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RESEARCH ARTICLE

Retrospective analysis of presymptomatic treatment in Sturge–Weber syndrome

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Abstract

Background: Ninety percent of infants with Sturge–Weber syndrome (SWS) brain involvement have seizure onset before 2 years of age; early-onset seizures are associated with worse neurological outcome. Presymptomatic treatment before seizure onset may delay seizure onset and improve outcome, as has been shown in other conditions with a high risk of developing epilepsy, such as tuberous sclerosis complex. The electroencephalogram (EEG) may be a biomarker to predict seizure onset. This retrospective clinical data analysis aims to assess the impact of presymptomatic treatment in SWS.
Methods: This two-center, Institutional Review Board–approved, retrospective study analyzed records from patients with SWS brain involvement. Clinical data recorded included demographics, age of seizure onset (if present), brain involvement extent (unilateral versus bilateral), port-wine birthmark (PWB) extent, family history of seizures, presymptomatic treatment if received, Neuroscore, and antiseizure medications. EEG reports prior to seizure onset were analyzed.
Results: Ninety-two patients were included (48 females), and 32 received presymptomatic treatment outside of a formal protocol (five aspirin, 16 aspirin and levetiracetam; nine aspirin and oxcarbazepine, two valproic acid). Presymptomatically treated patients were more likely to be seizure-free at 2 years (15 of 32, 47% versus 7 of 60, 12%; $p < 0.001$). A greater percentage of presymptomatically treated patients had bilateral brain involvement (38% treated versus 17% untreated; $p = 0.026$). Median hemiparesis Neuroscore at 2 years was better in presymptomatically treated patients. In EEG reports prior to seizure onset, the presence of slowing, epileptiform discharges, or EEG-identified seizures was associated with seizure onset by 2 years ($p = 0.001$).
Conclusion: Presymptomatic treatment is a promising approach to children diagnosed with SWS prior to seizure onset. Further study is needed, including prospective drug trials, long-term neuropsychological outcome, and prospective EEG analysis, to assess this approach and determine biomarkers for presymptomatic treatment.

Keywords: epilepsy; presymptomatic treatment; Sturge–Weber syndrome; vascular malformation

Introduction

Sturge–Weber syndrome (SWS) is a neurovascular disorder characterized by a vascular anomaly of the brain. It is a rare disorder that occurs in about one in 20 000 to 50 000 live births worldwide and is usually caused by an R183Q somatic mosaic mutation in the *GNAQ* gene.[1–7] As a spectrum disorder, patients with SWS can have eye, skin, and/or brain involvement (Figure 1) with varying degrees of severity. Seizures are the most common neurological symptom in patients with brain involvement.[8] Perfusion deficits and venous hypertension result from the brain vascular malformations, and seizures further impair cerebral blood flow, resulting in brain atrophy, calcification, and injury over time.[9–12] SWS affects brain development in childhood, causing intellectual disability, motor impairments, and developmental delay.[13] The extent of brain involvement as seen on contrast-enhanced magnetic resonance imaging (MRI); presence of high-risk port-wine birthmark (PWB; see Figure 1, panel A) on the forehead, temple, or eyelids; and age at the time of seizure onset have all been suggested as predictors of severity of neurological, cognitive, and epilepsy outcomes.[14–17]

Most infants with SWS brain involvement experience seizures by 2 years of age, and seizure onset by age 2 years is a key milestone in the clinical course of SWS.[18] A greater extent of brain involvement has been associated with an earlier age of seizure onset and worse seizure severity.[16–20] Early seizure onset has been associated with lower IQ, increased hemiparesis severity, increased seizure activity, worse brain injury, and cognitive decline.[13,21–26] In a study of 33 young children with SWS, lower IQ was associated with younger age of seizure onset.[27] Studies have also suggested that the preservation of white matter may protect neurocognitive function and improve cognition in patients with SWS.[24] Other evidence from the epilepsy literature suggests that developmental and epileptic encephalopathies may cause intellectual disability.[28] Consequently, there is a pressing need to find treatments that can delay or even prevent seizure onset.

Presymptomatic treatment in SWS—treating patients before the onset of seizure symptoms—may delay or prevent seizure onset. Presymptomatic treatment for infants with SWS brain involvement was first suggested in 2002 with phenobarbital used presymptomatically. This 2002 retrospective study of 16 patients presymptomatically treated with phenobarbital, compared with 21 patients given standard treatment, suggested better seizure and cognitive outcome in individuals undergoing prophylactic treatment. Since then, two other small case series have been reported.[29,30] Research in conditions such as tuberous sclerosis has demonstrated that presymptomatic treatment delays seizure onset and decreases seizure severity.[31] It seems likely that other conditions associated with a high risk of early seizures would also benefit from presymptomatic treatment[28]; this

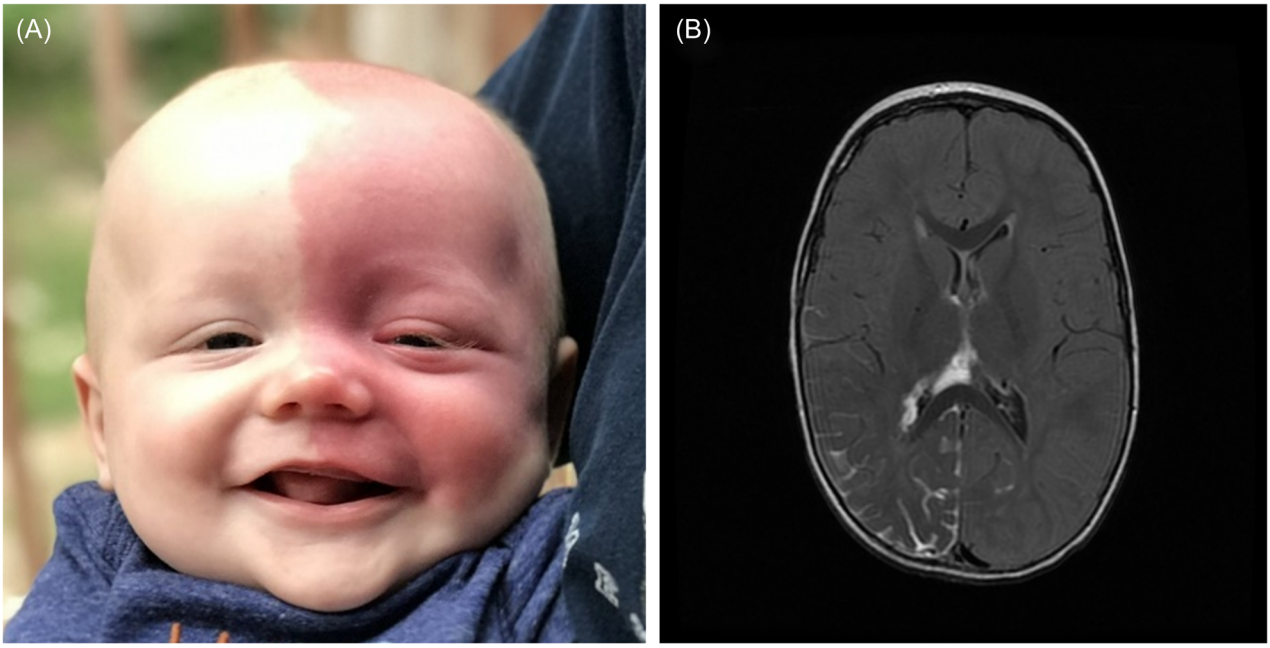

Figure 1. Infant with Sturge–Weber syndrome (SWS) in panel A has a high-risk left-sided facial port-wine birthmark covering the forehead, temple, and both eyelids. Magnetic resonance imaging (MRI) in panel B (from another patient) shows typical SWS right-sided leptomeningeal enhancement on axial postcontrast T2 fluid-attenuated inversion recovery MRI of the brain.

was hypothesized in earlier small cohorts of children with SWS.[29,30] We previously reported initial data from eight infants with SWS treated presymptomatically, prior to the onset of seizures, which suggested delayed seizure onset and improved seizure scores. Motivated by these early but small-sample-size studies, we hypothesized that presymptomatic treatment may delay seizure onset and improve the neurocognitive outcome in patients with SWS.

This multisite study aims to test this hypothesis using the largest number of patients to date. We analyzed 92 patients using retrospectively collected data from Boston Children's Hospital (BCH) and Kennedy Krieger Institute (KKI). We compared infants treated presymptomatically with those treated postsymptomatically (standard treatment) as part of a previously published protocol.[32] The effect was compared by the age of seizure onset, in these two groups, as well as SWS Neuroscores at 2 years of age.[33–35]

Research Methods

Ethics and dissemination

This study involves human participants and was approved by BCH Institutional Review Board (IRB): IRB-P00014482 and IRB-P00025916 and by Johns Hopkins School of Medicine Institutional Review Board: NA_00043846. Participants gave informed consent to participate in the study before taking part. Data were deidentified before being recorded in REDCap and combined for analysis.

Data collection

This two-center, retrospective, IRB-approved study analyzed data from 92 patients (30 from BCH and 62 from KKI) with SWS brain involvement, who either had consent waived (BCH) or previously consented to have their deidentified medical records studied (KKI). Inclusion criteria included (a) SWS brain involvement, including the typical leptomeningeal enhancement on contrast-enhanced brain MRI before 2 years of age as confirmed by an SWS expert (A. M. C. at KKI or A. P. at BCH), and (b) follow-ups to determine whether they had seizure onset by 2 years of age. Please see the flow diagram (Figure 2) for details on the subjects. Fifteen of these 92 children (eight given antiseizure medication [ASM] and aspirin and two given aspirin only presymptomatically; five standard treatments) had early data published previously.[16] Deidentified data were entered into a REDCap database.

Clinical data recorded include: demographics, PWB, and eye/glaucoma presence and extent (none, unilateral, or

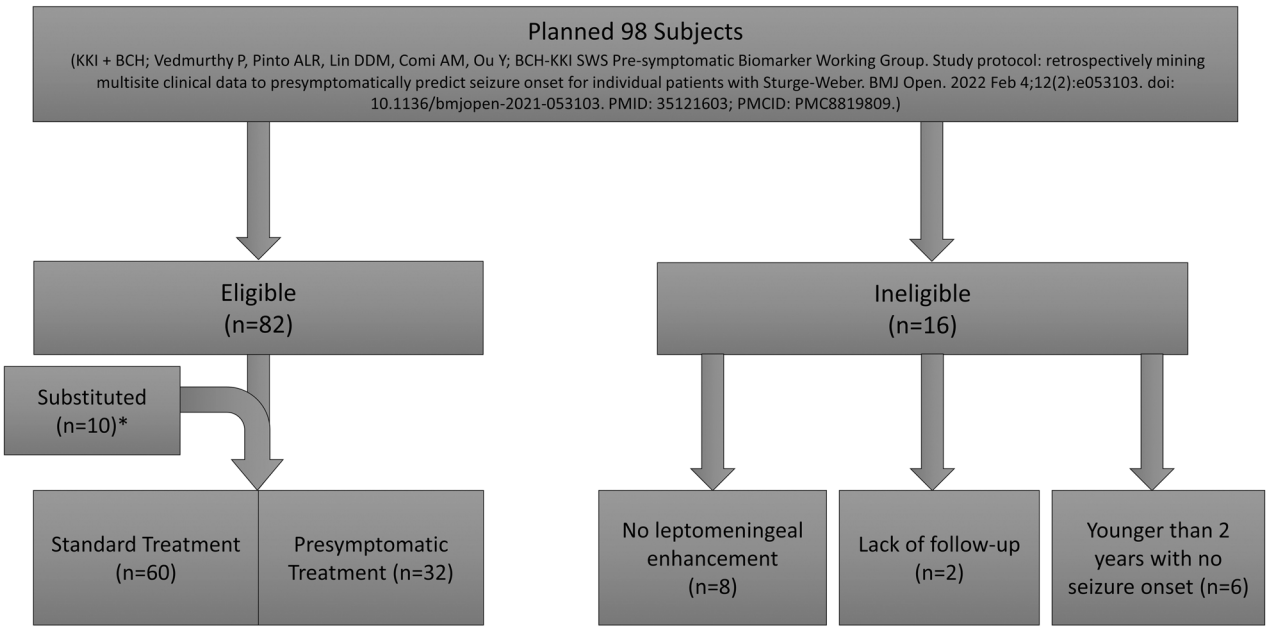

Figure 2. The flowchart depicts patients eligible for this study based on published protocol, including replacement of ineligible patients. Upon in-depth record review, 16 of the originally planned individuals had to be replaced due to a lack of Sturge–Weber syndrome brain involvement or sufficient follow-up. Those who were replaced were matched for sex, treatment, and extent of brain involvement.

bilateral); family history of seizure; clinical involvement scores (assigned for each subject based on laterality of brain involvement, eye, and skin involvement; see Supporting Information S1: Table 1); extent of brain involvement (none, unilateral, or bilateral); presymptomatic treatment used; presence or absence of seizures by 2 years of age; age of seizure onset (in days; if present); type of seizure (if present); and both current and discontinued seizure medications at 2 years old.[26] Among them, clinical involvement scores were assigned as follows: a score of 0 (no involvement), 1 (unilateral involvement), or 2 (bilateral involvement) for brain, eye, and skin. Possible total scores were between 1 (unilateral brain involvement) and 6 (bilateral brain, skin, and eye involvement).

SWS Neuroscore assigned at the clinical visit closest to 2 years was recorded. Neuroscores recorded more than 3 months before or after the participant's second birthday were not analyzed (see Supporting Information S1: Table 2). The Neuroscore (0–15) is composed of four subscores: presence/frequency of seizures (0–4), presence/severity of hemiparesis (0–4), presence of partial/full visual field cut (0–2), and cognitive function based on age (0–5). The cognitive function subscore scale is age dependent for the following age ranges: birth through preschool aged, school aged, and adult. Higher scores indicate a more severe disease presentation. This score has been previously validated through neuropsychological testing,[36] quantitative electroencephalogram (EEG),[37] and neuroimaging[10] and is used during other SWS treatment studies and prospective drug trials.[33–35] It is meant to be used as a clinical monitoring tool for patients with SWS. Clinical EEG reports were also reviewed by the same SWS expert clinicians before entry into the REDCap database. EEGs analyzed were completed before seizure onset and before 2 years of age; however, the availability of a presymptomatic EEG was not an inclusion criterion. Abnormal EEG activity recorded in the clinical database included the presence and location of asymmetry or decrease in voltage, excessive slowing, epileptiform discharges, and EEG-identified seizures.

Statistical analysis

All data were analyzed using nonparametric analyses (χ^2 tests of independence, Spearman correlations, Mann–Whitney *U*-test, Fisher exact test, Kruskal–Wallis test, and Kaplan–Meier survival estimator) to study (1) which factors were associated with earlier age of seizure onset, two-sided Mann–Whitney *U*-test and independent-samples Kruskal–Wallis tests; (2) EEG for development as a biomarker for age of seizure onset, two-sided χ^2 tests of independence and sensitivity, specificity, positive and negative predictive values were calculated for EEG data; (3) whether presymptomatic treatment was associated with a difference in seizure onset by 2 years, a two-sided χ^2 test of independence and the Kaplan–Meier survival estimator; and (4) whether presymptomatic treatment was associated with improved Neuroscore, a two-sided Mann–Whitney *U*-test. See Figure 3 for overview. A binary logistic model was performed including presymptomatic treatment and clinical factors that prior studies have indicated are predictive of outcome in patients with SWS (extent of brain involvement, extent of skin involvement, and sex) to determine which factors predicted seizure onset by 2 years. All analysis was performed with SPSS (Statistical Package for Social Sciences) version 28.0.1.1. The significance level for all analyses was $p < 0.05$.

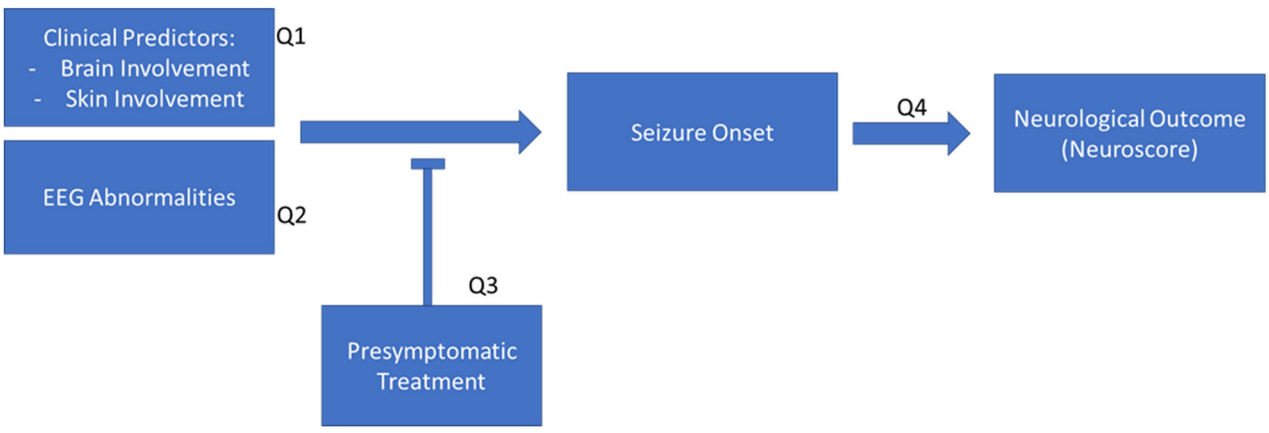

Figure 3. Diagram shows the questions that this study focuses on answering and the relationship between clinical and diagnostic predictors, presymptomatic treatment, seizure onset, and neurological outcome. EEG, electroencephalogram.

Results

Demographics

All patients were born between 2008 and 2021. This study included 92 patients (48 females and 44 males). Demographics are detailed in Table 1.

Of those with seizure onset by 2 years of age ($n = 70$; 41 females), the median age of seizure onset was 199 days for those with unilateral brain involvement versus 112 days for those with bilateral brain involvement ($p = 0.006$, Mann–Whitney *U*-test). For children with no PWB, the median age of seizure onset was 228 days, 261 days for those with unilateral PWB and 123 days for those with a bilateral PWB ($p = 0.005$, Kruskal–Wallis). This significant difference in seizure onset was driven by the relationship between unilateral and bilateral brain involvement ($p = 0.006$ Kruskal–Wallis, adjusted by the Dunn–Bonferroni correction for multiple tests). A family history of seizure was not associated with earlier seizure onset.

Table 1. Demographics for both standard treatment and presymptomatically treated children.

	Nonpresymptomatically treated ($n = 60$)	Presymptomatically treated ($n = 32$)
Male	29 (48%)	15 (47%)
Female	31 (52%)	17 (53%)
Brain involvement	50 unilateral; 10 bilateral	20 unilateral; 12 bilateral
Race	39 White 3 Black 6 Asian 5 multiracial 3 other 4 unknown	24 White 2 Asian 1 multiracial 1 other 4 unknown
Ethnicity	46 non-Hispanic or Latino 10 Hispanic or Latino 4 unknown	25 non-Hispanic or Latino 3 Hispanic or Latino 4 unknown

Presymptomatic treatments

Sixty children (31 females) were not presymptomatically treated and 32 were presymptomatically treated (17 females); 20% of BCH patients and 42% of KKI patients ($p = 0.038$). The median age at first visit to the centers was 227 days in the standard treatment group and 101.5 days in the presymptomatically treated group ($p < 0.001$, Mann–Whitney *U*-test). Presymptomatic treatment included five patients on low-dose aspirin only, 16 on low-dose aspirin with levetiracetam, nine on low-dose aspirin with oxcarbazepine, and two on valproic acid only. Due to limited sample size in individual treatment types, all presymptomatically treated patients were merged into one group for analysis, regardless of the specific ASM. This strategy is the same as what was used in our previous hypothesis paper.[29]

Presymptomatic treatment and seizure onset by 2 years of age

Seizure onset by age 2 was experienced by 88% of standard postsymptomatic treated children and 53% of those who were presymptomatically treated ($\chi^2(1, 92) = 14.2$, $p < 0.001$). In those with seizure onset, the median age of seizure onset was 166 days in the standard treatment group and 297 days in the presymptomatic treatment group (nonsignificant). A Kaplan–Meier survival estimate and curve were generated for age of seizure onset (in days) in presymptomatically treated and nonpresymptomatically treated groups (see Figure 4). Survival distributions between the two groups were significantly different ($p < 0.001$), with the age of seizure onset being significantly older in the presymptomatically treated group. Thirty-three percent of those on low-dose aspirin and oxcarbazepine ($n = 16$) experienced seizure onset by age 2. This is compared with the 69% of those on low-dose aspirin and levetiracetam ($n = 9$) who had seizure onset by age 2 ($p = 0.115$; with no significant difference between these two groups in extent of brain or skin involvement, clinical involvement score, or Neuroscore at 2 years of age).

There was a significantly higher total clinical involvement score in the presymptomatically treated group when compared with the standard treatment group (median score 4, interquartile range: 2–4 versus a median of 3, interquartile range: 2–4, $p = 0.023$; see Table 2). A significantly higher percentage of individuals with bilateral brain involvement were in the presymptomatically treated group (38% versus 17%) than in the standard treatment group ($\chi^2(1, 92) = 5.0$, $p = 0.026$; see Figure 5). Children in the presymptomatically treated group also had a greater extent of skin involvement (53% bilaterally affected in the presymptomatic group versus 28% in the standard treatment group, $p = 0.004$; see Table 3).

The binary logistic regression model correctly predicted seizure onset by two in 77.2% of participants, including 90% of those who experienced seizure onset and 36% of those who did not. Model estimates suggested that standard postsymptomatically treated patients were 9.24 times more likely to have seizure onset by 2 years ($p < 0.001$, 95% CI: 2.74–31.19). In this regression model, females were 3.67 times more likely to have seizure onset by 2 years ($p = 0.029$, 95% CI: 1.139–11.834). Extent of brain and skin involvement was not significant in explaining seizure onset by 2 years in the model estimate.

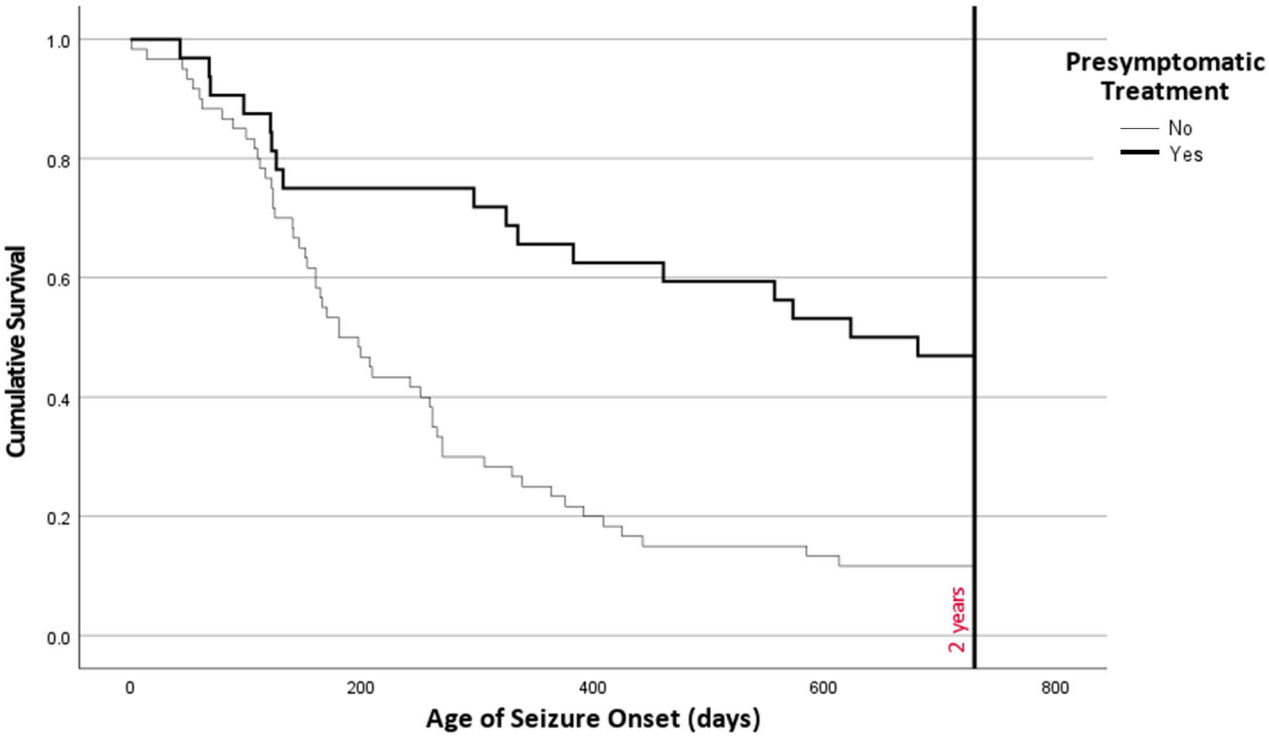

Figure 4. Kaplan–Meier survival curves show the age of seizure onset data in the presymptomatic and standard treatment groups, with a follow-up duration of two years after birth (in days). At age 2, 45.2% of presymptomatically treated patients (bolded line) had not experienced seizure onset, while in the standard treatment group, only 13.2% had no seizure onset by 2 years of age.

Table 2. Extent of SWS involvement grouped by age of seizure onset.

Comparison between seizure onset by 2 years and Sturge–Weber extent							
		Seizure onset before 2		No seizure onset before 2		Median age of	
Sturge–Weber extent	Extent of involvement	*n*	%	*n*	%	seizure onset (days)	*p* value
Brain involvement	Unilateral	53	75.5	17	77.3	199.0	**0.006**
	Bilateral	17	24.3	5	22.7	112.0	
Skin involvement	None	10	14.3	0	0	228.0	**0.005**
	Unilateral	33	47.1	15	68.2	261.0	
	Bilateral	27	38.6	7	31.8	123.0	
Eye involvement	None	34	48.6	13	59.1	198.0	0.272
	Unilateral	23	32.9	6	27.3	180.0	
	Bilateral	13	18.6	3	13.6	110.0	
Total SWS involvement	1	10	14.3	0	0	228.0	0.057
	2	14	20.0	11	50.0	267.5	
	3	19	27.1	2	9.1	180.0	
	4	16	22.9	7	31.8	140.5	
	5	3	4.3	0	0	62.0	
	6	8	11.4	2	9.1	84.5	

Note: *n* is the number of patients per group. % indicates the percentage of patients who presented with the indicated extent of SWS brain, skin, or eye involvement. Individuals with bilateral brain or skin involvement had a younger median age of seizure onset. Bolded *p* values have achieved significance with $p < 0.05$.
Abbreviation: SWS, Sturge–Weber syndrome.

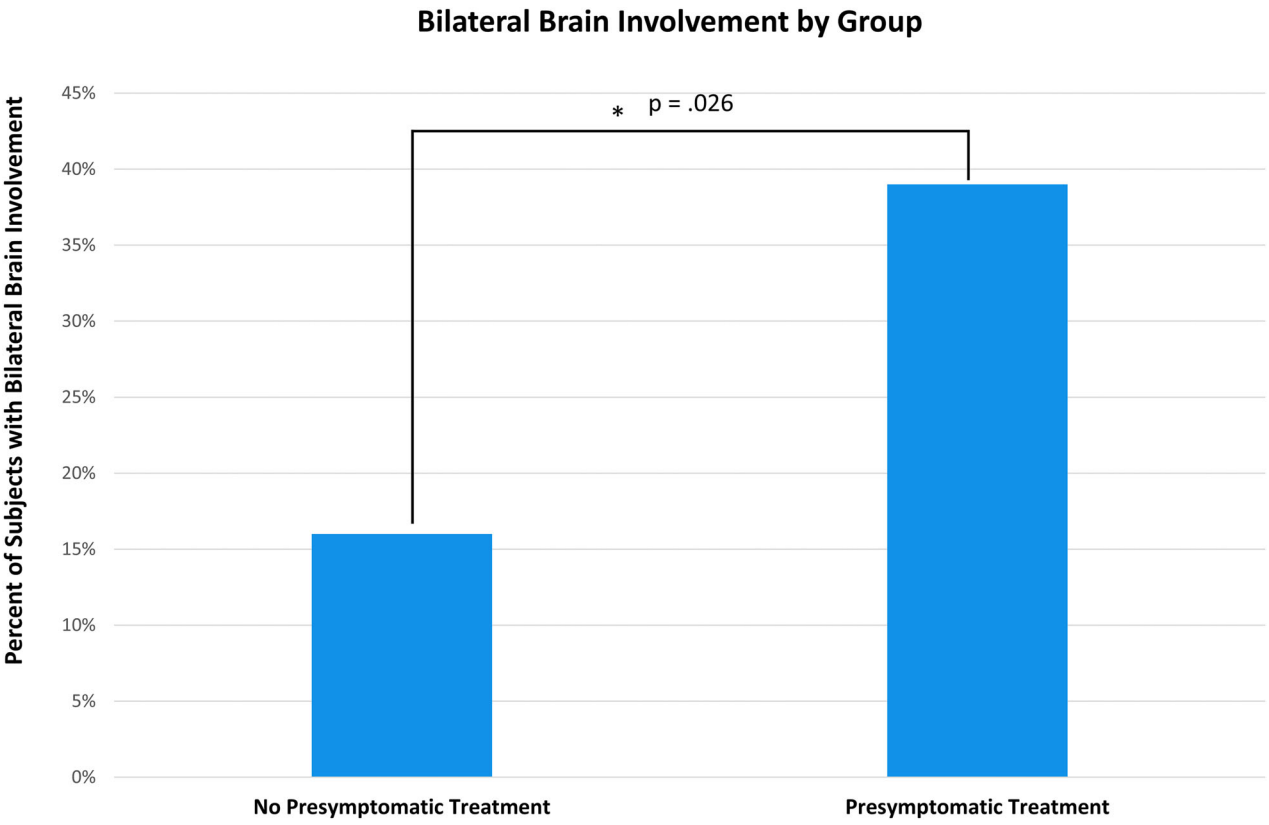

Figure 5. Bar graph shows a significantly higher percentage of patients with bilateral brain involvement in the presymptomatically treated group compared with patients in the standard treatment group.

Table 3. Extent of SWS involvement by treatment groups.

Comparison between treatment groups and Sturge–Weber extent						
		Standard treatment group		Presymptomatic treatment group		
Sturge–Weber extent	Extent of involvement	*n*	%	*n*	%	*p* value
Brain involvement	Unilateral	50	83.3	20	62.5	**0.026**
	Bilateral	10	16.7	12	37.5	
Skin involvement	None	10	16.7	0	0	**0.004**
	Unilateral	33	55.0	15	46.9	
	Bilateral	17	28.3	17	53.1	
Eye involvement	None	31	51.7	16	50.0	0.836
	Unilateral	19	31.7	10	31.3	
	Bilateral	10	16.7	6	18.8	
Total SWS involvement	1	10	16.7	0	0	**0.023**
	2	16	26.7	9	28.1	
	3	16	26.7	5	15.6	
	4	10	16.7	13	40.6	
	5	3	5.0	0	0	
	6	5	8.3	5	15.6	

Note: *n* is the number of patients per group. % indicates the percentage of patients in the standard or presymptomatic treatment group, who presented with the indicated extent of brain, skin, or eye involvement. Individuals in the presymptomatically treated group were more likely to have bilateral brain or skin involvement and higher total involvement scores. Bolded *p* values have achieved significance with $p < 0.05$.
Abbreviation: SWS, Sturge–Weber syndrome.

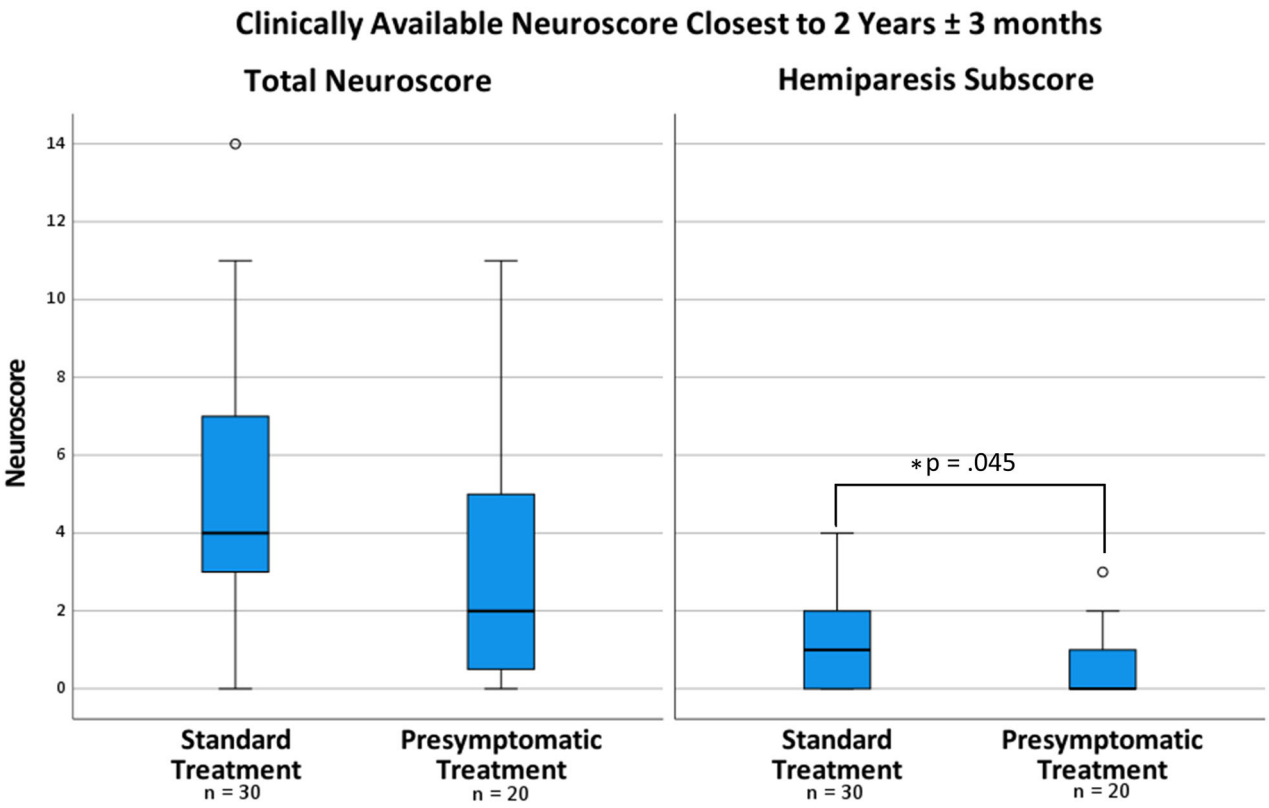

Figure 6. Box plots for total Sturge–Weber syndrome Neuroscore and hemiparesis subscore closest to age 2 years ± 3 months. In the presymptomatically treated group, there is a trend for a lower total Neuroscore and a significantly lower hemiparesis subscore (where lower scores indicate better neurological function) when compared with the standard treatment group.

Presymptomatic treatment and other neurological outcome at 2 years of age

Total SWS Neuroscore demonstrated a trend for better neurological outcome at 2 years ± 3 months in the presymptomatically treated group (see Figure 6); $p = 0.064$. Hemiparesis subscores were significantly better in the presymptomatically treated patients compared with the nonpresymptomatically treated patients (see Figure 6); $p = 0.045$.

EEG abnormality and seizure onset by 2 years of age

In the entire data set (both presymptomatic and standard treatment groups; see Supporting Information S1: Table 3), children who had seizure onset before 2 years of age were also significantly more likely to have an EEG that reported either slowing, epileptiform discharges, or EEG seizures, $n = 14$ EEGs (10 patients). Ninety-three percent (13/14) of EEGs had seizure onset by 2 years of age, $\chi^2(1, 56) = 10.6$, $p = 0.001$. These data result in a sensitivity of 41.9% and a specificity of 96% for seizure onset by 2 years of age, and with a 90% prevalence of seizure onset by 2 years, these clinical EEG reports have a positive predictive value of 99% and a negative predictive value of 16%. Adding asymmetric or decreased voltage as a factor did not increase the predictive value.

The time between the first reported abnormal EEG and seizure onset ranged from 6 to 516 days, median = 67 days; 6 (five patients) of these EEGs were from presymptomatically treated children. Only three children with these abnormalities had more than one EEG performed before seizure onset; of these, two had consistently reported slowing. All three EEGs (two subjects) with reported subclinical EEG seizures prior to clinical seizure onset experienced clinical seizure onset before 2 years.

Discussion

We aimed to study whether presymptomatic treatment can effectively delay seizure onset in SWS and result in improved neurological outcome. Without intervention, about 90% of patients with SWS brain involvement will experience seizure onset by 2 years of age.[18] The results of this multisite and relatively large sample ($N = 92$)

extension of a prior single-site and small sample ($N = 15$) study[29] are consistent with previously reported studies; 88% of the subjects in the group receiving treatment only after seizure onset (e.g., standard care at this time) developed clinical seizures by 2 years. Only about half of the 32 presymptomatically treated patients with SWS brain involvement had seizure onset by 2 years of age, suggesting that presymptomatic treatment is beneficial in delaying seizure onset. These data support our previous pilot case series.[29] In addition, this study's results indicate that neurological status at 2 years of age may be better in those who were presymptomatically treated than in children with SWS brain involvement receiving standard, postsymptomatic treatment; this has not been previously reported. While long-term cognitive, epilepsy, and neurological data are still needed in these patients, the data reported here support offering presymptomatic treatment to patients with extensive brain involvement.

Early seizure onset is associated with worse long-term neurocognitive outcome and seizure activity in SWS.[13,22] This may be attributed to the cortical–subcortical structure abnormalities causing impaired blood flow. The onset of seizures can further disrupt blood flow and cause cortical damage, which in turn worsens long-term outcome; potentially as a result, cognitive impairment by school age is common in SWS.[10,38] Early seizure onset is associated with status epilepticus; therefore, seizures in SWS worsen blood flow, and venous strokes or stroke-like episodes associated with seizures are common in young children with SWS.[18,22,39] A significant delay in seizure onset may allow for more normal neurological development in infants with SWS brain involvement and may result in decreased brain injury and neurological impairment.[29,30]

The most commonly received postsymptomatic ASM given to infants and young children at our centers for SWS is either oxcarbazepine or levetiracetam in combination with low-dose aspirin (about 3–5 mg/kg/day). These were also the most commonly used presymptomatic treatment methods in our patients; moderate doses of ASM between 35 and 45 mg/kg/day have been the most effective. The combination of ASM and low-dose aspirin aims to address the blood flow issues and seizures underlying brain injury in SWS. Oxcarbazepine has been associated with better seizure control than levetiracetam in SWS[40]; while this difference did not achieve significance in our analyses, a higher percentage of patients remained seizure-free by age 2 years on oxcarbazepine and low-dose aspirin than those on levetiracetam and low-dose aspirin. Further evaluation of oxcarbazepine as a presymptomatic treatment in SWS is needed, especially in light of the widespread use of levetiracetam in the United States as a first-line treatment. Low-dose aspirin use in SWS is associated with decreased seizures and decreased stroke-like episodes.[41–43] Side effects associated with low-dose aspirin use include increased bruising and bleeding of the gums or nosebleeds[41–43]; serious side effects of low-dose aspirin use are rarely reported. With dosage adjustments, most children with SWS tolerate low-dose aspirin well[41,42]; however, this approach is still controversial among some centers and clinicians.

Historically, a greater extent of brain involvement in SWS is associated with an earlier age of seizure onset,[16–18] and data from this study also indicate that bilateral brain involvement is associated with an earlier age of seizure onset. Early age of seizure onset is associated with intellectual disability and great seizure severity.[22] PWB extent is also associated with earlier age of seizure onset,[16] and our data indicated this as well. The presymptomatic use of low-dose aspirin and ASMs may be most beneficial in patients with extensive unilateral involvement or bilateral involvement who have the highest risk of seizures and neurocognitive deficits. Typically, at both our sites, parents of patients with three or more lobes of SWS brain involvement are offered presymptomatic treatment. Furthermore, there was a significantly higher percentage of bilaterally involved children in the presymptomatic treatment group; providers typically target patients with more extensive brain involvement for presymptomatic treatment, but this does suggest that later seizure onset in this group is likely not due to less SWS brain involvement. A single prior study indicated that a family history of seizures and a greater extent of skin involvement may impart a higher risk of early seizure onset[16]; however, results from our data were not consistent with this finding. Extent of PWB and brain involvement may be useful markers for prognosis and may help identify children who may benefit the most from presymptomatic treatment. Further studies are needed to determine what combination of factors best predicts the onset of seizures by 2 years of age.

EEG abnormalities and quantitative EEG have been used to screen for SWS brain involvement in high-risk infants,[44,45] but the question of whether EEG abnormalities can predict the age of seizure onset by 2 years of age has not been evaluated. Our EEG data analysis suggests that the presence of slowing, epileptiform discharges or subclinical seizures through an EEG is strongly associated with seizure onset by 2 years of age. Importantly, the time between obtaining both the EEG and the MRI where abnormality is first detected and seizure onset suggests that in most cases, clinicians have several weeks to initiate pharmacological intervention. Further prospective studies are needed to confirm these findings and assess the timing and frequency of EEGs to predict seizure onset.

Much like patients with SWS, patients with tuberous sclerosis complex are at a high risk of developing epilepsy, and these patients have been shown to benefit from presymptomatic diagnosis and treatment.[46,47] Presymptomatic treatment in tuberous sclerosis complex has been shown to improve seizure control and reduce the risk of intellectual disability.[48] Treatment during the presymptomatic phase in tuberous sclerosis complex sets precedence for presymptomatic treatment in other developmental epilepsy disorders, like SWS, where a high percentage of patients will have seizure onset in the first few years of life, and where early age of seizure onset has been repeatedly associated with worse neurological and developmental outcome.[49–51] More studies are needed to establish that presymptomatic treatment improves long-term neurological and cognitive outcomes in SWS. In the meantime, however, these results strongly suggest that presymptomatic treatment can significantly delay seizure onset in these infants.

We propose, therefore, that for now infants with a high-risk facial PWB be seen by a Sturge–Weber specialist so that early diagnosis of brain involvement on MRI can be made and presymptomatic treatment considered. Based on this preliminary data, EEG may be considered to facilitate prediction of seizure onset by 2 years and, along with obtaining a nonsedated, noncontrast MRI in very young infants, may aid timing for initiation of treatment. However, there is an urgent need for more extensive prospective trials to determine whether EEGs can help to identify those patients who will most benefit from presymptomatic treatment and provide clinically useful information, such as when seizure onset is expected and the optimal presymptomatic dosing of medication.

Limitations

While this study is the first to present the results of presymptomatic treatment from more than one center and a comparatively large number of subjects, this is a retrospective study with the limitations inherent in that study design. Physicians typically recommended presymptomatic treatment in patients who have three or more lobes of involvement, and caregivers decided whether treatment would be initiated. SWS is a rare disease, making prospective clinical trial studies very challenging; nevertheless, additional prospective studies are needed. This study is also limited by not having longer term neuropsychological data to analyze as an additional outcome measure to assess whether delaying seizure onset improves neurocognitive outcome. More study of the long-term efficacy of presymptomatic treatment is necessary. Small sample size for specific types of ASM also limits our ability to identify whether certain ASMs are more effective than others when presymptomatically treating infants with SWS. The retrospective nature of the study led to an inconsistent therapeutic design, and we could only faithfully document the inconsistency in the treatments. Future larger, prospective, and randomized studies are needed to systematically compare different presymptomatic treatment strategies. Due to the nature of this study, the exact age when patients initiated monitoring for possible SWS was not readily available for all patients. Nevertheless, the median age at first visit to our centers was statistically younger in the presymptomatically treated group. Most individuals in this study were White. As we currently understand it, SWS has no known race predilection. This important limitation likely reflects disparities in referral patterns, as well as in the ability of patients to travel to these tertiary care centers of SWS expertise. Only patients who consented to have their records studied were included in this study, and this introduces a self-selection bias that could also be a factor, especially in whether a family consented to start presymptomatic treatment. Further studies are needed to determine whether PWB on darker-skinned infants is less likely to be readily apparent and to trigger appropriate referrals. Understanding these underlying disparities will be important to addressing them and ensuring that all children have access to optimal medical care.

Future directions

Prospective, randomized studies on presymptomatic treatment are needed to determine whether that treatment improves neurocognitive outcome in SWS. A study to confirm biomarkers for seizure onset is also necessary in this population. Large-scale, multisite, and comprehensive data will be needed to power multivariate analysis and data-driven biomarker discovery. Future studies combining clinical factors and MRI variables are planned to determine which patients will most benefit from presymptomatic treatment. If it is proven that early seizure onset results in worse neurological outcome and that presymptomatic treatment both delays the age of seizure onset and improves neurodevelopmental outcome, then early identification of SWS brain involvement and subsequent intervention of those at high risk for seizure activity would become a medical imperative.

Author Contributions

Chelsea B. Valery: Data curation; formal analysis; writing—original draft; writing—review & editing. **Isabelle Iannotti:** Data curation; formal analysis; writing—original draft; writing—review & editing. **Eric H. Kossoff:**

Conceptualization; writing—review & editing. **Andrew Zabel:** Conceptualization; writing—review & editing. **Bernard Cohen:** Conceptualization; writing—review & editing. **Yangming Ou:** Funding acquisition; methodology; writing—review & editing. **Anna Pinto:** Conceptualization; funding acquisition; methodology; supervision; writing—review & editing. **Anne M. Comi:** Conceptualization; funding acquisition; methodology; supervision; writing—review & editing.

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Conflicts of Interest

Anne M. Comi, Anna Pinto, and Eric H. Kossoff are members of the ACNS editorial board.

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