. Our study is novel because of the size of the cohort, the largest epilepsy cohort reported to date, and the focus on early predictors of drug-resistant focal epilepsy. Although prior smaller series have described the natural history of epilepsy in TSC, our study is novel in that we specifically examined the subset of individuals with drug-resistant epilepsy, comprehensively analyzing both neurologic and non-neurologic variables to identify a variety of predictors of more severe disease. Epilepsy severity in TSC is widely variable, and in our study, the epilepsy characteristics associated with an unfavorable outcome (i.e. drug-resistant epilepsy) included younger age at epilepsy onset, the presence of infantile spasms, and infantile spasms resistant to therapy. Smaller series^{10, 11} have reported similar findings, and we have confirmed these findings with our larger cohort. Prior studies have also reported an association between duration of exposure to infantile spasms and degree of intellectual disability, with longer duration of infantile spasms correlating with more severe IQ impairment.^{12, 13} Although our study did not confirm this association, the duration of symptoms in our patient cohort was limited by incomplete data fields, which diminished the power of our statistical analysis for this variable. Multivariable analysis was not feasible, as clinical information was not available for every data field, accounting for different denominators and limiting combined data on variables found to be significant on univariate analysis.

Epilepsy was reported in 86.4% of individuals in our database, which is similar to reports in the literature.^{6, 14, 15} Of those individuals with focal epilepsy, 59.6% met criteria for drug-resistant epilepsy. This confirms the findings of prior reports, which have estimated drug-resistant epilepsy at some point during life in roughly 55–62% of individuals with epilepsy in TSC.^{6, 11} Of those individuals who responded to therapy, medical therapy accounted for remission of focal seizures in 83.1% of responders. Medical therapy included a variety of anti-seizure medications, with no one medication accounting for a majority of treatment successes. Surgical therapy accounted for successful treatment of focal epilepsy in 15.4% of responders.

Neuropsychiatric characteristics associated with an unfavorable epilepsy outcome included autism spectrum disorder and intellectual disability, with an increasing degree of intellectual disability being correlated with an increasing risk for drug-resistant epilepsy. Autism spectrum disorder, intellectual disability, and epilepsy have been shown to be closely intertwined in TSC.^{17–19} A question that has been raised in the field is whether early, even preventative epilepsy treatment could positively affect long-term epilepsy and neuropsychiatric outcomes. Small prospective trials have reported that both

presymptomatic⁷ and early²⁰ treatment with antiseizure medication may positively influence epilepsy outcomes, specifically the likelihood of developing epilepsy and the likelihood of drug-resistant epilepsy. Cognitive outcomes were also positively influenced, with presymptomatic and early treatment being associated with a decreased likelihood of intellectual disability. One limitation of our study was that neuropsychiatric data was obtained at any age, thus only limited associations could be drawn between epilepsy and IQ data. A recent prospective study²¹ examined the influence of seizures on early development, and they found that seizure freedom during the first 12 months of life was associated with superior developmental measures, suggesting that 12 months may be an important time point in determining developmental outcome. One retrospective study examined infants with TSC and epilepsy in the first year of life and found that earlier epilepsy treatment was associated with improved epilepsy and neuropsychiatric outcomes, including autism spectrum disorder and intellectual disability.¹⁰ Although our study was unable to examine the role of early epilepsy treatment on outcome, we confirmed that autism spectrum disorder, intellectual disability, and drug-resistant epilepsy are strongly associated, begging the question of whether successful epilepsy treatment might positively affect the other neuropsychiatric comorbidities.

Attention deficit hyperactivity disorder and anxiety were associated with a decreased odds of drug-resistant epilepsy. The significance of this finding is unclear, as one would most likely predict more severe neuropsychiatric symptoms in those with more severe neurological dysfunction, as evidenced by refractory epilepsy. One explanation might be that in those individuals with severe neurological symptoms and refractory epilepsy, intellectual disability may have limited the assessment of diagnoses such as attention deficit hyperactivity disorder and anxiety.

Prior studies have demonstrated an association between *TSC2* mutation and worse neurological outcomes, including a higher odds of infantile spasms and intellectual disability.²² Our study indicates that *TSC2* mutations are also associated with an increased risk of drug-resistant epilepsy. Although clinical symptoms and disease severity are influenced by genetic mutation, we identified a persistent association between drug-resistant epilepsy and a number of disease characteristics including age at epilepsy onset, presence of infantile spasms, rate of infantile spasms resistant to therapy, and the presence of autism spectrum disorder and intellectual disability, even after controlling for mutation status. This suggests that although genetic mutation makes a significant contribution to the neurological phenotype, other mechanisms play a role in determining the severity of disease.

A prior study examining this database identified a relationship between systemic and neurological structural lesions of TSC and the presence of epilepsy.²³ However in the current study, drug-resistant epilepsy was not predicted by the presence of systemic disease manifestations such as cardiac rhabdomyomas, renal angiomyolipomas, and hypopigmented macules, or brain lesions such as cortical tuber hamartomas and subependymal giant cell astrocytomas.

A priority in future TSC research includes the identification of reliable biomarkers to assess disease burden and prognosis.²⁴ Large database studies such as ours may assist in

identifying such biomarkers and in turn individuals at highest risk for the development of epilepsy, drug-resistant epilepsy, and poor neuropsychiatric outcomes. Early patient characteristics such as young age at seizure onset, the presence of infantile spasms, and the presence of refractory infantile spasms, may identify those individuals who may have the most to gain from innovative therapies, with these early risk factors potentially tipping the risk-benefit balance in favor of more aggressive therapeutic options.

Although epilepsy surgery is not an option for every TSC patient, perhaps those patients with a poor neurological prognosis based on patient characteristics and biomarkers such as EEG²⁵ should at least be referred for surgical evaluation to determine their candidacy for such an intervention. In refractory childhood epilepsy, younger age at epilepsy surgery has been associated with the widest developmental gains,²⁶ lending further support to the notion that early referral could positively affect outcomes. With upwards of two-thirds of TSC patients with epilepsy being resistant to medications, innovative surgical techniques must be considered, and the most appropriate surgical candidates should be identified and referred as early as possible.

The main limitation of this study was its retrospective nature. Although data collection was on a continual basis, the longitudinal nature of epilepsy was difficult to capture through this database. For example, data from infancy or early childhood may have been difficult to ascertain from older subjects enrolled in the study. The duration of treatments or latency of response to treatment may not be precise. Although the study design was retrospective, a main strength of our study is the large size of the cohort. A similar international registry including over 2000 individuals with TSC has been assembled,²⁷ but the data reported from this registry has been purely descriptive to date. Our study is novel given our ability to analyze variables that would be difficult to study in smaller cohorts. Lastly, this study represents the first “subproject” of the TSC Natural History Database Project, for which we were able to query sites regarding specific epilepsy variables related to drug resistance, generating a supplementary data set for more detailed analysis.

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Table 1

Patient characteristics of 1546 subjects with epilepsy

Parameter	
Male (%)	803 (51.9%)
Median age (25–75%ile)	16.0y (9.6y–25.5y)
Race (available for 1308 subjects)	
Caucasian (%)	1151 (88.0%)
Black or African American (%)	99 (7.6%)
Other	58 (4.4%)
Mutation (available for 711 subjects)	
TSC1 (%)	152 (21.4%)
TSC2 (%)	483 (67.9%)
NMI (%)	76 (10.7%)

NMI, no mutation identified

Table 2

Features of infantile spasms and focal seizures

Infantile spasms (available for 1450 subjects)	
History of infantile spasms (%)	656 (45.2%)
Median age of onset (25–75%ile)	5.0m (3.0m–7.2m)
Infantile spasms controlled	458 (81.2%)
Duration for those controlled (25–75%ile)	4.0m (1.0m–12.0m)
Focal seizures (available for 1474 subjects)	
Presence of focal seizures (%)	1244 (84.4%)
Median age of onset (25–75%ile)	1.1y (5.2m–3.5y)
Drug-resistance (%)	650 (59.6%)

Table 3

Therapies leading to control of seizures

Infantile spasms (458 subjects)	Number of subjects (%)
Medical therapy	387 (84.5%)
vigabatrin	245 (63.3%)
ACTH	49 (12.7%)
topiramate	18 (4.6%)
Other	75 (19.4%)
Surgical therapy	21 (5.0%)
Tubectomy	13 (62.0%)
Lobectomy	4 (19.0%)
Other/unknown	4 (19.0%)
Ketogenic diet	5 (1.2%)
Other	4 (1.0%)
Focal seizures (540 subjects)	
Medical therapy	438 (83.1%)
levetiracetam	73 (16.7%)
lamotrigine	69 (15.7%)
oxcarbazepine	65 (14.8%)
carbamazepine	55 (12.6%)
valproic acid	30 (6.8%)
Surgical therapy	81 (15.4%)
Tubectomy	37 (4.6%)
Lobectomy	19 (23.4%)
Hemispherotomy	4 (4.9%)
Other/unknown	21 (25.9%)
Ketogenic diet	3 (0.6%)
Other	4 (0.7%)

Table 4

Univariate comparison of drug-resistant and drug-responsive subject groups

Parameter	n	OR	95% CI	p-value
Male	1091	1.0	0.8–1.3	0.94
Race	945			0.40
Age at focal seizure onset (<1 vs. >1 year) *	821	1.9	1.4–2.5	<0.001
Genetic mutation	568			0.04
TSC1 vs. NMI		0.6	0.3–1.1	0.12
TSC2 vs. NMI		1.1	0.6–1.6	0.84
TSC2 vs. TSC1		1.7	1.1–2.5	<0.001
Infantile spasms				
History of infantile spasms	1047	2.0	1.5–2.5	<0.001
IS unable to be controlled with therapy	389	47.6	6.7–333.3	<0.001
Duration of infantile spasms *	63			0.90
Autism	930	1.9	1.4–2.6	<0.001
ADHD	918	0.5	0.4–0.8	<0.001
Anxiety	910	0.6	0.4–0.9	0.02
Depression	904	0.6	0.4–1.1	0.08
Clinical assessment of IQ	437			<0.001
Normal **				
Mild to moderate intellectual disability		2.3	1.4–3.6	<0.001
Severe to profound intellectual disability		4.3	2.3–7.9	<0.001

*
by Mann-Whitney *U* test**
Reference category with which other categories are compared.

OR, odds ratio; CI, confidence interval; IS, infantile spasms