ORIGINAL ARTICLE

Effect of Gene Mutation on Seizures in Surgery for Tuberous Sclerosis Complex

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ABSTRACT: ***Background:*** Tuberous sclerosis complex (TSC) is a rare genetic disorder that commonly leads to drug-resistant epilepsy in affected patients. This study aimed to determine whether the underlying genetic mutation (TSC1 vs. TSC2) predicts seizure outcomes following surgical treatments for epilepsy. ***Methods:*** We retrospectively assessed TSC patients using the TSC Natural History Database core registry. Data review focused on outcomes in patients treated with surgical resection or vagus nerve stimulation. ***Results:*** A total of 42 patients with a TSC1 mutation, and 145 patients with a TSC2 mutation, were identified. We observed a distinct clinical phenotype: children with TSC2 mutations tended to be diagnosed with TSC at a younger age than those with a TSC1 mutation ($p < 0.001$), were more likely to have infantile spasms ($p < 0.001$), and to get to surgery at a later age ($p = 0.003$). Among this TSC2 cohort, seizure control following resective epilepsy surgery was achieved in less than half (47%) the study sample. In contrast, patients with TSC1 mutations tended to have more favorable postsurgical outcomes; seizure control was achieved in 66% of this group. ***Conclusion:*** TSC2 mutations result in a more severe epilepsy phenotype that is also less responsive to resective surgery. It is important to consider this distinct clinical disposition when counseling families preoperatively with respect to seizure freedom. Larger samples are required to better characterize the independent effects of genetic mutation, infantile spasms, and duration of epilepsy as they relate to seizure control following resective or neuromodulatory epilepsy surgery.

RÉSUMÉ : Effets d'une mutation génétique sur des crises convulsives à la suite d'une opération chirurgicale dans des cas de sclérose tubéreuse de Bourneville. ***Contexte*** **:** La sclérose tubéreuse de Bourneville (STB) est une maladie génétique rare qui conduit généralement à une épilepsie résistante aux médicaments chez les patients affectés. Cette étude vise ainsi à déterminer dans quelle mesure une mutation dans les gènes TSC1 et TSC2 permet de prédire la fréquence de crises convulsives consécutives à un traitement chirurgical de l'épilepsie. ***Méthodes*** **:** Nous avons évalué de façon rétrospective des patients atteints de STB au moyen du registre principal de la *TSC Natural History Database* (NHD). L'examen de ces données s'est concentré sur l'évolution de l'état des patients ayant bénéficié d'une résection chirurgicale ou de la stimulation du nerf vague (STV). ***Résultats*** **:** Au total, nous avons identifié 42 patients présentant une mutation du gène TSC1 et 145 patients présentant une mutation du gène TSC2. Nous avons également observé un phénotype clinique distinct, à savoir que les enfants présentant une mutation du gène TSC2 avaient tendance à recevoir un diagnostic de STB à un plus jeune âge si on les compare à ceux présentant une mutation du gène TSC1 ($p < 0{,}001$). Ces mêmes 145 enfants étaient en outre plus susceptibles de souffrir de spasmes infantiles ($p < 0{,}001$) et de se faire opérer à un âge plus avancé ($p = 0{,}003$). Au sein de cette cohorte présentant la mutation du gène TSC2, le contrôle des crises convulsives après une résection chirurgicale a été obtenu chez moins de la moitié (47 %) des sujets à l'étude. En revanche, les patients présentant une mutation du gène TSC1 ont eu tendance à montrer une évolution davantage favorable de leur état de santé. À cet égard, un contrôle des crises convulsives a été obtenu chez 66 % d'entre eux. ***Conclusion*** **:** Les mutations du gène TSC2 entraînent un cadre épileptique plus grave qui répond aussi moins bien à la résection chirurgicale. Il est donc important de tenir compte de cette prédisposition clinique différente au moment de discuter, en phase préopératoire, avec les familles de la possibilité de ne plus souffrir de crises convulsives. Des échantillons plus importants de patients sont en outre nécessaires afin de mieux caractériser les effets indépendants des mutations génétiques, les spasmes infantiles et la durée des épisodes épileptiques en lien avec le contrôle des crises convulsives à la suite d'une résection chirurgicale ou d'une chirurgie neuro-modulatoire.

Keywords: VNS, TSC, TSC1, TSC2, Tuberous sclerosis, Seizure, Outcomes

doi:10.1017/cjn.2020.185 Can J Neurol Sci. 2021; 48: 327–334

Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder with an incidence of approximately 1 in 6000 live births.[1] It is thought to arise from a mutation in one of two genes: TSC1 and TSC2. TSC1 encodes hamartin, a protein widely expressed in adult tissues that has been demonstrated to influence cell adhesion and the actin-based cytoskeleton.[2] TSC2 encodes tuberin, a protein associated with regulating the cell cycle and with normal

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Received May 17, 2020. Final Revisions Submitted July 28, 2020. Date of Acceptance August 15, 2020.

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brain development.[3–5] The gene products of TSC1 and TSC2 interact to form the hamartin–tuberin complex, an essential regulator of the mammalian target of rapamycin (mTOR), which directly impacts cell growth, proliferation, and protein synthesis.[6,7] With either genetic mutation, TSC manifests as a multisystem disorder, with an overall lifetime epilepsy prevalence of approximately 85%.[8,9] In patients with TSC-related epilepsy, seizure outcomes vary widely, and prognostic variables are yet to be firmly established.[10] Within this context, an important question remains: how does genetic mutation impact seizure outcomes following epilepsy surgery?

Children harboring a TSC2 mutation tend to express a more severe disease phenotype than children with a TSC1 mutation. In comparing TSC1 and TSC2 patients, Dabora et al. reported that patients with sporadic TSC2 mutations more commonly experienced seizures, were more developmentally delayed, and radiographically harbored more tubers than those patients with sporadic TSC1 mutations.[11,12] Independently, Sancak et al. also noted a lower incidence of intellectual disability in TSC1 patients.[11] Jansen et al. reported that patients with TSC2 mutations tended to present with seizures at an earlier age and were more likely to experience infantile spasms than those with TSC1 mutation.[13] These different phenotypic expressions are significant in that developmental delay and generalized seizure semiology may be significant prognosticators of outcomes following resective epilepsy surgery.[10] Additionally, the type of mutation may be an indicator of the likelihood of drug-resistant epilepsy in patients with TSC.[14]

Nearly two-thirds of children with TSC fail to respond to antiepileptic drugs (AEDs) and may be candidates for either resective epilepsy surgery or vagus nerve stimulation (VNS).[10] Studies among TSC patients suggest that only approximately two-thirds of patients experience favorable seizure reduction (to Engel I or II) following resective surgery.[15–17] We postulated that this difference may arise at least in part from the grouping together of patients with genetic mutations that appear to result in distinct clinical phenotypes. In this study, we examine this hypothesis: children affected by the TSC2 mutation (the more severe disease phenotype) may experience worse seizure outcomes following resective epilepsy surgery or VNS, compared to those children with TSC1 mutations.

Methods

Patient Demographics

Data were obtained from the TSC Natural History Database (NHD) core registry in July 2017. This database was compiled by the Tuberous Sclerosis Alliance beginning in 2006. Patients with TSC were enrolled from 19 participating clinical sites throughout the USA and Belgium. A request was submitted to this alliance to obtain data from all patients with TSC who had experienced any form of epilepsy, whether past or present. We obtained de-identified data regarding patient demographics (gender, handedness, and type of genetic mutation), epilepsy characteristics (epilepsy subtype, its remission/treatment status, and treatments received), and treatment outcomes (controlled or not controlled). A total of 1763 patients were identified in the database, of whom 348 were sub-selected who had undergone either resective epilepsy surgery or VNS implantation.

Patients were grouped by their TSC genetic mutation. Patients who had mutations in both the TSC1 gene and TSC2 gene were categorized into either the TSC1 mutation group or the TSC2 mutation group based on the mutation that was deemed pathogenic. Information regarding the pathogenicity of the genetic variance was included in the database. Patients with no recorded mutation or whose TSC mutation could not be categorized as being of either the TSC1 or the TSC2 types were excluded. Per these criteria, our sample comprised 187 patients as shown in Figure 1.

The epilepsy types were divided into three separate categories within the database. These were reported as either infantile spasms, focal seizures, or "epilepsy other," and each of these epilepsy types had separate seizure outcome data. The outcomes were recorded as "controlled" (defined as seizure-freedom), "not controlled" (defined as persistent seizures), or "unknown." For the purposes of our study, we considered a patient's epilepsy status as "controlled" only if all types of seizures the patient presented with were controlled by the treatment. Patients who were in the unknown group were not included in our statistical analysis, leaving us with 183 patients in our study of epilepsy outcomes: 42 in the TSC1 group and 141 in the TSC2 group. The outcome data for patients who underwent surgical resection or VNS were compared, categorized by mutation type (i.e., TSC1 or TSC2 mutation). Resective surgery included tuberectomies, lobectomies, and hemispherectomies. For patients who underwent a VNS implantation, we defined "responsive" as corresponding to greater than 50% reduction in seizures, while "not responsive" corresponds to less than 50% reduction in seizures. The patients who had been treated with both surgical resection and VNS were also separately analyzed.

Statistical Analyses

Patient demographics, epilepsy characteristics, and seizure outcomes were summarized using descriptive statistics. For continuous data, we reported mean and standard deviations. For dichotomous outcomes, we reported frequencies and percentages. Independent variables with fewer than 10 observations were excluded from inferential statistics. Outcomes and demographics were compared between patients with TSC1 and TSC2 mutations using chi-squared and Student *t*-tests. A *p*-value of less than 0.05 was considered statistically significant. Data were collected using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA) and analyzed using SPSS (Version 19.0, SPSS, Inc., Chicago, IL).

Results

Patient demographics are shown in Table 1. In total, our sample comprised 187 TSC patients across 19 clinical sites, 42 (23.33%) of whom had a TSC1 mutation, while 145 (77.54%) patients had a TSC2 mutation. The TSC1 group comprised 23 (54.76%) males, while the TSC2 mutation group included 73 (50.34%) males. Among patients with a TSC2 mutation, the mean age at diagnosis was 0.91 years (SD, 1.77 years), significantly lower ($p < 0.001$) than that within the TSC 1 group (mean, 3.88 years; SD, 3.32 years). The mean age at surgery, however, was significantly higher ($p = 0.003$) among the TSC2 group (8.12 ± 5.14 years), compared to the TSC1 group (5.56 ± 3.77 years).

https://doi.org/10.1017/cjn.2020.185 Published online by Cambridge University Press

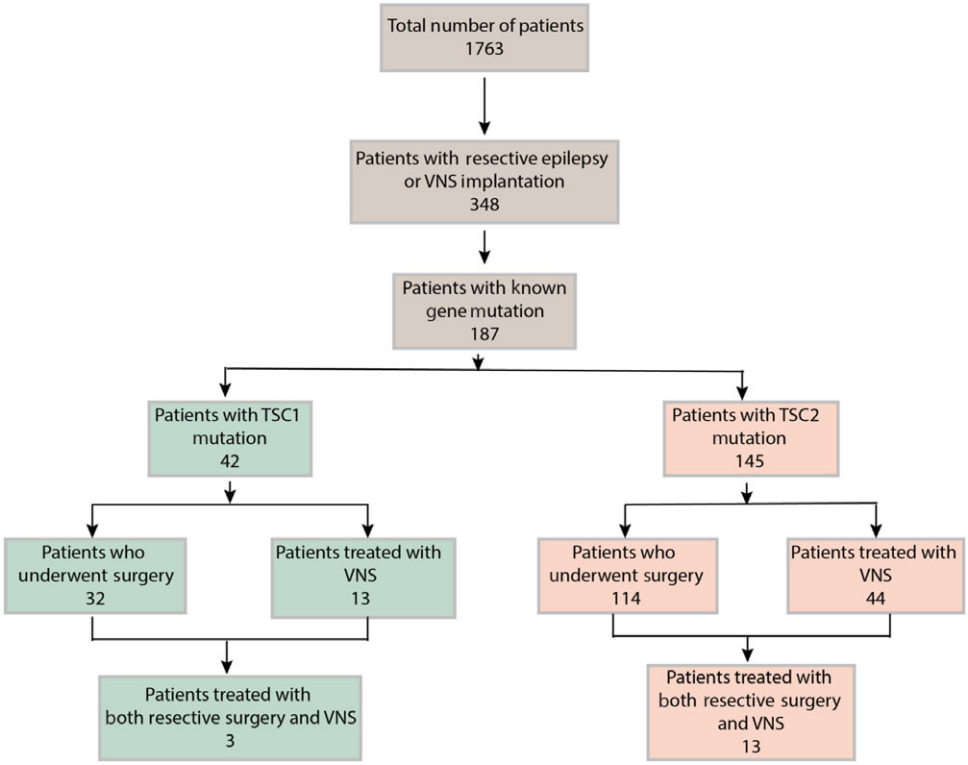

Figure 1: *Flow diagram for study sample selection.*

The different forms of epilepsy manifested within our study group are shown in Table 2. Infantile spasms were more common in the TSC2 group, present in 100 (69%) of patients, compared to only 10 (24%) of patients within the TSC1 group ($p < 0.001$). Focal seizures were incident at rates of 95% and 92% within the TSC1 and TSC2 groups, respectively.

A total of 146 patients underwent surgical resection for treatment of their epilepsy, of whom 32 (21.92%) had a TSC1 mutation and 114 (78.08%) of whom had a TSC2 mutation. Seizure outcomes are tabulated in Table 3. Seizure control was higher among the TSC1 group (65.63%) following surgical resection than amongst the TSC2 group (47.37%), although this difference was not statistically significant ($p = 0.09$). Several variables demonstrated significant collinearity, including age at diagnosis, age at surgery, the presence/absence of infantile spasms, and genetic mutation. We conducted a multivariate multiple regression using a forward conditional model to determine whether seizure control was influenced by these factors, but found no statistical significance for age at diagnosis ($p = 0.087$), genetic mutation ($p = 0.096$), or presence/absence of infantile spasms ($p = 0.081$).

A total of 57 patients were treated with VNS. This included 13 (22.81%) patients from the TSC1 group and 44 (77.19%) patients from the TSC2 group. Seizure outcomes following VNS therapy were similar among both groups, shown in Table 4. Seizures were responsive to VNS in 4 (30.77%) patients from the TSC1 group and in 16 (36.36%) patients from the TSC2 group. In 16 patients, VNS implantation was preceded by resective surgery. Of these, 3 (18.75%) patients had TSC1 mutations and 13 (81.25%) had TSC2 mutations. Seizure outcomes appear to be more favorable amongst TSC1 patients (66.67% controlled) compared to the TSC2 group (15.38% controlled), although sample sizes were small and this difference was not significant at an α of 5% ($p = 0.060$).

Because our data were obtained from a registry, we performed a hierarchical linear regression to evaluate the effects on seizure outcomes in TSC patients undergoing surgery as they related not only to patient age, genetic mutation, and the presence or absence of infantile spasms but also to the center at which the surgeries were performed. The results of this multiple hierarchical regression are shown in Table 5. The effect of the "center" variable, the site at which surgery was performed, was statistically significant within this comparative regression. While this is noteworthy, we note that the R^2 for the regression model is 0.064, indicating that there are likely other, unincluded variables that are influencing the dependent variable (seizure control).

For reference, available search terms within the TSC NHD are provided in Supplementary Material Appendix 1. We make note that available data fields in the database are categorized. More categories including associations of TSC with renal issues or with cardiac issues are available, for example. To avoid providing overwhelming detail within this manuscript, we have chosen to provide selectively data fields within all categories relevant to the goals of the current report. These include those data fields related to demographics, genetics, neurological issues, AEDs, and neuropsychiatric conditions.

Discussion

Tuberous sclerosis carries a significant disease burden. Two predisposing genetic mutations have been identified – TSC1 and TSC2 – that are associated with widely varying severities in clinical disease phenotype. Although disease manifestations in

https://doi.org/10.1017/cjn.2020.185 Published online by Cambridge University Press

Table 1: Patient demographics

	TSC1 mutation		TSC2 mutation		*p*
	N = 42		*N* = 145		
Characteristics	**Mean**	**SD**	**Mean**	**SD**	
Age at diagnosis (years)	3.88	3.32	0.91	1.77	<0.001*
Male	3.76	8.40	0.92	1.78	
Female	3.88	8.32	0.92	1.78	
Age at surgery (years)	5.56	3.77	8.12	5.14	0.003*
	n	%	*n*	%	
Gender					0.614
Male	23	54.76	73	50.34	
Female	19	45.24	72	49.66	
Verbal					0.563
Yes	31	73.81	95	65.51	
No	5	11.90	26	17.93	
Unknown	6	14.29	24	16.56	
Handedness					0.788
Right	12	28.57	46	31.72	
Left	5	11.90	19	13.10	
Both	1	2.38	1	0.69	
Unknown	24	57.14	79	54.48	
Family history					
Paternal diagnosis					0.507
Yes	3	7.14	8	5.52	
No	10	23.81	48	33.10	
Unknown	29	69.05	89	61.38	
Maternal diagnosis					0.114
Yes	5	11.90	8	5.52	
No	9	21.43	52	35.86	
Unknown	28	6.68	85	58.62	

TSC = tuberous sclerosis complex.
*Values that are less than 0.05 are considered statistically significant.

relation to genetic makeup have been analyzed by prior studies, a central question in TSC-related epilepsy treatment remains: is there an association between the type of genetic mutation leading to TSC and seizure outcomes following resective seizure surgery? In this report, we examine the hypothesis that the gene mutation (TSC1 or TSC2) may relate to seizure outcomes following resective epilepsy surgery. We find that TSC2 patients tend to be diagnosed at an earlier age, are more likely to have infantile spasms, and have a lower rate of seizure control following surgery. We suspect that the gene mutation underlying the TSC presentation is the causative factor for these differences, but acknowledge that the high degree of collinearity amongst variables in our study precludes such a conclusion.

Limitations

To our knowledge, this study represents the first and largest evaluation of seizure outcomes following resective surgery amongst TSC patients in relation to their genetic makeup. Despite its singularity, it is important to note at the outset that it is not without significant limitations. Importantly, this is a retrospective study of data obtained from a national registry. As such, analyses are limited to curated data, not always consistently available across all patients. Seizure frequency, for instance, is unavailable in the registry, which precludes Engel classification scores for study subjects. Moreover, a universal, systematic classification is necessary to enable studies to be more broadly received and interpreted. Sufficient information to determine the International League Against Epilepsy classification for resective surgical patients or the McHugh Burden in VNS patients was not recorded in the database and therefore was unavailable to the current report and analyses. We acknowledge this as a limitation to our study. Similarly, while resective surgery could be consistently evaluated, it could not always be ascertained whether this was a tuberectomy, a lobectomy, or a hemispherectomy, necessitating their grouping.

https://doi.org/10.1017/cjn.2020.185 Published online by Cambridge University Press

Table 2: Seizure phenotypes among study subjects

Characteristics	TSC1 mutation N = 42		TSC2 mutation N = 145		p
	n	%	n	%	
Infantile spasms					0.001*
Yes	10	23.81	100	68.97	
No	26	61.90	38	26.21	
Unknown	6	14.29	7	4.83	
Focal seizures					0.573
Yes	40	95.24	134	92.41	
No	1	2.38	9	6.21	
Unknown	1	2.38	2	1.38	
Epilepsy other					0.558
Yes	11	26.19	43	29.66	
No	26	61.90	92	63.45	
Unknown	5	11.90	10	6.90	

TSC = tuberous sclerosis complex.
*Values that are less than 0.05 are considered statistically significant.

Table 3: Seizure outcomes following resective surgery

Gene mutation	Controlled n (%)	Not controlled n (%)	Unknown n (%)	Total N	p
TSC1	21 (65.66)	11 (34.38)	0	32	0.090
TSC2	54 (47.37)	56 (49.12)	4 (3.51)	114	
Total	80 (48.78)	80 (48.78)	4 (1.83)	164	

TSC = tuberous sclerosis complex.

With regard to treatment modalities, although many subjects received multimodality management (surgical, medical, dietary, etc.) their chronological order was not universally available. It does not escape our attention that this order, as well as conservative measures including mTOR inhibition and anticonvulsant drugs, behavioral data including neuropsychiatric evaluations, as well as operative surgical information (neuromonitoring used, single or staged surgery) could affect treatment outcomes following resective surgery or VNS. However, the database represents our best opportunity at evaluating a large study sample to begin to understand factors implicit in TSC and its treatment. Gaps in the database reflect a limited data availability that precluded comprehensive subgroup analyses. Yet, the findings may serve as a springboard for future endeavors to evaluate these conditions in greater detail.

We make a final note on a limitation which may also reflect the strength in a registry study. In evaluating the variables which may have a significant bearing on seizure outcomes following resective epilepsy surgery in TSC patients, we identified that the effect of the site at which surgery was performed was a statistically significant regressor. Analyzing pooled data across multiple centers can help in evaluating infrequent pathologies with significant disease burden such as TSC, but such statistically significant center effects remind us to be mindful in interpreting results that the data may be biased by site specificity. In other words, these data serve as a preliminary assessment of the many variables that may influence seizure outcomes but require future studies with greater homogeneity and larger sample sizes to definitively evaluate their individual effect sizes.

TSC Genetic Makeup May Affect Seizure Phenotype and Surgical Treatment Outcome

To appropriately risk stratify TSC subgroups and optimize treatment options, it is critical to understand the variables that prognosticate good outcomes.[18] Previous studies among TSC patients with seizures suggest that factors that bear on surgical outcomes for epilepsy include brain tuber load.[19] These influences of these variables have each been analyzed further. In a recent report, for instance, we described that amongst patients with tuber-related epilepsy, resecting all epileptogenic tissue surrounding a tuber affords higher rates of seizure freedom than tuberectomies alone.[20]

https://doi.org/10.1017/cjn.2020.185 Published online by Cambridge University Press

Table 4: Seizure outcomes following VNS alone or following resective surgery

Gene mutation	Controlled (%)	Not controlled (%)	Total	*p*
	n (%)	*n* (%)	*N*	
VNS				0.710
TSC1	4 (30.77)	9 (69.23)	13	
TSC2	16 (36.36)	28 (63.64)	44	
Resective surgery + VNS				0.060
TSC1	2 (66.67)	1 (33.33)	3	
TSC2	2 (15.38)	11 (84.62)	13	
Total	24 (31.17)	52 (67.53)	77	

TSC = tuberous sclerosis complex; VNS=vagus nerve stimulation.

Table 5: Comparative regression models evaluating center effects

	R^2	*F*	df	B	SE B	*β*	*p*
Model	0.064	2.154	4				0.078
Constant				0.458	0.233		
Center				0.022	0.010	0.193	0.029*
Age				0.006	0.010	0.052	0.576
TSC mutation				0.123	0.123	−0.032	0.742
Infantile spasms				0.103	0.103	−0.108	0.268

R^2 = coefficient of determination; *F* = *F* statistic; df = degrees of freedom; B = unstandardized coefficients; SE B = standard error on unstandardized coefficients; β = standardized coefficients; TSC = tuberous sclerosis complex.
*Values that are less than 0.05 are considered statistically significant.

In the first of its kind, we examined in this study the effects of the underlying genetic mutation predisposing to TSC on seizure outcomes following their surgical management. Evidence suggests that TSC2 mutations tend to result in more severe seizures than TSC1 mutations, with higher rates of infantile spasms, epilepsy, and medically refractory epilepsy.[6–9] This held true in our cohort. Moreover, we found that amongst TSC2 patients the mean age at TSC diagnosis was lower, likely reflecting a more aggressive phenotype. Age at diagnosis and age at surgery by themselves may be independent prognosticators of outcome. Indeed, studies have demonstrated that TSC patients who underwent surgery at an older age (and more specifically, had seizures for longer durations) were more likely to continue to experience postoperative seizures than those who underwent surgery at a younger age.[17]

Critically, we observed that TSC1 patients tended to have better seizure outcomes following resective seizure surgery than did TSC2 patients, although we acknowledge that this difference did not reach statistical significance at an α of 5% ($p = 0.090$). This trend did not hold true for patients who had undergone VNS implantation. Among this sample, both TSC1 and TSC2 subgroups had similar outcomes ($p = 0.071$). It may be that the genetic mutation does not associate as closely with nonspecific therapy (VNS) as it does with targeted, resective surgery. This latter hypothesis appears to be supported by our findings in a smaller subset of patients in our cohort underwent both resective surgery and VNS. Among this sample, TSC1 patients who underwent both tended to have a greater likelihood of a positive outcome than did TSC2 patients.

A Note on the Resective Surgery and VNS

As noted earlier, we grouped tuberectomies, lobectomies, and hemispherectomies together because of limitations in working with registry data. The inclusion of VNS as a surgical treatment option was intentional. In contrast to targeted resective surgery, VNS is a neuromodulatory approach to seizure mitigation, less specific but effective in a selected subgroup. The current study represents a large sample evaluation of surgical outcomes for seizure management in TSC patients. While we found no significant difference between genetic mutation and surgical outcomes, we urge the reader to bear in mind the several limitations inherent to this study in concluding that this is a definitive inference. While this may be true, given the relative significance of this result at an acceptable type I error rate of 10%, we are of the opinion that this topic requires further evaluation. Future, prospective, randomized trials with larger sample sizes, and controlled for confounds and collinear variables will be necessary to examine these findings in a robust manner to perform rigorous subgroup, or age-matched cohort analyses for optimizing the surgical management of seizures in patients with TSC.

https://doi.org/10.1017/cjn.2020.185 Published online by Cambridge University Press

Conclusion

In treating children with TSC, it is not fully understood what features can better predict optimal candidacy for surgery. Our analyses suggest that children with TSC1 mutations may have better seizure outcomes following resective surgery in the management of their epilepsy, when compared to patients with TSC2 mutations. Due to the relatively low prevalence of TSC, further studies including a larger sample size using an external dataset are warranted to confirm these findings. We also found that patients with TSC2 mutations more commonly present with infantile spasms and are diagnosed at an earlier age. These covariates suggest a widespread network disorder that may explain the poor seizures outcomes following epilepsy surgery. As noted, older age at diagnosis, younger age at surgery, the presence of a TSC1 mutation, and absence of infantile spasms appear to bear on seizure control following surgery amongst patients with TSC. Future prospective, randomized studies with larger samples will help to clarify their individual or combined influences to assist in candidate risk stratification, selection, and treatment optimization.

Acknowledgements

We would like to acknowledge the Tuberous Sclerosis Alliance. We would also like to acknowledge the Tuberous Sclerosis Natural History Database Consortium and the following participating database sites:

1. Minnesota Epilepsy Group, P.A., St. Paul, MN (Michael Frost, MD); 2. Texas Scottish Rite Hospital for Children, Dallas, TX (Steven Sparagana, MD); 3. New York University School of Medicine, New York, NY (Josiane LaJoie, MD, 2007–2011; James Riviello Jr, MD, 2011–2013; Orrin Devinsky, MD, 2013–2015; Josiane LaJoie, MD); 4. Massachusetts General Hospital, Boston, MA (Elizabeth Thiele, MD, PhD); 5. Children's Research Institute, Washington, DC (William McClintock, MD); 6. The University of Chicago, Chicago, IL (Michael Kohrman, MD, 2007–2016; Patricia Ogden, APN, FNP, NP-C); 7. UCSF Benioff Children's Hospital Oakland, Oakland, CA (Candida Brown, MD, 2007–2010; Rachel Kuperman, MD); 8. University of California Los Angeles, Los Angeles, CA (Joyce Wu, MD); 9. The University of Texas Health Science Center at Houston, Houston, TX (Hope Northrup, MD); 10. University of Alabama at Birmingham, Birmingham, AL (E. Martina Bebin, MD, MPA, 2008–2011; Bruce Korf, MD, PhD, and Martina Bebin, MD, MPA, 2012–2014; Bruce Korf, MD, PhD); 11. Cleveland Clinic, Cleveland, OH (Ajay Gupta, MD); 12. Children's Hospital Colorado, Aurora, CO (Paul Levisohn, MD, 2008–2011; Susan Koh, MD); 13. Nicklaus Children's Hospital Miami, Miami, FL (Ian O'Neil Miller, MD, and Michael Duchowny, MD, 2008–2015; Ian O'Neil Miller, MD); 14. Loma Linda University, Loma Linda, CA (Stephen Ashwal, MD); 15. UZ Brussels, Belgium (Anna Jansen, MD, PhD); 16. University of Pennsylvania, Philadelphia, PA (Peter Crino, MD, PhD, 2009–2012; John Pollard, MD, 2012–2013; Kate Nathanson, MD); 17. Boston Children's Hospital, Boston, MA (Mustafa Sahin, MD, PhD); 18. Cincinnati Children's Hospital Medical Center, Cincinnati, OH (Darcy A. Krueger, MD, PhD); 19. Washington University St. Louis, St. Louis, MO (Michael Wong, MD, PhD).

Conflicts of Interest

Dr. Mathern reports grants from NIH during the conduct of the study. The remaining authors have nothing to disclose.

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.

Statement of Authorship

OM, DB, SC, and AF contributed to the conception and design of the study. OM, DB, and SC contributed to acquisition and analysis of data. All authors (OM, AK, DB, SC, GMI, AGW, AT, JYW, GWM, and AF) contributed to drafting a significant portion of the manuscript or figures and approval of the final draft.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2020.185.

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https://doi.org/10.1017/cjn.2020.185 Published online by Cambridge University Press