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Research Paper

Multicenter Research Data of Epilepsy Management in Patients With Sturge-Weber Syndrome

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ABSTRACT

Background: Epilepsy in typical Sturge-Weber syndrome (SWS) is common, and many questions remain regarding the treatment outcomes. We analyzed a large multicenter database with focus on neurological drug treatment in different demographic and SWS characteristic groups.
Methods: A total of 268 patients with brain involvement and a history of seizures were selected from a research data registry generated from a multicenter cross-sectional questionnaire. We examined associations between medication use and binary variables such as sex, ethnicity, and brain, skin, and eye involvement laterality. We analyzed group differences in mean number of antiseizure medications and age at diagnosis, enrollment, and seizure onset and examined differences in median SWS neurological scores in groups of interest.
Results: The most frequently used medications were levetiracetam (48.1%), low-dose aspirin (44.8%), oxcarbazepine (39.9%), and phenobarbital (14.9%). Lamotrigine was more frequently used in adults than in children ($P = 0.001$). History of neurosurgery was associated with no current antiseizure medication use ($P = 0.001$), whereas bilateral brain involvement and family history of seizures were associated with using a higher number of antiseizure medications ($P = 0.002$, $P = 0.027$, respectively). Subjects with bilateral brain involvement and early seizure onset were associated with using a higher number of antiseizure medications ($P = 0.002$) and phenobarbital use (0.003).

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Conclusions: Levetiracetam, low-dose aspirin, and oxcarbazepine were the most frequently used medications. More severely affected patients were frequently on a greater number of antiseizure medications. Surgery for epilepsy was associated with the ability to discontinue antiseizure medication. Longitudinal studies are needed to further investigate medication use in patients with SWS.

Introduction

Sturge-Weber syndrome (SWS) is a noninherited neurovascular disease associated with a port-wine birthmark, glaucoma, and leptomeningeal capillary venous malformation resulting in supratentorial hemisphere atrophy. The disease is caused by an activating somatic mutation in the gene *GNAQ,* encoding the Gαq subunit.[1]

The neurological manifestations of SWS occur with variable severity, resulting in large part from the variable extent of brain involvement with the leptomeningeal vascular malformation. The neurological consequences of this condition are often debilitating and may consist of cerebral atrophy, seizures, acquired hemiparesis, various degrees of intellectual disability, and, the most recently described, autistic behavior.[2,3] Approximately from 75% to 90% of patients with SWS brain involvement develop epilepsy, mostly during the first year of life.[4] Early onset of seizures and medically refractory epilepsy are indicative of a poor prognosis.[5] Early recognition and aggressive management of symptoms remain the foundation of the management in this syndrome. Patients with extensive unilateral and bilateral brain involvement more frequently have drug-resistant epilepsy.[6]

For a subset of patients who are medically refractory, medical care remains very challenging. The goal of this study was to analyze the largest yet available multicenter database for information on the neurological management of patients with SWS with a focus on certain key groups: unilateral versus bilaterally involved patients, pediatric versus adult patients, those with early seizure onset versus later onset, surgically treated patients, and patients receiving low-dose aspirin. We aimed to identify risk factors associated with medication use for epilepsy in SWS, to describe the most commonly used antiseizure medications (ASMs), and to report the frequency of aspirin use in patients with SWS. In addition, we aimed to identify factors associated with key subgroups. We hypothesized that both early onset of seizures and bihemispheric brain involvement were more likely to result in the use of multiple ASMs. With the rapidly increasing number of available ASMs, it is important to periodically review treatment options. This study utilizes the largest research database of patients with SWS and ASMs to address this important issue.

Methods

Data collection

All subjects provided written informed consent before participating. Approval for this study was obtained from the National Institutes of Health, Johns Hopkins University Institutional Review Board, and all local institutional review boards.

The data analyzed in this study were compiled from a patient/parent questionnaire administered at seven different sites (Johns Hopkins University/Kennedy Krieger Institute, Baltimore, MD; Baylor College of Medicine, Houston, Texas; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Nationwide Children's Hospital, Columbus, OH; New York University, New York, NY; Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA; Wayne State University, Detroit, MI) participating in the Brain Vascular Malformation Consortium. Data analyzed in this study were collected from August 2010 through November 2018. Only patients with SWS brain involvement demonstrated by contrast-enhanced magnetic resonance imaging were eligible to participate. Patients with neurological symptoms, including developmental delay and seizures, with a normal magnetic resonance imaging were excluded.

Questionnaires were administered as described in the inaugural study of these data[7]; questionnaires were completed by one of the following three methods: by the participant themselves, by the participant's parent or guardian, or by the study staff reading the questions to the participants, and their responses were transcribed directly. The questionnaire was most often completed in person, after a clinic visit, but could also be completed over the phone. All questions were answered based on patient or parent reporting; patient records were not consulted to verify responses. If the patient did not want to answer a question, or if they were unable, they could leave it blank, or mark “unknown” or “Not Applicable.” Enquiries about phrasing or questions on the questionnaire were answered by the study staff. To be included in this study, medication questions must have been answered.

Database creation

Data were uploaded into the Rare Diseases Clinical Research Network online database by the study staff at each center. Before data analysis, all entries were cleaned by the University of California San Francisco; missing data or entries with inconsistencies were addressed in cooperation with the site from which the data were collected. Changes were made only if the error was related to data entry onto the online form, or if there was an inconsistency that could be clarified based on clinic notes from that time.

Statistical methodology

All data analysis was completed in IBM SPSS Statistics 25 at the Kennedy Krieger Institute. Simple frequencies were generated to understand which ASMs were most commonly used among patients with SWS. The medications included in this study were ASMs and low-dose aspirin. All analyses were run only among patients with a history of seizures. A P value less than or equal to 0.05 was used to determine significance.

Two-tailed chi-square or Fisher's exact tests were done to determine if using a medication was associated with another binary variable (sex, ethnicity, laterality of brain involvement, presence/laterality of the port-wine birthmark and glaucoma, history of brain surgery, concatenate use with another medication) or race, or if a specific SWS characteristic was associated with a medication.

Two-tailed t tests were done to determine if using a medication was associated with a difference in the mean number of ASMs at the time of enrollment, age at diagnosis, enrollment, or seizure onset. Mann-Whitney U tests were used to determine if there was a significant difference in median seizure, hemiparesis, visual field

cut, cognitive function, or total neuroscores.[8] The SWS neuroscore, previously validated through neuropsychological testing,[9] quantitative electroencepalographiy,[10] and perfusion imaging,[11] is a 15-point scale used to assess seizure frequency (0 to 4), hemiparesis severity (0 to 4), visual field cut extent (0 to 2), and cognitive function (0 to 5), where higher scores indicate poorer outcomes. In all reported analyses, patients using the medication were compared with those who were not.

Data analysis

Having a history of seizures, but not using ASMs at the time the questionnaire was completed, was considered to be an indicator of seizure freedom. To understand SWS, demographic, or medication variables related to eventual "seizure freedom," patients with a history of seizures not using ASMs were compared with those using ASMs. These analyses were repeated in adults (18+ years at enrollment, based on rounded age) and patients with a history of brain surgery. History of seizures was defined by the responses to two questions: "*Has the participant ever experienced any of the following conditions- Epilepsy?*" or "*Does the subject have a history of seizures?*" If either question was answered as "yes," the patient was considered to have a history of seizures. A patient did not have a history of seizures if both questions were answered "no," or if one question was answered as "no" and the other was left blank. If both questions were left as blank or unknown, the subject was excluded.

To understand how demographics and SWS outcomes were related to medications used, patients with variables of interest (bilateral brain involvement, family history of seizures, patients younger than two years, adults, patients with seizure onset before age one year) were compared with the rest of the group. An additional analysis focused on patients using aspirin, levetiracetam, oxcarbazepine, phenobarbital, lamotrigine, lacosamide, and clobazam and associated SWS and demographic factors.

Results

Sample demographics

A total of 312 patients completed the database questionnaire; 268 patients with a history of seizures (55.2% female, 86.2% younger than 18 years at enrollment, 78.4% white, 6.3% black, 6.3% Asian, 4.9% multiracial, 3.4% unknown, 0.4% Native Hawaiian Pacific Islander, and 0.4% American Indian/Alaskan Native; Table 1) were included in this study. In the 268 patients with seizures, the most frequently used ASMs were levetiracetam (48.1%), oxcarbazepine (39.9%), and phenobarbital (14.9%). One hundred and twenty (44.8%) were using aspirin; medication frequencies for patients with seizures can be seen in Table 2. One hundred and one patients (37.7%) were using one ASM, 91 (34.0%) were using two ASMs, 38 (14.2. %) were using three ASMs, and 10 (3.7%) were using four or more ASMs. In subjects who were using two ASMs (n = 91), not including aspirin, levetiracetam, and oxcarbazepine was the most frequent combination of seizure medications (34.1%). In subjects using three ASMs (n = 38), not including aspirin, the most frequent combination of seizure medications was levetiracetam, oxcarbazepine, and lacosamide (10.5%) or phenobarbital (10.5%).

For brevity and clarity, only significant values of clinical relevance are reported. All *P* values can be found in Tables 3-5.

History of brain surgery

Twenty-eight participants had a history of brain surgery. Among patients who continued ASM therapy (n = 18, 64%), levetiracetam (N = 7) and oxcarbazepine (N = 7) were the most frequently used ASMs and six subjects were using low-dose aspirin. Only one subject with a history of brain surgery also had bilateral brain involvement. This subject, female and aged four years at the time of enrollment, continued to use phenobarbital.

TABLE 1.
Demographics and Medications Used in N = 268 Respondents With Seizures

Population or SWS Demographic	Respondents With History of Seizures (N = 268)
Sex	
Female	148 (55.2%)
Male	120 (44.8%)
Adult versus child	
Child	231 (86.2%)
Adult	37 (13.8%)
Ethnicity	
Hispanic/Latino origin	27 (10.1%)
Not Hispanic/Latino origin	227 (84.7%)
Unknown	14 (5.2%)
Race	
American Indian/Alaskan Native	1 (0.4%)
Asian	17 (6.3%)
Black	17 (6.3%)
Native Hawaiian Pacific Islander	1 (0.4%)
White	210 (78.4%)
Multiracial	13 (4.9%)
Unknown	9 (3.4%)
Brain involvement	
Unilateral	216 (80.6%)
Bilateral	52 (19.4%)
Port-wine birthmark	
Not present	38 (14.2%)
Unilateral	126 (47.0%)
Bilateral	104 (38.8%)
Glaucoma	
Not present	128 (47.8%)
Unilateral	103 (38.4%)
Bilateral	32 (11.9%)
Unknown	5 (1.9%)
Using an antiseizure medication	
Yes	240 (89.6%)
No	28 (10.4%)
Using aspirin	
Yes	120 (44.8%)
No	148 (55.2%)

Abbreviation:
SWS = Sturge-Weber syndrome

Patients not using ASMs

All patients

Of the N = 268 patients with a history of seizures, N = 28 patients were not using ASMs at the time the questionnaire was completed. A history of brain surgery (n = 10 of 28, 36% not on ASM) was associated with being off of seizure medications at the time the questionnaire was administered ($P = 0.001$). Of the subjects not using an ASM with no history of neurosurgery (n = 15 with full data available, mean age = 11.4 years, range from 0 to 32 years), 13 had unilateral brain involvement and seven were using aspirin.

Adults

Of the N = 37 adults with history of seizures, six (16.2%) were not using ASMs at the time the questionnaire was administered. Of the adults who were not using ASMs, one subject, a 31-year-old female with unilateral brain involvement, had history of brain surgery. Not using ASMs as an adult was significantly associated with female sex ($P = 0.022$) and a unilateral port-wine birthmark ($P = 0.020$, among patients with port-wine birthmarks only).

TABLE 2.
Antiseizure Medications Used in Patients With Seizures

ASM	Number of Subjects Using
Any ASM	240 (89.6%)
Levetiracetam	129 (48.1%)
Oxcarbazepine	107 (39.9%)
Phenobarbital	40 (14.9%)
Topiramate	33 (12.3%)
Carbamazepine	25 (9.3%)
Lamotrigine	22 (8.2%)
Lacosamide	21 (7.8%)
Valproic acid	16 (6.0%)
Zonisamide	13 (4.9%)
"Other" ASM	13 (4.9%)
Phenytoin	11 (4.1%)
Clobazam	7 (2.6%)
Clonazepam	5 (1.9%)

Abbreviation:
ASM = Antiseizure medication

Analysis by Sturge-Weber syndrome characteristics

Bilateral brain involvement

Fifty-two patients had bilateral brain involvement (19.4%). Bilateral brain involvement was associated with using phenobarbital ($P = 0.003$) and using a greater number of ASMs overall ($P = 0.002$, mean = 2.0 ± 1.1 versus 1.6 ± 1.0 in patients with bilateral and unilateral brain involvement, respectively). Extent of brain involvement (unilateral versus bilateral) was significantly associated with extent of eye involvement ($P < 0.001$) and extent of skin involvement ($P < 0.001$).

Eye involvement

One hundred and thirty-six subjects had glaucoma. One hundred and three had unilateral and 32 had bilateral involvement. Presence of glaucoma was associated with use of carbamazepine ($P = 0.011$) and phenytoin ($P = 0.001$). Subjects with glaucoma also used a greater number of ASMs compared with subjects without glaucoma ($P = 0.036$; mean = 1.88 ± 1.1 versus 1.5 ± 0.9). Bilateral glaucoma was associated with use of carbamazepine ($P = 0.008$), phenytoin ($P = 0.001$), and phenobarbital ($P = 0.023$).

Family history of seizures

Sixty-four participants had a family history of seizures. A family history of seizures was associated with using levetiracetam ($P = 0.006$, 41 of 64 versus 85 of 195), whereas using zonisamide was associated with not having a family history of seizures ($P = 0.042$, zero of 64 versus 12 of 195 where one zonisamde user did not answer the family history of seizures question). A family history of seizures was associated with using a significantly greater number of ASMs overall ($P = 0.027$, mean = 1.9 ± 1.0 versus 1.6 ± 1.0 in patients with and without a family history of seizures, respectively).

Adults

Thirty-seven participants were adults. Levetiracetam (40.5%) and lamotrigine (24.3%) were the most frequently used ASMs in adults. Adult status was associated with using lamotrigine ($P = 0.001$; nine of 37 adults versus 13 of 231 children), whereas child status was associated with using oxcarbazepine ($P < 0.001$; 102 of 231 children versus five of 37 adults), phenobarbital ($P = 0.004$; 40 of 231 children versus zero of 37 adults), and aspirin ($P = 0.001$; 113 of 231 children versus seven of 37 adults).

Patients younger than two years

Seventy-one patients were two years of age or younger at the time of enrollment. Using levetiracetam ($P < 0.001$) and phenobarbital ($P < 0.001$) was associated with the two years and younger group, whereas using carbamazepine ($P = 0.031$) and lamotrigine ($P = 0.004$) was associated with the three years and older group.

Seizure onset before age one year

One hundred and ninety-six patients had seizure onset at or before age 12 months. Seizure onset at or before age 12 months was associated with using phenobarbital ($P = 0.003$).

Bilateral brain involvement and seizure onset before age one year

Forty-two patients had bilateral brain involvement and seizure onset at or before age 12 months. This group of interest was associated with using a greater number of ASMs as opposed to all other subjects with a history of seizures ($P = 0.002$; mean = 2.1 ± 1.1 versus 1.6 ± 1.0). Phenobarbital was more frequently used ($P = 0.003$). Those with bilateral brain involvement and seizure onset at or before 12 months were more frequently associated with having a more extensive (bilateral) port-wine birthmark ($P < 0.001$) and having more extensive (bilateral) glaucoma ($P < 0.001$). This group was also associated with more severe hemiparesis scores ($P = 0.049$; median = 3 versus 1 in those with bilateral brain involvement and seizures at or before 12 months [n = 9] versus all others with a history of seizures). Cognitive impairment scores were also worse ($P = 0.044$; median = 2 versus 1) in those with bilateral brain involvement and seizures at or before 12 months.

TABLE 3.
Associations Between Using a Given Antiseizure Medication and SWS Characteristics

Medication	Using Levetiracetam	Using Oxcarbazepine	Using Phenobarbital	Unilateral Versus Bilateral B.I.	Bilateral B.I. and Early Sz Onset	Fam Hx of Sz	Adult Versus Child Status	Under Versus Over 2 Years
Aspirin	1.000	0.134	1.000	0.163	0.176	0.561	**0.001**▲	0.579
Carbamazepine	**0.037**	**0.000**	**0.033**▲	1.000▲	0.389▲	0.807	0.060▲	**0.031**
Lamotrigine	1.000	0.112	0.217▲	0.396▲	0.362▲	0.427	**0.001**▲	**0.004**
Levetiracitam	——	0.173	**0.025**	0.440	0.402	**0.006**	0.377	**0.000**
Oxcarbazepine	0.173	——	0.053	0.753	0.305	0.556	**0.000**	0.324
Phenobarbital	**0.025**	0.053	—	**0.003**	**0.003**	0.687	**0.004**	**0.000**
Zonisamide	0.259	0.573	0.420▲	0.140▲	0.104▲	**0.042**▲	1.000▲	0.524▲

Abbreviations:
B.I. = Brain involvement
Fam = Family
Hx = History
SWS = Sturge-Weber syndrome
Sz = Seizure
Bold face denotes a significant *P* value.
▲Fisher's exact test.

TABLE 4.
Demographic and SWS Characteristics Related to ASM Use in Patients With Seizures

Characteristic	Using Levetiracetam Versus Not Using	Using Oxcarbazepine Versus Not Using	Using Phenobarbital Versus Not Using	Off versus On ASMs	Using Aspirin Versus Not Using	Adults Off Versus On ASMs	Hx of Brain Surgery, Off Versus On ASMs
Sex	0.713	0.531	0.389	0.555	0.217	**0.022**▲	0.236
Ethnicity	0.420	0.302	0.248▲	0.182▲	0.684	0.310▲	0.370▲
Race	0.181▲	**0.010**▲	0.127▲	0.180▲	0.790▲	1.000▲	1.000▲
B.I. laterality	0.440	0.753	**0.003**	0.126	0.163	0.571▲	1.000▲
Brain surgery	**0.004**	0.389	0.420▲	**0.001**▲	**0.037**	1.000▲	–
Glaucoma present	1.000	0.262	0.866	0.691	1.000	0.394▲	0.703▲
Uni versus bi glaucoma	0.068	0.146	**0.023**▲	0.300▲	0.105	0.130▲	1.000▲
PWB present	0.862	0.592	0.228	0.777▲	0.165	1.000▲	0.128▲
Uni versus bi PWB	0.597	1.000	0.281	1.000	0.509	**0.020**▲	1.000▲

Abbreviations:
ASM = Antiseizure medication
B.I. = Brain Involvement
Bi = Bilateral
Hx = History
PWB = Port-wine birthmark
SWS = Sturge-Weber syndrome
Uni = Unilateral
Bold face denotes a significant *P* value.
▲Fisher's exact test.

Analysis by medication

Aspirin

One hundred and twenty patients (44.8%) were using aspirin. Aspirin use was associated with a significantly younger age at enrollment ($P < 0.001$; 7.18 ± 6.68 years versus 11.76 ± 12.69 years in patients using and not using aspirin, respectively).

Levetiracetam

One hundred and twenty-nine (48.1%) patients were using levetiracetam. Using levetiracetam was associated with younger age of seizure onset ($P = 0.015$; mean = 14.05 ± 23.32 months versus 28.17 ± 61.18 months in patients using and not using levetiracetam, respectively), younger mean age at diagnosis ($P = 0.021$; mean = 12.1 ± 25.5 months versus 26.7 ± 67.7 months for patients using and not using levetiracetam, respectively), and younger mean age at enrollment ($P = 0.023$; mean = 8.18 ± 11.6 years versus 11.13 ± 9.57 years for patients using levetiracetam and not using levetiracetam, respectively). Patients using levetiracetam were likely neither to have a history of epilepsy surgery ($P = 0.004$) nor to be using carbamazepine ($P = 0.037$). Patients on levetiracetam were more frequently using phenobarbital compared with patients who were not using levetiracetam ($P = 0.025$).

Oxcarbazepine

One hundred and seven (39.9%) patients with seizures used oxcarbazepine. Using oxcarbazepine was associated with a significantly younger age at enrollment ($P < 0.001$; mean = 6.54 ± 5.63 years versus 11.81 ± 12.55 years for patients using and not using oxcarbazepine, respectively).

Phenobarbital

Forty (14.9%) patients with seizures were using phenobarbital. Patients using phenobarbital had a younger mean age at enrollment ($P < 0.001$; mean = 3.48 ± 3.6 years versus 10.80 ± 11.1 years for patients using phenobarbital and not using phenobarbital, respectively), younger mean age at diagnosis ($P < 0.001$; mean = 4.05 ± 4.8 months versus 22.4 ± 56.1 months for patients using and not using phenobarbital, respectively), and younger age at seizure onset ($P < 0.001$; mean = 7.18 ± 11.67 months versus 23.88 ± 50.7 months in patients using phenobarbital and not using phenobarbital, respectively). Phenobarbital was associated with a greater hemiparesis neuroscore ($P = 0.002$; median = 3 versus 1 in those using and not using phenobarbital, respectively) and greater total neuroscore ($P = 0.013$; median = 6 versus 4 in those using [n = 14] versus not using phenobarbital [n = 62], respectively). Bilateral brain involvement and bilateral glaucoma were associated with using phenobarbital ($P = 0.003$ and $P = 0.023$, respectively). Phenobarbital was likely to be used with leviteracetam ($P = 0.025$); it was unlikely to be used with oxcarbazepine ($P = 0.053$) or carbamazepine ($P = 0.033$).

Other ASMs

Lamotrigine

Twenty-two (8.2%) patients with history of seizures were using lamotrigine. Patients who were using lamotrigine were associated with using a greater number of ASMs ($P < 0.001$; mean = 2.5 ± 1.1 versus 1.6 ± 1.0). Patients using lamotrigine were also associated with higher age at enrollment ($P < 0.001$; mean = 18.7 ± 15.2 years versus 8.9 ± 9.7 years in those using and not using lamotrigine respectively).

Lacosamide

Twenty-one (7.8%) patients with seizures were using lacosamide. Patients who were using lacosamide were associated with using a greater number of ASMs ($P < 0.001$; mean = 2.7 ± 1.0 versus 1.6 ± 1.0 in patients using and not using lacosamide, respectively).

Clobazam

Seven (2.6%) patients with seizures were using clobazam. Those who were using clobazam were associated with using a greater number of ASMs ($P < 0.001$; mean = 3.0 ± 0.6 versus 1.6 ± 1.0 in patients using and not using clobazam, respectively).

ASMs as monotherapy

One hundred and one (37.7%) patients with seizures were using one ASM. Oxcarbazepine (34.7%), levetiracetam (32.7%), and carbamazepine (11.9%) were the most frequently used ASMs for monotherapy. Fifty (49.5%) subjects on ASM monotherapy were also using low-dose aspirin.

Discussion

We present the results of the largest multicenter registry, and here we provide the evidences that levetiracetam and

TABLE 5.
P Values for Difference in Median Neuroscore for SWS Characteristics Related to ASM Use

Neuroscore Subscale	Lev (Median Using, Not Using)	Oxcarb (Median Using, Not Using)	Phenob (Median Using, Not Using)	Lamotr (Median Using, Not Using)	Lacos (Median Using, Not Using)	ASMs (Median Using, Not Using)	Aspirin (Median Using, Not Using)	Adults (Median Using ASMs, Not Using)	Hx of Brain Surgery (Median Using ASMs, Not Using)
Seizure	0.081 (2, 1)	0.686 (1.5, 2)	0.096 (2, 1)	0.911 (1.5, 2)	0.237 (2, 1.5)	0.063 (2, 0)	0.736 (2, 2)	0.273 (1, 0)	1.000 (1, 0)
Hemiparesis	0.132 (2, 1)	0.570 (1, 2)	**0.002** (3, 1)	0.629 (0.5, 1)	0.966 (1.5, 1)	0.667 (1, 0)	0.185 (2, 0.5)	1.000 (0, 0)	1.000 (1, 3)
Visual field cut	0.651 (0, 0)	0.694 (0, 0)	0.160 (0.5, 0)	0.244 (0, 0)	0.427 (0.5, 0)	1.000 (0, 0)	0.321 (0, 0)	1.000 (0, 0)	1.000 (0, 2)
Cognitive function	0.766 (1, 1.5)	0.914 (1, 1)	0.968 (1, 1)	0.517 (2, 1)	0.946 (1, 1)	0.706 (1, 1)	0.647 (1, 1)	1.000 (1, 1)	1.000 (1, 2)
Composite score	0.313 (5, 4)	0.690 (4.5.4.5)	**0.013** (6, 4)	0.933 (4, 5)	0.573 (5, 4.5)	0.269 (5, 2)	0.293 (5.5, 4)	0.364 (3, 1)	1.000 (3, 7)

Abbreviations:
ASM = Antiseizure medication
Hx = History
Lacos = Lacosamide
Lamotr = Lamotrigine
Lev = Levetiracetam
Oxcarb = Oxcarbazepine
Phenob = Phenobarbital
SWS = Sturge-Weber syndrome
Bold face denotes a significant *P* value.
"Lev"- Levetiracetam; "Oxcarb"- Oxcarbazepine; "Phenob"- Phenobarbital; "Lamotr"- Lamotrigine; "Lacos"- Lacosamide; Hx-History. Clobazam was not included because there was only one subject using clobazam with a neuroscore.

oxcarbazepine are the most common ASMs used in patients with SWS and seizures. The two medications were also the most common combination, and when a third medication was needed, lacosamide and phenobarbital were frequent adjuvant therapy. Low-dose aspirin was used in almost half of the patients with SWS and seizures. Our data revealed that bilateral brain involvement, early seizure onset, and positive family history for epilepsy were the most predictive factors for simultaneous use of multiple ASMs. Epilepsy surgery allows a subset of patients to come off ASMs and aspirin. Approximately 16% of adults with a history of epilepsy were not taking a seizure medication suggesting that some subjects may be able to wean off ASMs.

Risk factors associated with epilepsy outcome in SWS include age of seizure onset, bilateral brain involvement, extensive unilateral hemispheric disease, and positive family history of epilepsy.[6] In our study, a positive family history for epilepsy was associated with simultaneous multiple ASM use. In addition, patients with SWS with bilateral brain involvement were more likely to be using multiple ASMs. This data analysis confirms the results of previous studies that indicated worse prognosis in patients with bilateral brain disease suggesting more severe epilepsy.[2]

The epilepsy in SWS is often associated with focal seizures. The goal of the treatment is total seizure freedom and low risk of adverse effects of treatment. Based on evidence for efficacy and effectiveness as initial monotherapy for seizures with focal mechanism of onset, levetiracetam and oxcarbazepine are often the first choices.[12] These ASMs are the most frequently used ones in this observational study. The results of a previous study suggest that carbamazepine and oxcarbazepine should be preferred as the initial therapy, given better seizure control when compared with levetiracetam.[13]

SWS results in lesional epilepsy. The early mechanisms for epileptogenesis are certainly different in the mature brain, and the abnormal neuronal excitability may stabilize[14] as the patient ages. However, the low threshold for seizures remains and therefore long-term treatment with ASMs is likely necessary. Lamotrigine can be considered as monotherapy in adults,[12] and in our study levetiracetam and lamotrigine were the most common ASMs used by adults. More studies with longitudinal data in natural history are necessary.

Phenobarbital is a highly effective broad-spectrum ASM and has a significant role as adjuvant therapy in medically resistant epilepsy; however, because of its sedative and cognitive effects, it is rarely a drug of first choice. In this study, phenobarbital use was associated with bilateral SWS brain involvement and younger age at enrollment. The frequent use of phenobarbital in SWS is likely due to the refractory nature of seizures in SWS, where phenobarbital is used as a second- or third-line ASM as an attempt to gain control of seizures. Extent of glaucoma was associated with carbamazepine, phenytoin, and phenobarbital use; however, the relationship between these ASMs and glaucoma is uncertain given that the extent of brain involvement is significantly related to the extent of both the birthmark and glaucoma.

Lacosamide, approved as monotherapy for focal epilepsy,[12] was commonly reported in combination with levetiracetam and oxcarbazepine. Clobazam, a US Food and Drug Administration-approved ASM for adjuvant treatment of drug-resistant epilepsies,[15] was found to be typically used in combination with a greater number of ASMs in this cohort, suggesting that it is not often used early on in treatment and was chosen after failing medications more specifically indicated for focal seizures.

One of the hallmarks of SWS in the central nervous system is abnormalities in the medullary and subependymal veins as well as deep venous structures associated with impaired venous outflow.[16] Because venous congestion, stasis, and thrombosis predispose

patients with SWS to ischemia-related progressive brain injury, low-dose aspirin has been considered for management of seizures and stroke-like episodes. Retrospective studies and case reports have reported the potential benefits of aspirin in SWS.[17,18] In addition, there is a hypothesis that aspirin could be used in pre-symptomatic patients.[19] Prospective randomized studies will be necessary to establish the full spectrum of benefits of aspirin use in patients with SWS.

Epilepsy surgery in SWS offers the best option for the majority of the refractory epilepsy cases. Surgical modalities include lesionectomy, selected disconnection, callosotomy, and hemispherectomy.[20] Despite the well-documented effectiveness of surgery in SWS, optimal timing and patient selection remain controversial. The decision for surgery is often easier when patients with intractable epilepsy also present significant hemiparesis and developmental delay. However, determining the optimal timing for surgical intervention is more difficult for patients with relatively mild deficits. According to the database, patients who had epilepsy surgery were likely to come off ASMs.

Although the development of new medications and surgical options have helped seizure control in SWS, future considerations in management of neurological symptoms in SWS is necessary. Cannabidiol (CBD), a cannabinoid with nonpsychotropic action available in drug-resistant epilepsies, recently received US Food and Drug Administration approval in tuberous sclerosis complex (TSC) where focal seizures are most common, similar to SWS.[21] Kaplan et al. published the first series of patients with SWS treated with CBD. Based on the limited report, it seems that this is a safe choice for patients with SWS and intractable epilepsy.[22] Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus have been implicated in the treatment of SWS[23] for cognitive impairments, particularly in those with history of stroke-like episodes or impaired processing speed.[24]

Despite advances in the discovery of new ASMs and alternative epilepsy treatment, prevention of epilepsy remains one of the most important goals in individuals with SWS because seizures can increase the risk of stroke and brain injury. Early seizure onset has been associated with lower cognitive function neuroquality of life.[25] We therefore postulate that children with controlled seizures will have better prognosis. Animal studies have found that epilepsy can be prevented or modified before seizure onset.[26] From laboratory to clinical trials, disease-modifying treatments for epilepsy or use of ASMs have been considered in other diseases such as tuberous sclerosis.[27] A successful multicenter trial concluded that preventative ASM treatment of infants with TSC and high risk of epilepsy markedly improves their neurodevelopmental outcome and reduces the incidence of drug-resistant seizures.[28] Patients with TSC who will develop infantile spasms/epilepsy can be identified by electroencephalography during infancy. This reliable biomarker allows early and effective interventions in this population.[29] There are insufficient data to provide guidance on pre-symptomatic treatment for patients with SWS. However, SWS is a good disease model to develop presymptomatic approach given the opportunity to triage the high-risk patients by the port-wine birthmark characteristics. The symptoms typically occur after the neonatal period, providing a window for intervention. Work is underway to identify the mechanisms that enable the prevention or modification of epileptogenesis before seizure onset. Previous studies have used phenobarbital,[30] valproic acid, oxcarbazepine, and levetiracetam as well as low-dose aspirin in pre-symptomatic cases.[19] The most effective intervention is yet to be determined, but steps should be taken to modify or prevent epileptogenesis in SWS.

We acknowledge that there are limitations to our study, including that it was retrospective and included patient/parent-reported data. There is an unmet need to understand the natural history in SWS with neurological symptoms. This study design was not appropriate to evaluate the longitudinal aspects of SWS, to draw conclusions on long-term use of ASMs.

Conclusion

In patients with SWS, bilateral brain involvement and early onset of seizures were predictive factors for multiple ASM use. Levetiracetam, oxcarbazepine, and low-dose aspirin were the most commonly used medications. However, new options such as lacosamide, clobazam, and CBD might be considered.[22] Lamotrigine and levetiracetam were the most frequently used ASMs in adults. Epilepsy surgery was associated with ASM discontinuation. This is a questionnaire-based study, and it will be necessary to have a multicenter longitudinal study design to allow definite conclusions regarding long-term use of ASM and presymptomatic treatment in SWS.

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References

1. Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013;368:1971–1979.
2. Comi AM. Presentation, diagnosis, pathophysiology, and treatment of the neurological features of Sturge-Weber syndrome. Neurologist. 2011;17:179–184.
3. Gittins S, Steel D, Brunklaus A, Newsom-Davis I, Hawkins C, Aylett SE. Autism spectrum disorder, social communication difficulties, and developmental comorbidities in Sturge–Weber syndrome. Epilepsy Behav. 2018;88:1–4.
4. Sujansky E, Conradi S. Sturge-Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children. J Child Neurol. 1995;10:49–58.
5. Kossoff EH, Hatfield LA, Ball KL, Comi AM. Comorbidity of epilepsy and headache in patients with Sturge-Weber syndrome. J Child Neurol. 2005;20:678–682.
6. Kaseka ML, Bitton JY, Décarie J-C, Major P. Predictive factors for epilepsy in pediatric patients with Sturge–Weber syndrome. Pediatr Neurol. 2016;64:52–58.
7. Day AM, McCulloch CE, Hammill AM, et al. Physical and family history variables associated with neurological and cognitive development in Sturge-Weber syndrome. Pediatr Neurol. 2019;96:30–36.
8. Kelley TM, Hatfield LA, Lin DD, Comi AM. Quantitative atrophy analysis correlation with clinical severity in unilateral Sturge-Weber syndrome. J Child Neurol. 2005;20:867–870.
9. Kavanaugh B, Sreenivasan A, Bachur C, Papazoglou A, Comi A, Zabel TA. [Formula: see text] Intellectual and adaptive functioning in Sturge-Weber syndrome. Child Neuropsychol. 2016;22:635–648.
10. Hatfield LA, Crone NE, Kossoff EH, et al. Quantitative EEG asymmetry correlates with clinical severity in unilateral Sturge-Weber syndrome. Epilepsia. 2007;48:191–195.
11. Lin DD, Barker PB, Hatfield LA, Comi AM. Dynamic MR perfusion and proton MR spectroscopic imaging in Sturge-Weber syndrome: correlation with neurological symptoms. J Magn Reson Imaging. 2006;24:274–281.
12. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018;91:74–81.
13. Kaplan EH, Kossoff EH, Bachur CD, et al. Anticonvulsant efficacy in Sturge-Weber syndrome. Pediatr Neurol. 2016;58:31–36.
14. Pinto A, Sahin M, Pearl PL. Epileptogenesis in neurocutaneous disorders with focus in Sturge Weber syndrome. F1000Res. 2016;5. F1000 Faculty Rev-1370.
15. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Curr. 2018;18:269–278.
16. Sudarsanam A, Ardern-Holmes SL. Sturge-Weber syndrome: from the past to the present. Eur J Paediatr Neurol. 2014;18:257–266.

17. Lance EI, Sreenivasan AK, Zabel TA, Kossoff EH, Comi AM. Aspirin use in Sturge-Weber syndrome: side effects and clinical outcomes. J Child Neurol. 2013;28:213–218.
18. Triana Junco PE, Sánchez-Carpintero I, López-Gutiérrez JC. Preventive treatment with oral sirolimus and aspirin in a newborn with severe Sturge-Weber syndrome. Pediatr Dermatol. 2019;36:524–527.
19. Day AM, Hammill AM, Juhász C, et al. Hypothesis: presymptomatic treatment of Sturge-Weber syndrome with aspirin and antiepileptic drugs may delay seizure onset. Pediatr Neurol. 2019;90:8–12.
20. Di Rocco C, Tamburrini G. Sturge–Weber syndrome. Child's Nervous Syst. 2006;22:909.
21. Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia. 2016;57:1617–1624.
22. Kaplan EH, Offermann EA, Sievers JW, Comi AM. Cannabidiol treatment for refractory seizures in Sturge-Weber syndrome. Pediatr Neurol. 2017;71:18–23 e12.
23. Stafstrom CE, Staedtke V, Comi AM. Epilepsy mechanisms in neurocutaneous disorders: tuberous sclerosis complex, neurofibromatosis type 1, and Sturge-Weber syndrome. Front Neurol. 2017;8:87.
24. Sebold AJ, Day AM, Ewen J, et al. Sirolimus treatment in Sturge-Weber syndrome. Pediatr Neurol. 2021;115:29–40.
25. Harmon KA, Day AM, Hammill AM. Quality of life in children with Sturge-Weber syndrome. Pediatr Neurol. 2019;101:26–32.
26. Devinsky O, Vezzani A, O'Brien TJ, et al. Epilepsy. Nat Rev Dis Primers. 2018;4:18024.
27. Słowińska M, Jóźwiak S, Peron A, et al. Early diagnosis of tuberous sclerosis complex: a race against time. How to make the diagnosis before seizures? Orphanet J Rare Dis. 2018;13(1):25.
28. Jóźwiak S, Kotulska K, Domańska-Pakieła D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paediatr Neurol. 2011;15:424–431.
29. Wu JY, Goyal M, Peters JM, et al. Scalp EEG spikes predict impending epilepsy in TSC infants: a longitudinal observational study. Epilepsia. 2019;60:2428–2436.
30. Ville D, Enjolras O, Chiron C, Dulac O. Prophylactic antiepileptic treatment in Sturge-Weber disease. Seizure. 2002;11:145–150.