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Original Article

Physical and Family History Variables Associated With Neurological and Cognitive Development in Sturge-Weber Syndrome

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ABSTRACT

Background: Sturge-Weber syndrome (SWS) is caused by a somatic mutation in *GNAQ* leading to capillary venous malformations in the brain presenting with various neurological, ophthalmic, and cognitive symptoms of variable severity. This clinical variability makes accurate prognosis difficult. We hypothesized that the greater extent of physical factors (extent of skin, eye, and brain involvement), presence of possible genetic factors (gender and family history), and age of seizure onset may be associated with greater symptom severity and need for surgery in patients with SWS.
Methods: The questionnaire was collected from 277 participants (age: two months to 66 years) with SWS brain involvement at seven US sites.

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Brain involvement
Port-wine birthmark
Glaucoma

Results: Bilateral brain involvement was associated with both learning disorder and intellectual disability, whereas port-wine birthmark extent was associated with epilepsy and an increased likelihood of glaucoma surgery. Subjects with family history of vascular birthmarks were also more likely to report symptomatic strokes, and family history of seizures was associated with earlier seizure onset. Learning disorder, intellectual disability, strokelike episodes, symptomatic stroke, hemiparesis, visual field deficit, and brain surgery were all significantly associated with earlier onset of seizures.
Conclusion: The extent of brain and skin involvement in SWS, as well as the age of seizure onset, affect prognosis. Other genetic factors, particularly variants involved in vascular development and epilepsy, may also contribute to neurological prognosis, and further study is needed.

Introduction

Sturge-Weber syndrome (SWS) is a neurocutaneous disorder characterized by capillary venous malformations in the skin, eye, and brain. Characteristic signs include facial port-wine birthmark (PWB), glaucoma and choroidal hemangioma, and a leptomeningeal vascular malformation with other brain malformations and cognitive abnormalities. The disorder is caused by a R183Q somatic mutation in *GNAQ* leading to abnormal blood vessels.[1] Symptoms and presentation can vary widely. Brain involvement can range from a small area of unilateral parietal-occipital brain involvement to extensive bilateral whole-hemisphere involvement. Symptoms can range from controlled seizures, mild learning issues, and fine motor deficits to vision loss, hemiparesis, medically refractory seizures, symptomatic strokes/strokelike episodes, and severe intellectual disability.

The extent of brain involvement is an important predictor of patient prognosis, with bilateral involvement being associated with earlier seizure onset and increased risk of intellectual disability.[2] The pattern and severity of a patient's PWB have been shown to predict not only the presence of SWS brain involvement but also brain involvement extent and severity of neurological impairment based on neurological scores.[3-5] In addition, the extent of PWB predicts ophthalmic involvement.[6] Regardless of the extent of brain involvement, early seizure onset, itself, is associated with a greater risk of early developmental delay and greater incidence of patients requiring special education classes.[7] Those with seizure onset before age six months are associated with a more severe hemiparesis.[8]

The extent of involvement in SWS has been hypothesized to be due to the timing of the somatic mutation in fetal development, with more extensive involvement of the brain, skin, and eye likely being due to a somatic mutation earlier in embryogenesis and therefore more likely have (1) an impact on a greater number of structures (brain, skin, and eye), (2) more extensive involvement of the body, and (3) an impact on a greater number of cell types.[1] This hypothesis may explain, in part, why patients with brain and skin involvement have earlier onset and more severe seizures compared with those with brain involvement only. We hypothesized that our analysis would support associations of physical factors such as brain, skin, and/or eye involvement with more extensive symptom presentations/comorbidity presentations such as hemiparesis or intellectual disability, which would suggest that these factors contribute to the severity of outcome. Our second hypothesis predicted a possible association of inherited genetic factors to the variability in SWS.

To address this hypothesis, we used a questionnaire to further develop an understanding of how physical factors (brain involvement and PWB), genetic factors (gender and family history [FHx]), and seizure onset may be associated with the symptoms, comorbidities, and need for surgery in patients with SWS.

Methods

Data collection

The data analyzed in this study were collected through a patient/parent questionnaire (Supplemental Figure 1) collected from seven different sites participating in the Brain Vascular Malformation Consortium. National Institutes of Health, Johns Hopkins University, and local institutional review board approvals were obtained, and all subjects consented to participate. Questionnaires were filled out in one of three ways; by the participant themselves, by the participant's parent/guardian, or by the study staff reading the questions to the participant and transcribing their answers onto the sheet. The questionnaire could be filled out either in person (in most cases) or over the phone. Twenty-three participants were recruited through phone or e-mail without being seen at the clinic but only after magnetic resonance imaging (MRI) source documentation was obtained. Subjects with brain involvement, determined by contrast-enhanced MRI of the brain, were eligible. Review of the imaging was done whenever possible; however, potential subjects were required to provide a neuroradiology report at minimum to qualify. All answers in the questionnaire were from patient or parent report rather than from direct clinical notes. “unknown” or “unattainable” were both given as options for the questionnaire. Definitions of certain symptoms/comorbidities have not been entirely agreed upon within the academic and medical communities. Symptomatic stroke in this context pertains to “an abrupt onset of a new neurological deficit which does not fully resolve within a period of one month.” Strokelike episodes are defined as “a period of weakness or other deficit on one side of the body lasting longer than 24 hours.” These definitions can be found in the questionnaire as part of Supplemental Figure 1. Intellectual disability in this article refers to the co-morbidity of mental retardation in the questionnaire. Visual field deficit in this article refers to visual field cut in the questionnaire. At analysis, attention deficit disorder (ADD) and attention-deficit/hyperactivity disorder (ADHD) were combined into one variable. This variable was marked “yes” if the participants had one or both of the disorders checked.

Database creation

All data were uploaded by the study staff at the individual sites into the Rare Diseases Clinical Research Network database. Data were compiled into a unified database on the Rare Diseases Clinical Research Network and checked by each respective site before

analysis. All data were then cleaned by the University of California San Francisco in cooperation with the participating sites to detect and correct any inaccurate or incomplete data points using source documentation, clinic notes, and patient contact, if necessary. Brain involvement extent reported by the participant was checked for accuracy against MRIs (disks or reports) obtained by the enrollment site as part of enrollment criteria.

Data analysis

Data analysis was done in IBM SPSS Statistics 24 at the Kennedy Krieger Institute (KKI). Frequencies were compared between KKI and all the other groups together to determine if there were any significant differences in participant answers based on clinic location because the majority of subjects were recruited from the KKI site (see Supplemental Table 1).

Population Demographics

Simple frequencies were generated to analyze the makeup of the study population in the areas of FHx, gender, ethnicity, race and age, and the frequency of SWS characteristics and symptoms.

SWS involvement

Chi-square analyses were done to determine the associations between the extent of brain involvement (uni- or bilateral), glaucoma presence/extent (none, uni- or bilateral) or presence/extent of PWB (none, uni- or bilateral), and symptoms/comorbidities/surgeries.

Gender analysis

Gender was analyzed for associations with comorbidities/symptoms using either chi-square or Fisher's exact tests.

Family history analysis

FHx collection included the patient's siblings, parents, and grandparents. FHx was analyzed using chi-square statistics and Fisher's exact tests to determine associations between the presence of conditions within the family and the likelihood of reporting comorbidities, brain involvement extent, and PWB extent.

Age subgroup analyses

Demographic, FHx, and gender analyses were performed using the entire database population and then again using only those older than six years at the time of data collection. During analysis, we found that participants were more likely to answer “unknown” at younger ages of enrollment for symptoms that are usually diagnosed later in development as many of the co-morbidities would not be properly identified or diagnosed until roughly school age (approximately six years old). For example, headaches and learning disorders are difficult to diagnose before the child is talking and in school. Headaches, ADHD, ADD, autism spectrum disorder, mood disorder, intellectual disability, learning disorder, and behavioral disorder were analyzed in this way. Puberty problems were analyzed using those nine years old or older as puberty problems are not identified until even later in development. A subset analysis was performed using participants with seizure onset before age six months to analyze potential gender differences in comorbidities linked to symptomatic strokes and strokelike episodes similar to what has been seen in past stroke literature.[9-11]

Age of seizure onset

Associations with age of seizure onset were tested using survival analysis techniques. If no seizure onset occurred, age of follow-up was censored at the participant's age at questionnaire collection. Group comparisons were conducted using log-rank tests.

TABLE 1.
Population Statistics

Demographics	Number of SWS Participants (n = 277)
Age	
Children (<18 years old)	237 (85.6%)
Adults	40 (14.4%)
Gender	
Female	149 (53.8%)
Race	
Caucasian (white)	233 (84.1%)
African American (black)	24 (8.7%)
Asian	21 (7.6%)
American Indian or Alaskan native	4 (1.4%)
Native Hawaiian or other Pacific Islander	2 (0.7%)
Brain involvement	
Unilateral	226 (81.6%)
Bilateral	51 (18.4%)
Port-wine birthmark	
None	33 (11.9%)
Unilateral	145 (52.3%)
Bilateral	99 (35.7%)
Glaucoma	
None	141 (50.9%)
Unilateral	100 (36.1%)
Bilateral	33 (11.9%)
History of seizures	
Yes	240 (86.6%)
No	37 (13.4%)
Year of enrollment	
2010	31 (11.2%)
2011	52 (18.8%)
2012	23 (8.3%)
2013	58 (20.9%)
2014	35 (12.6%)
2015	26 (9.4%)
2016	45 (16.2%)
2017	7 (2.5%)

Abbreviation:
SWS = Sturge-Weber syndrome

Interactions between FHx and symptoms were performed using a Cox proportional hazards regression. The first analysis looked at the interaction of symptomatic stroke with FHx of vascular birthmarks. The second looked at the interaction of extent of PWB with FHx of seizures. These two interactions were chosen and performed based on preliminary data (see subsections Age of seizure onset and Family history under the Results section).

Significance

To correct for multiple analyses but still maintain the ability to identify potential new findings for follow-up in future studies, only $P < 0.01$ threshold was considered significant.

Results

Population statistics

The study sample consisted of 277 participants who consented. The majority were children (age less than 18 years), Table 1. The mean age was 10 years with a range of two months to 66 years. The ethnicity and race distributions were similar to the population statistics in the United States according to the Census Bureau. The majority of participants were recruited from KKI (n = 173), and the rest were recruited from Wayne State University/Children's Hospital of Michigan (n = 43), New York University (n = 21), Baylor College of Medicine (n = 14), Cincinnati Children's Hospital Medical Center (n = 13), Nationwide Children's Hospital (n = 10), and Thomas Jefferson University (n = 3).

Sturge-Weber syndrome demographics and symptoms

The majority of participants (88.1%) presented with a PWB (n = 244). Unilateral birthmarks were reported in 52.3% of participants, and bilateral birthmarks were reported in 35.7% of participants. Glaucoma was present in 48.4% of participants, with 36.1% of participants reporting glaucoma in one eye, whereas 11.9% reporting glaucoma in both eyes. The majority of participants reported unilateral brain involvement (81.6%). Epilepsy, learning disorders, visual field abnormalities, hemiparesis, and headaches were common symptoms/comorbidities (Table 2).

SWS involvement

Of those with bilateral PWB, 42.4% had bilateral brain involvement, whereas 6% of those with no PWB and 4.8% of those with unilateral PWB showed bilateral brain involvement ($P < 0.001$). Likewise, 60.6% of those with bilateral glaucoma showed bilateral brain involvement compared with 17% with unilateral glaucoma and 9.9% with no glaucoma ($P < 0.001$). Bilateral brain involvement was also associated with a higher likelihood of intellectual disability ($P < 0.001$), learning disorder ($P = 0.004$), and glaucoma surgery ($P < 0.001$) (Table 3). Greater extent of PWB was associated with epilepsy (94.0% no PWB, 76.4% unilateral PWB, 88.9% bilateral PWB, $P = 0.009$; Supplemental Table 2). Greater extent of glaucoma was associated with visual field deficit ("visual field cut" in questionnaire) (36.7% no glaucoma, 59.0% unilateral glaucoma, 75.9% bilateral glaucoma, $P < 0.001$), intellectual disability (9.4% no glaucoma, 19.1% unilateral glaucoma, 39.3% bilateral glaucoma $P < 0.001$), thyroid disorder (2.8% no glaucoma, 10.0% unilateral glaucoma, 18.2% bilateral glaucoma, $P = 0.003$), and learning disorder (39.3% no glaucoma, 53.5% unilateral glaucoma, 83.3% bilateral glaucoma, $P < 0.001$) (Supplemental Table 3).

Gender analysis

We found no significant differences in symptom presentation based on gender except for those with seizure onset less than or equal to six months (n = 119). Of those with seizure onset less than or equal to six months, males were more likely to experience strokelike episodes (57% males, 34% females, $P = 0.016$).

Family history analysis

The most prevalent FHx conditions were type II diabetes, migraines, ADHD/ADD, psychiatric disease, seizures, and hypothyroidism (Table 4). Subjects with vascular birthmarks in their family were more likely to report experiencing symptomatic strokes (28.2% with FHx of vascular birthmarks versus 8.1% without FHx of vascular birthmarks, $P < 0.001$) (Table 5). Those with PWB in the family were more likely to report growth hormone problems (14.6% with FHx of PWB, 2.6% without FHx of PWB, $P = 0.001$; Table 5). Subjects with migraines in the family were more likely to report experiencing headaches than those without migraines in their family (68.6% with FHx of migraines versus 43.3% without FHx of migraines, $P < 0.001$; Supplemental Table 4). Those with psychiatric diseases in the family were more likely to report mood disorders (20% with FHx psychiatric disease versus 6.8% without FHx psychiatric disease, $P = 0.007$; Supplemental Table 5). Those with hypothyroidism in the family were more likely to report the patient with SWS experiencing thyroid disorder (18.2% with FHx of hypothyroidism versus 4.1% without FHx of hypothyroidism, $P \leq 0.001$) and strabismus (16.7% with FHx of hypothyroidism versus 4.9% without FHx of hypothyroidism, $P = 0.004$) (Supplemental Table 4). Subjects with ADHD/ADD in their family were more likely to report having ADHD/ADD themselves (25.3% with FHx of ADHD/ADD versus 9.9% without FHx of ADHD/ADD, $P = 0.001$; Supplemental Table 5).

TABLE 2.
Prevalence of Symptoms/co-morbidities

Symptom	Prevalence in SWS Population (n = 277)	Prevalence in SWS Population Older Than 6 Years (n = 147)
Epilepsy	226 (81.6%)	122 (83.0%)
Learning disorder	116 (41.9%)	82 (55.8%)
Visual field cut	116 (41.9%)	71 (48.3%)
Hemiparesis	115 (41.5%)	55 (37.4%)
Headaches	109 (39.4%)	86 (58.5%)
Strokelike episode	105 (37.9%)	54 (36.7%)
Glaucoma surgery	96 (34.6%)	54 (36.7%)
Amblyopia	47 (17.0)%	30 (20.4%)
Intellectual disability	41 (14.8%)	30 (20.4%)
ADHD/ADD	39 (14.1%)	35 (23.8%)
Behavioral disorder	30 (10.8%)	26 (17.7%)
Symptomatic stroke	29 (10.5%)	16 (10.9%)
Brain surgery	25 (9.0%)	14 (9.5%)
Strabismus	22 (7.9%)	13 (8.8%)
Mood disorder	21 (7.6%)	20 (13.6%)
Thyroid disorder	20 (7.2%)	18 (12.2%)
Immune problem	12 (4.3%)	9 (6.1%)
Growth hormone deficiency	12 (4.3%)	7 (4.8%)
Autism spectrum disorder	8 (2.9%)	7 (4.8%)

Abbreviations:
ADHD/ADD = attention deficit hyperactivity disorder and/or attention deficit disorder
SWS = Sturge-Weber syndrome

Age group subanalyses

In participants older than six years at enrollment (n = 147), an FHx of intellectual disability was significantly associated with intellectual disability (70% with FHx of intellectual disability versus 17.4% without FHx of intellectual disability, $P = 0.001$). Those who reported FHx of migraines were more likely to report mood disorder (26.5% with FHx migraines versus 6.4% without FHx migraines, $P = 0.002$). An FHx of psychiatric diseases was associated with mood disorder (30.3% with FHx of psychiatric disease versus 10.3% without FHx of psychiatric disease, $P = 0.006$) and behavioral disorders (37.5% with FHx of psychiatric disease versus 13.7% without FHx of psychiatric disease, $P = 0.003$). An FHx of ADHD/ADD continued to be associated with the presence of ADHD/ADD (40.5% with FHx of ADHD/ADD versus 17.1% without FHx of ADHD/ADD, $P = 0.003$).

Bilateral brain involvement was associated with intellectual disability (16.2% without intellectual disability, 50% with intellectual disability, $P < 0.001$). A greater extent of glaucoma was associated with intellectual disability (10.9% no glaucoma, 25.9% unilateral glaucoma, 50% bilateral glaucoma, $P = 0.002$) and learning disorder (47.5% no glaucoma, 62.7% unilateral glaucoma, 94.1% bilateral glaucoma, $P = 0.001$). No significant associations with symptoms were found between gender or the extent of PWB. Puberty problems were found in four of 109 participants who enrolled at age nine years or later, making up 3.7% of that subpopulation.

Age at seizure onset

Those with bilateral PWB showed a younger age of seizure onset (median = five months; 95% confidence interval [CI] [3.80, 6.19]) than those with unilateral PWB (median = 10 months; 95% CI [8.038, 11.96]) or no PWB at all (median = 17 months, 95% CI [7.99, 26.003], $P = 0.004$). Early age at seizure onset was associated with an increased likelihood of brain surgery ($P = 0.003$) (Table 6). In

TABLE 3.
Brain Involvement and Symptoms/comorbidities

Symptom	Association with Greater Brain Involvement		
	Unilateral	Bilateral	*P*
Epilepsy	185/221 (83.7%)	41/51 (80.4%)	0.57
Headaches	94/166 (56.6%)	1/31 (3.2%)	0.40
Strokelike episode	84/215 (39.1%)	21/51 (41.2%)	0.78
Symptomatic stroke	22/202 (10.9%)	7/48 (14.6%)	0.47
Hemiparesis	89/213 (41.8%)	26/50 (52%)	0.19
Visual field deficit	92/197 (46.7%)	24/38 (63.2%)	0.063
Intellectual disability	**23/207 (11.1%)**	**18/40 (45.0%)**	**<0.001**
Learning disorder	**87/189 (46.0%)**	**29/41 (70.7%)**	**0.004**
ADHD/ADD	31/226 (13.7%)	8/51 (15.7%)	0.72
Autism spectrum disorder	5/196 (2.6%)	3/38 (7.9%)	0.12
Behavioral disorder	22/197 (11.2%)	8/41 (19.5%)	0.14
Mood disorder	17/183 (9.3%)	4/37 (10.8%)	0.76
Strabismus	19/210 (9.0%)	3/48 (6.3%)	0.78
Amblyopia	36/211 (17.1%)	11/44 (25.0%)	0.22
Immune problem	8/213 (3.8%)	4/46 (8.7%)	0.24
Growth hormone problems	9/226 (4.0%)	3/51 (5.9%)	0.47
Puberty problems	4/226 (1.8%)	1/51 (2.0%)	1.00
Thyroid disorder	15/226 (6.6%)	5/51 (9.8%)	0.43
Glaucoma surgery	**65/224 (28.8%)**	**31/50 (60.8%)**	**<0.001**
Brain surgery	24/146 (16.4%)	1/35 (2.9%)	0.052

Abbreviations:
ADHD/ADD = attention deficit hyperactivity disorder and/or attention deficit disorder
SWS = Sturge-Weber syndrome
Multiple associations found between patient history of Sturge-Weber syndrome symptoms/comorbidities and brain involvement extent.
Bold values indicates the significance of $P < 0.01$.

addition, intellectual disability ($P = 0.001$), strokelike episodes ($P = 0.001$), hemiparesis ($P < 0.001$), visual field deficit ($P < 0.001$), and learning disorders ($P < 0.001$) were all associated with a younger age at seizure onset (Table 6). No significant differences were found in age of seizure onset based on gender (male versus female) or brain involvement (unilateral versus bilateral). An FHx of seizures was associated with a lower age at seizure onset (median = six months, 95% CI [4.17, 7.82], $P = .008$) than those without FHx of seizures (median = 9 months, 95% CI [6.77, 11.22]. There was no significant interaction between symptomatic stroke and an FHx of vascular birthmarks with the age of seizure onset or between PWB extent, FHx of seizures, and the age of seizure onset.

TABLE 4.
Prevalence of Family History Conditions

Symptom	Prevalence in the Family Histories of the SWS Population (n = 277)
Type II diabetes	123 (44.4%)
Migraines	117 (42.2%)
ADHD/ADD	75 (27.1%)
Psychiatric disease	62 (22.4%)
Seizures	59 (21.3%)
Hypothyroidism	55 (19.9%)
Neurological disease	47 (17.0%)
Other vascular birthmarks	43 (15.5%)
Port-wine birthmarks	41 (14.8%)
Type I diabetes	36 (13.0%)
Hyperthyroidism	24 (8.7%)
Intellectual disability	24 (8.7%)
Autism spectrum disorder	20 (7.2%)
Stroke younger than 50 years	20 (7.2%)
Growth hormone deficiency	5 (1.8%)

Abbreviations:
ADHD/ADD = attention deficit hyperactivity disorder and/or attention deficit disorder
SWS = Sturge-Weber syndrome

Discussion

These results summarize the findings of the largest grouping of SWS subjects to date, which provided a significant opportunity to assess the importance of FHx, gender, and seizure onset in this sporadic disorder. The newest and most important result from this study is the suggestion that, in SWS, genetic factors identified through FHx may help predict or contribute to the development of common comorbidities, supporting our hypothesis of a possible contribution of genetic factors to the variability in SWS.

Infants with SWS and an FHx of vascular malformations may be more likely to develop symptomatic strokes; genetic factors involved in vascular birthmarks may contribute to stroke risk in patients with SWS. There are familial forms of vascular birthmarks, the genetics of which are only beginning to be understood; variants in these and other genes important to vascular development and function could potentially influence the outcomes in patients with SWS. These hypotheses require further study and confirmation to understand the acute neurological deteriorations seen in SWS and the potential mechanisms involved.

Furthermore, those with an FHx (siblings, parents, and grandparents) of epilepsy had an earlier age of seizure onset, pointing to the possibility that genetic factors contributing to seizure susceptibility may affect the age of seizure onset in SWS. Early age of seizure onset was associated with several neurological comorbidities, including symptomatic stroke, intellectual disability, learning disabilities, and focal neurological deficits, consistent with prior studies.[12-14] Subjects with these neurological comorbidities had seizure onset of about five to six months of age, whereas those without these issues had seizure onset after age one year. With further investigation, these data could lead to a greater understanding of the underlying variables influencing the development of seizures in SWS and allow for improved management and presymptomatic treatment. Furthermore, males with seizure onset at or before six months were more likely to report visual field deficit and strokelike episodes than females. Age six months was selected because evidence indicates that infants with SWS and seizure onset before six months are more likely to develop hemiparesis.[8] Gender differences have been noted in similar age groups in studies on ischemic conditions showing males to be more likely to experience ischemic episodes (hypoxic-ischemic encephalopathy, strokes, etc.) early in life and having a worse prognosis after ischemic episodes.[9-11] This literature and our results indicate that males may be more susceptible to pediatric stroke and may develop worse symptoms and outcomes, which emphasizes the need to screen for strokelike symptoms, particularly in males with early-onset seizures.[9-11,15]

Those with an FHx of migraines were more likely to report headaches. Similarly, those with ADHD/ADD in the family were more likely to report the same. Although not surprising, these associations are important to recognize and inquire about from patients and parents as prior studies have demonstrated that headaches in SWS are likely to present at an early age and may be very debilitating, and attention deficits in SWS are treatable.[16,17] Anticipatory guidance and aggressive management of patients at high risk for these issues may be helpful.

Previous studies have noted that patients with SWS with bilateral brain involvement are more likely to experience earlier seizure onset and a worse prognosis for mental development with increased risk of intellectual disability.[2] Although the difference in seizure onset was not significant in our analyses based on brain involvement laterality, analysis with cognitive disabilities (intellectual disability, learning disability) agreed with the literature showing an association with increased brain involvement. It is important to recognize that neuroimaging in early infancy

TABLE 5.
Associations Between History of Symptoms/Comorbidities at the Time of Data Collection and Family History of Port-Wine Birthmarks or Other Vascular Birthmarks

Symptom in Participant	Present in Family History					
	Vascular Birthmarks N (%)			Port-Wine Birthmarks N (%)		
	Yes	No	*P*	Yes	No	*P*
Epilepsy	35/43 (81.4%)	181/216 (83.8%)	0.70	34/40 (85.0%)	189/229 (82.5%)	0.70
Headaches	12/23 (52.2%)	88/162 (54.3%)	0.85	17/33 (51.5%)	91/162 (56.2%)	0.62
Strokelike episode	17/41 (41.5%)	84/211 (39.8%)	0.84	12/38 (31.6%)	91/224 (40.6%)	0.29
Symptomatic stroke	**11/39 (28.2%)**	**16/198 (8.1%)**	**<0.001**	5/39 (12.8%)	23/208 (11.1%)	0.75
Hemiparesis	21/42 (50.0%)	86/207 (41.5%)	0.31	17/39 (43.6%)	96/219 (43.8%)	0.98
Visual field deficit	20/40 (50.0%)	89/183 (48.6%)	0.88	16/34 (47.1%)	97/196 (49.5%)	0.79
Intellectual disability	10/35 (28.6%)	29/198 (14.6%)	0.042	6/35 (17.1%)	34/207 (16.4%)	0.92
Learning disorder	16/34 (47.1%)	91/184 (49.5%)	0.80	19/33 (57.6%)	94/193 (48.7%)	0.35
ADHD/ADD	4/43 (9.3%)	32/219 (14.6%)	0.35	6/41 (14.6%)	32/231 (13.9%)	0.89
Autism spectrum disorder	1/35 (2.9%)	7/185 (3.8%)	0.79	0/36 (0%)	8/193 (4.1%)	0.36
Behavioral disorder	4/34 (11.8%)	25/191 (13.1%)	0.83	1/33 (3.0%)	28/200 (14.0%)	0.90
Mood disorder	2/27 (7.4%)	17/180 (9.4%)	0.73	4/32 (12.5%)	16/183 (8.7%)	0.51
Strabismus	5/41 (12.2%)	15/206 (7.3%)	0.29	5/36 (13.9%)	16/218 (7.3%)	0.19
Amblyopia	11/41 (26.8%)	31/203 (15.3%)	0.074	6/34 (17.6%)	40/216 (18.5%)	0.90
Immune problem	2/41 (4.9%)	8/204 (3.9%)	0.77	2/40 (5.0%)	10/215 (4.7%)	1.00
Growth hormone problems	3/43 (7.0%)	9/219 (4.1%)	0.41	**6/41 (14.6%)**	**6/231 (2.6%)**	**0.001**
Puberty problems	1/43 (2.3%)	4/219 (1.8%)	0.82	0/41 (0%)	5/231 (2.2%)	1.00
Thyroid disorder	1/43 (2.3%)	19/219 (8.7%)	0.15	2/41 (4.9%)	18/231 (7.8%)	0.75

Abbreviations:
ADHD/ADD = attention deficit hyperactivity disorder and/or attention deficit disorder
SWS = Sturge-Weber syndrome
Bold values indicates the significance of $P < 0.01$.

underestimates the full extent of SWS brain involvement. In addition, the question of whether a patient has subtle bilateral brain involvement (brain involvement of one side and possible subtle involvement of the other side) often arises. Nevertheless, the extent of brain involvement is a useful biomarker in imaging done after age one year for discussing prognosis with parents and for selecting subjects for clinical trials.

Age of seizure onset is unique from the physical and genetic factors described above, as seizure onset is associated with more severe brain involvement.[2] The complexity of studying age of seizure onset may be due to the hypothesis that seizures in SWS may, themselves, lead to further neurological deterioration leading to further seizures.[7,8,18,19] Nevertheless, they raise questions on important potential prognostic factors that may affect how patients are treated and screened and allow for the discovery of novel potential pathogenic contributors.

Our findings are also consistent with our first hypothesis and also prior research suggesting that more extensive facial PWB is associated with an increased severity of neurological impairment.[5] Here the more severe (bilateral versus unilateral versus none) facial PWB was associated with epilepsy, hemiparesis, and visual field deficit. These results would be consistent with the hypothesis that patients with both brain and extensive skin involvement have an earlier somatic mutation and therefore more cell types are involved (potentially resulting in focal cortical dysplasia diagnoses as has been described).[20,21] Unlike brain involvement, PWB is present to its fullest extent from birth and therefore is another useful biomarker for prognosis.

TABLE 6.
Age of Seizure Onset Associated With Symptoms/Comorbidities Using Log-Rank Test*

Symptom	Age of Seizure Onset for Those Reporting Symptom (Median ± Standard Error in Months)	Age of Seizure Onset for Those Not Reporting Symptom (Median ± Standard Error in Months)	*P* value
Headaches	12 ± 2.15	8 ± 1.44	0.29
Strokelike episode	**7 ±0.82**	**10 ± 1.33**	**0.001**
Symptomatic stroke	6 ± 0.66	9 ± 1.26	0.012
Hemiparesis	**5 ± 0.48**	**15 ± 1.67**	**<0.001**
Visual field deficit	**6 ± 0.89**	**12 ± 2.70**	**<0.001**
Intellectual disability	**6 ± 0.45**	**12 ± 1.07**	**0.001**
Learning disorder	**6 ± 0.85**	**13 ± 2.68**	**<0.001**
ADD/ADHD	9 ± 1.33	8 ± 1.07	0.96
Autism spectrum disorder	4 ± 2.12	10 ± 1.08	0.10
Behavioral disorder	9 ± 1.09	10 ± 1.29	0.33
Mood disorder	18 ± 9.16	9 ± 1.28	0.22
Strabismus	8 ± 1.15	9 ± 1.0	0.79
Amblyopia	8 ± 1.14	9 ± 1.13	0.56
Immune problem	9 ± 14.72	8 ± 0.96	0.99
Growth hormone problem	5 ± 1.73	8 ± 0.91	0.049
Puberty problem	36 ± 32.86	8 ± 0.90	0.90
Thyroid disorder	9 ± 4.47	8 ± 0.92	0.68
Glaucoma surgery	6 ± 0.69	10 ± 1.09	0.023
Brain surgery	**4 ± 1.23**	**10 ± 1.27**	**0.003**

* Significance in the log-rank test represents significant differences in estimated age of seizure onset based on the presence of the various symptoms.
Bold values indicates the significance of $P < 0.01$.

The greater extent of glaucoma was significantly associated with many comorbidities including visual field deficit, intellectual disability, and learning disorder. Greater extent of glaucoma was also significantly associated with bilateral brain involvement and bilateral PWB. Although only half of the participants reported glaucoma, making it less common than a PWB or brain involvement, about three-quarters of participants with glaucoma reported a history of glaucoma surgery. Therefore those with greater severity of brain involvement or PWB should also be closely followed for seizures and glaucoma requiring surgical intervention, particularly if found presymptomatically.

This research reflects an effort to bring together a network of major centers dedicated to the research and care of SWS, which is needed for the longitudinal research currently planned and underway, as advocated for by the recent SWS multidisciplinary consensus meeting, the results of which were recently published.[22] This is a multicentered questionnaire-based study allowing for a relatively large number of subjects; however, there are several limitations in these data. A large percentage of the group came from one site, and therefore the results disproportionately reflect their subjects. All sites participating in the study are tertiary care centers, and therefore this study likely is skewed toward the more severely involved patients. Although most questionnaires were completed in person, this was not always the case and a small proportion were completed by subjects who had not been formally clinically evaluated at one of the participating sites ($n = 23$); therefore the quality of the data collected is not all equally high. When completing the analysis without these 23 participants, the only key finding to change in significance was the association of FHx of seizures with a lower age of seizure onset whose P value changed from $P = 0.008$ to $P = 0.021$. Another potential limitation lies in the medical terminology used. For example, a consensus has not yet been reached for the use of terminologies such as “stroke-like episode” or “symptomatic stroke.” It is clear from studies to date that these symptoms do not happen from typical arterial stroke; rather venous hypertension in some form likely underlies the pathogenesis of these deficits. Future efforts are needed to arise at consensus for these terms and to better understand their pathogenesis. Reporting of FHx may not be entirely accurate, and follow-up studies are needed to confirm and understand the association seen in this study.

The conclusions in this study suggest future studies, including roles of genetic and physical factors in the variability of the disease progression. Future studies should include assessments of neuroimaging, such as on specific venous anomalies in the patients with strokelike episodes or the role of cortical dysplasia in patients with seizures and the associations with the FHx of the same. The association between specific genetic factors should be a focus in future studies with particular attention to FHx of vascular birthmarks and epilepsy as these variables were associated with stroke and seizures, both of which are associated with considerable developmental impairment. In addition, a study is currently underway analyzing the role of current management and medication use in this population of participants.

Conclusion

One of the most important clinical questions in the management of infants with SWS brain involvement is how aggressive to be with treatment, given the wide variability in neurological progression and morbidity. Studies have shown that prolonged seizure freedom (however it is managed) results in improved brain glucose metabolism and neurodevelopmental progress. This suggests that infants with worse prognostic factors, such as extensive SWS brain and skin involvement and early age of seizure onset, should be more aggressively managed in an effort to prevent seizures and strokes and allow for neurological development. In addition, infants who are more severely impaired than would be expected based only upon the extent of their SWS brain and skin involvement, and who have an FHx of epilepsy and/or intellectual disability, should be considered for additional genetic testing. These infants may have inherited other genetic conditions important to their treatment and prognosis. Follow-up studies are needed to further determine the role of FHx in determining prognosis in SWS and in identifying other genetic factors that may in some cases influence outcome.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2018.12.002.

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