Recent Developments Concerning Sturge-Weber Syndrome

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ABSTRACT: Sturge-Weber-Syndrome (SWS) is an uncommon, non-genetic neuro-vascular disorder considered by nonstandard blood vessel development in the eye, skin and brain. People with SWS often present with dermal capillary malformations, recognized as port-wine-birthmarks (PWBs), along with leptomeningeal vascular malformations visible on contrast-enhanced MRI, abnormal eye blood vessels, health risk and glaucoma. Those affected experience reduced brain blood flow, increasing their risk for venous stroke, stroke-like episodes, seizures, as well as mechanical and rational impairments. The R183-Q GNAQ somatic mutation, which activates this gene, is the most communal mutation linked to SWS; however, new exploration also points to somatic mutations in GNA11 and GNB2 as contributors. Current retroactive studies recommend that low dose aspirin and Vitamin-D are effective treatments for SWS, while forthcoming drug trials have sustained the use of cannabidiol and Sirolimus. Early intervention with low dose aspirin and antiepileptic drugs has shown promise in suspending seizure inception in some patients. This study explores recent progress in SWS research and highlights potential areas for future exploration.

Keywords: Sturge-Weber Syndrome, cannabidiol, Sirolimus, Electroencephalography, health risk and port-wine-birthmarks

INTRODUCTION

SWS is a neurocutaneous syndrome marked by irregular development and functioning of blood vessels in the skin, eyes, and brain. It is commonly associated with a facial capillary malformation (port-wine stain) on the upper face, leptomeningeal vascular malformations in the brain visible on contrast-enhanced MRI, and glaucoma. Neurological symptoms include strokes and stroke-like episodes, acquired hemiparesis, brain atrophy and calcifications, seizures, visual field issues, and cognitive impairments. People with facial port-wine stains have a higher risk of developing glaucoma [1]. Due to the complex nature of SWS, which involves endocrine, psychiatric, ophthalmologic, rehabilitative, dermatologic, and other medical complications, optimal care is provided by a multidisciplinary team that includes a neurologist, ophthalmologist, dermatologist, neuropsychologist, physical therapist, and occupational therapist. The recent identification of the underlying somatic mosaic mutation and possible over activity of downstream pathways, along with the development of biomarkers and outcome measures, has facilitated current prospective treatment studies. While the R183-Q GNAQ mutation is frequently associated with SWS, new research suggests that mutations in GNA-11 and GNB-2 are also linked to the condition. Quantitative electroencephalography (EEG) and transcranial Doppler have recently been suggested as potential biomarkers for diagnosing and monitoring SWS in clinical settings [2]. Increasingly, low-dose aspirin is being used to reduce stroke-like episodes and seizures in patients. Recent trials of oral medications for SWS have shown hopeful results in treating stroke-like episodes, seizure control, and improving cognitive function. This review summarizes recent advances in SWS research relevant to treatment and lays the groundwork for future multicenter pharmacological trials designed at precluding stroke damage and preserving neurological function in SWS patients [3]. When a newborn or young child with SWS experiences a protracted seizure lasting several hours, they often develop fresh or significantly degraded hemiparesis, a fresh visual field defect, and may retreat in language and other intellectual milestones. This often surpasses the typical presentation of Todd's paralysis, as it may not completely resolve; however, improvement can occur over the course of weeks or months if the child remains free from seizures and stroke-like episodes [4]. Two studies have demonstrated ictal SPECT in four individuals, showing that during seizures, there is either reduced blood flow to the affected hemisphere or a complete reduction in blood flow to ischemic levels in both the involved and distant brain regions in SWS. As a result, impaired autoregulation of cerebral blood flow during extended or frequent seizures is likely a mechanism by which seizures contribute to further brain injury in SWS. This highlights the importance of destructive seizure administration in SWS, especially in the early stages of the condition. Unrestrained seizures, particularly in infants under one-year-old, are associated with poorer neurological and cognitive outcomes [5].

1. DIAGNOSIS OF SWS

Infants at risk for SWS typically exhibit a port-wine-birthmark (PWB) on one or more facial areas, such as the eyelids, temples, and fore-head. The chance of brain contribution in SWS is about 26% when the PWB is located on the upper face. In the past, it was believed that brain participation was associated with atypical formation of the initial division of the trigeminal nerve (V1) [6]. However, this superior facial distribution is now understood to be connected to the formation of embryonic placodes. Brain involvement in SWS can be diagnosed through neuroimaging, particularly by showing leptomeningeal improvement on contrast enhanced brain MRI. This is best visualized on T1 post-contrast spin-echo and T2 post-contrast FLAIR sequences [7]. Other abnormalities seen in neuroimaging include brain atrophy, enlarged deep draining veins, cortical or subcortical calcifications, and a distended choroid plexus, although these findings are not specific to SWS and can be seen in other circumstances. In the first one to two months of life, a non-sedated MRI (often without contrast) may be performed to evaluate for brain atrophy, choroid plexus size, or signal changes. If abnormalities are noted, a follow-up MRI with sedation and contrast is necessary for diagnostic confirmation [8]. However, early neuroimaging misses brain involvement in 75% of children with SWS.

Therefore, negative early imaging does not exclude brain involvement, and a repeat MRI at one year of age is recommended. A thorough medical history, physical exam, and EEG should be performed; if concerns arise, early neuroimaging is advised. Initial imaging with head CT or MRI in the first months has limited sensitivity for detecting leptomeningeal improvement, which may result in negatives [9]. Yet, a brain MRI with contrast after the age of one is more dependable in excluding brain involvement in SWS. Given that SWS is a spectrum disorder, the extent of brain involvement can differ. Recent research indicates that non-contrast brain MRI might detect indirect indicators of SWS, such as enlargement of the choroid plexus, cerebral atrophy, and alterations in signal on apparent diffusion coefficient maps, as well as T1 or T2 sequences [10]. These studies are constrained by small sample sizes, so caution is advised when employing this screening approach. Newborns without symptoms and without brain involvement should not be given seizure medications, low-dose aspirin, or other therapies. Arterial spin-labeling perfusion imaging (ASL) has recently been used to detect hypo-perfusion in SWS patients, but further research is needed to confirm its effectiveness for diagnosing brain involvement. EEG is used to diagnose and monitor seizure activity during sleep and wake states in SWS. Overnight EEG can detect subclinical or mild seizure activity, allowing for appropriate treatment. Between seizures, EEG typically displays decreased amplitude and frequency in the impacted regions of the brain. In individuals with managed seizures and almost normal neurological abilities, clinical EEGs might seem normal [11].

2. NEUROLOGICAL MANIFESTATIONS AND INDICATIONS IN SWS

Patients with brain involvement in SWS frequently experience seizures during infancy. These seizures are primarily focal motor seizures and are often mild in babies, though complex partial seizures are also common. A small but significant portion of patients may also experience atonic seizures, which can be worsened by carbamazepine or oxcarbazepine [12]. Infantile spasms are rare but have been documented, usually presenting asymmetrically. Status epilepticus is relatively common and is often associated with prolonged unilateral weakness or newly developed visual field deficits, which can last for days, weeks, or even months, referred to as stroke-like episodes. Seizures often occur in clusters, with long periods of seizure-free intervals lasting months or years in between. Epilepsy generally begins in infancy or early childhood, though seizures may sometimes start in adulthood, serving as the first symptom in individuals who otherwise show no neurological issues. Approximately 76% of patients with SWS who have unilateral brain contribution and about 96% of those with bilateral contribution experience seizures [13]. Occasionally, newborns with SWS brain involvement show signs such as initial handedness, hemiparesis, or a visual gaze partiality rather than sudden seizures. Neurological issues can develop gradually over time or occur due to stroke-like episodes linked to seizures or migraines. Toddlers and young children are more prone to stroke-like episodes triggered by minor head trauma from falls. Because of this risk, individuals with SWS should be discouraged from participating in activities that could result in repeated head impacts. Seizure onset before six months of age has been associated with more severe hemiparesis, as shown in a study of 78 patients at a single center. Most individuals with SWS and brain contribution have varying degrees of focal neurological deficits, often in the form of hemiparesis. Deterioration in neurological function is more frequent in infants and young children, but strokes and emerging neurological impairments may also happen in adults. Early-onset dementia has been noted in the fifth or sixth decade of life, although it is not well understood [14]. Research by Miller and co-authors [15] found that individuals with SWS have an 18-fold higher frequency of growth hormone shortage compared to the over-all population. Despite no clear abnormalities found in the hypothalamic-pituitary axis on neuroimaging, the source of this insufficiency remains unclear. A lack of growth hormone can be addressed as a cause of reduced height or impaired growth in individuals with SWS. Adults who are shorter and have SWS need assessment for a deficiency in growth hormone because without treatment, it may result in depression and other health problems. Additionally, central hypothyroidism associated with SWS has been reported, though the underlying cause remains uncertain. Every child with SWS diagnosed with central thyroid deficiency were receiving prolonged anticonvulsant treatment [16]. Central hypothyroidism, whether symptomatic or not,

has been linked to the use of certain anticonvulsants. However, the higher prevalence of growth hormone deficiency in SWS suggests that interruption of the hypothalamic pituitary axis might also play a role in central hypothyroidism. Low-dose aspirin is recommended for nearly all children under three years old with involvement of three or more brain lobes and may also be suggested for older or less severely affected children who experience stroke like episodes, unrestrained seizures or localized neurological insufficiencies. The use of low-dose aspirin is becoming more common globally among patients with SWS, especially at facilities that treat a large number of these individuals. A current multicenter research showed that aspirin use is widespread, though not universal. There have been anecdotal reports of bleeding complications, but patients with SWS rarely develop subdural hematomas, possibly due to hemispheric atrophy and the tearing of bridging veins. The exact appliance of action of low-dose aspirin in SWS remains unknown, requiring further research in this area [17].

3. RETROSPECTIVE OF OCULAR INVOLVEMENT

Glaucoma is the best communal eye-related impediment in individuals with SWS, affecting 35% to 75% of those with both upper and lower eyelid birthmarks [18]. Glaucoma, which results from increased intraocular pressure leading to eye damage, can develop at any age, with the most frequent onset occurring between infancy and early adulthood. Prolonged and recurrent seizures appear to accelerate brain damage, especially in infants and young children. Therefore, it is crucial to educate parents on how to identify and promptly respond to seizures in SWS patients. In babies, seizures often present as mild, rhythmic, and continuous twitching of the hands or feet, or as eye deviation or nystagmus. Parents who expect seizures to manifest as generalized tonic-clonic events may overlook these focused symptoms for long periods without seeking medical attention [19]. A somatic mutation or double-hit mechanism is believed to be the cause of SWS, given that the vascular malformation typically affects a localized area on one side of the body. During the first trimester of fetal growth, the primitive vascular plexus spreads through the developing brain, skin, and eyes, and a somatic mutation may interfere with normal vascular maturation. Dr. Parsa and co-authors offered an alternative theory, suggesting that the primary characteristics of SWS stem from a restricted venous dysplasia in the brain, with venous hypertension communicated to the overlying skin and eyes through persistent collateral venous arteries [20].

4. EXHIBITION OF CEREBRAL ENGAGEMENT

Persons with SWS who have cerebral involvement often experience seizures during infancy. These seizures are typically focal motor in nature, which may appear mild in infants, or composite incomplete seizures that affect awareness [21]. Less commonly, seizures may present as infantile spasms or myoclonic epilepsy. Status epilepticus repeatedly accompanies stroke like episodes, especially in younger patients. Seizures occur in 76% of individuals with unilateral brain involvement and in 96% of those with bilateral brain contribution. Although rarer, newborns with SWS brain contribution may show early handedness or a preference for visual gazing rather than sudden seizures. Neurological deficits may result from venous strokes, stroke like events, seizures, or migraines, often paired through progressive brain damage visible on neuroimaging. Cerebral involvement in SWS is marked by leptomeningeal vascular malformations, which are detectable on contrast-enhanced MRI scans [22]. Amplified deep draining veins beneath the pretentious cortical area and an enlarged choroid plexus on the involved side are typically observed in older children and adults. Cortical and subcortical calcifications may be identified through non contrast head CT scans or, less commonly, MRI. However, the limited sensitivity of neonatal brain MRI in pre-symptomatic detection of SWS means that an initial undesirable contrast improved MRI does not eliminate brain involvement. Nonetheless, if a standard neurological exam is normal, there is no seizure history, and a negative MRI with contrast is performed after one year of age, SWS brain contribution can often be ruled out. MRI arrangements should include SWI, T-1 post-contrast spin echo, T-2 post-contrast FLAIR, diffusion

weighted imaging, and apparent diffusion coefficient to aid in identifying cerebral involvement. Over time, patients may develop brain atrophy, calcifications, white matter loss, and diminished perfusion in the unnatural region. Leptomeningeal venous disfigurements cause a breakdown of functional posturing veins, leading to increased venous pressure and the formation of alternative drainage routes, evidenced by dilated deep veins on neuroimaging [23]. The natural progression of SWS varies widely. Some individuals develop significant neurological impairments, while others maintain good neurological function. A study of 277 SWS patients found that brain contribution and PWB were related with the severity of SWS symptoms. Bilateral brain contribution was linked to cognitive disorders and intellectual disabilities, whereas the severity of skin capillary malformations was related with epilepsy and the likelihood of glaucoma surgery. Early seizure onset was correlated with learning difficulties, rational disabilities, stroke like episodes, symptomatic strokes, hemiparesis, pictorial field deficits, and brain surgeries. This data supports earlier studies showing that the age at which seizures begin plays a vital role in the disease's course. Patients with a family history of seizures conveyed earlier seizure onset, while those with a family history of vascular abnormalities were more prospective to experience symptomatic strokes. The influence of family history of seizures and strokes on outcomes in SWS patients' needs further study. This association proposes the potential occurrence of genetic factors that predispose individuals to seizures and strokes, which may interact with brain involvement in SWS, leading to more severe neurological impairments [24].

5. EXHIBITION OF CUTANEOUS INVOLVEMENT

SWS typically presents at birth with a facial capillary abnormality, which specifies a heightened hazard of cerebral and ocular participation. A PWB on the face, or capillary anomaly on the forehead, eyelids, or temples, is linked to a high risk of SWS, with a likelihood of 25% to 55% of brain impact, based on the lesion's size, position, and spread. Occasionally, people can develop a frontonasal port-wine birthmark. Port-wine birthmarks might look red or pink, with the color sometimes briefly lightening under pressure. Although skin involvement in SWS is often seen on the upper face, the position, dimensions, and hue of the port-wine birthmark may vary significantly. Research by Dymerska and co-authors. shows that the size of facial PWBs relates with neurological sternness in individuals aged 6 and older who have SWS brain contribution. The size and position of PWBs, combined with brain MRI scans, can help predict the degree of neurological impairment. About 10% of individuals may have isolated SWS affecting only the brain or the eye, without a facial port wine stain [25].

6. GENETIC CONTRIBUTION TO SWS

Both SWS and inaccessible PWB result from a somatic stimulating mutation in the G-protein-alpha-q subunit (GNAQ) gene. Most mutations associated with SWS occur after fertilization, influencing the intermittent characteristics of both SWS and PWB. This somatic mutation can be detected in pretentious skin and brain tissues but is absent in nearby modest tissues. Germline mutations are thought to be embryonically lethal, and the timing of the SWS transmutation through embryonic vascular expansion can lead to phenotypic variations, with earlier mutations often linked to syndromic SWS. Approximately 90% of individuals with SWS and brain contribution have the somatic mosaic R183-Q GNAQ mutation, which involves an amino acid substitution from Arg183-Gln. Occasionally, mutations in GNAQ, GNB2, and GNA-11 (a paralogue of GNAQ) have also been related with SWS [26]. A phenotypic alteration has been noted between the R183-Q GNAQ mutation and the R183-Q GNA-11 mutation (a paralogue of GNAQ). The former typically presents as a confluent capillary malformation with a pink or red hue, while the latter generally appears as a more articulated capillary malformation. These alterations may be associated to the specific vascular possessions of these mutations. Mutations in GNA-11 may be linked to less severe neurological symptoms in SWS. Recent studies have identified early-onset hypertension in individuals with R183-Q GNAQ or GNA-11 mutations, with 18% of 29 patients diagnosed at a average age of 15 years. All

five patients with early-onset hypertension and either R183-Q GNAQ or GNA-11 mutations exhibited capillary abnormalities affecting the trunk and at least one extremity. Further genotype phenotype studies are essential to clarify these variations [27]. The venous capillary malformations related with SWS due to the R183-Q GNAQ mutation impair endothelial cell function and likely surge the initiation of downstream targets. Proposed hyperactive downstream pathways, include the ERK/MEK/RAS pathway, which affects gene appearance and endothelial cell function. This pathway influences the mammalian target of rapamycin (mTOR), leading to dysregulated cell development impacting skin, blood vessels, and tissue. Elevated mTOR activity has been observed in tissue samples from SWS patients, with increased expression of phospho-S6 in atypical leptomeningeal artery endothelial cells and skin vascular endothelial cells. The R183-Q GNAQ mutation in endothelial cells increases the expression of the PLCβ effector protein and triggers hyperactivity in downstream inflammatory mediators such as angiopoietin-2, which are involved in capillary malformation development. Dysfunction in effectors downstream of the G-protein alpha q subunit leads to abnormal vascular development, resulting in the tortuous, improperly innervated arteries seen in SWS. In SWS samples from leptomeningeal arteries, there is increased expression of vascular endothelial growth factor (VEGF) and its receptors (VEGFR), as well as the angiotensin 1 (TIE-2) receptor. We hypothesize that VEGF is stimulated by hypoxia-inducible factor-1α, which is elevated in affected brain tissue due to reduced cerebral blood flow. VEGFR and TIE2 receptors are essential for proper vascular development [28].

7. THERAPIES FOR SWS

Effective organization of seizures and stroke like events is essential for minimizing neurological damage in SWS. Initial detection and prompt intervention for seizures are crucial. There is growing interest in using preventive anti-epileptic medications, which may reduce the risk of intellectual disability. However, the significant variability in disease progression and practical difficulties in conducting prospective randomized controlled trials have limited the adoption of this approach as a standard treatment. Educating parents on early seizure recognition, particularly for mild seizures, and using benzodiazepines as liberation medication before confirmed brain contribution in at risk newborns is a rational next step. Developing care plans with parents and resident hospitals for administering phenytoin and starting regular anticonvulsant medication after a first focal seizure is recommended. Proactive organization of acute illness, including maintaining hydration, oxygenation, and temperature regulation, can inhibit seizures and stroke-like events, thus reducing brain damage. Screening and treating iron deficiency anemia offers a practical approach to stroke prevention [29]. Research into SWS pathophysiology highlights the role of venous congestion, stasis, and thrombosis in progressive brain damage. Historically, it has been suggested that the gradual decline in SWS may be due to ischemia rather than epilepsy, and that paroxysmal episodes might respond better to treatments targeting platelet aggregation rather than anticonvulsants, making aspirin a plausible option. In a case series, aspirin treatment resulted in a 65% reduction in strokes among children, though there was no reduction in seizure frequency. Given the multi-system nature of SWS, a multi-disciplinary approach is essential for assessing dermatological, neurological, cognitive, and motor issues and for developing suitable treatment strategies. Due to the progressive nature of SWS, early initiation of vigorous and suitable treatments is crucial [30]. Ablative laser therapies, such as CO2, Erbium: YAG, and Erbium: Glass, are used alongside PDL but invariably result in scarring. Currently, there is no specific therapy for SWS, although sirolimus has shown some benefits, potentially through indirect effects on the GNAQ pathway. Sirolimus interacts with FKBP-12, forming a complex that inhibits mTOR, affecting T-lymphocyte activation and proliferation, and potentially impacting downstream signaling pathways like PI3K/AKT/mTOR. However, GNAQ is not directly involved in this mechanism. A 2021 analysis showed that sirolimus might improve outcomes in vascular malignancies, particularly with severe coagulopathy, as well as venous and lymphatic malformations. mTOR's role in cellular development and proliferation has led to its use in treating vascular abnormalities, including capillary malformations in SWS [31]. In a phase II, intra-individual placebo-controlled trial, double-blind, randomized, topical rapamycin combined with

PDL proved more effective than either treatment alone, based on subjective and objective evaluations. This approach is thought to be especially beneficial in children, potentially inhibiting the development of larger, more difficult-to-treat vessels. Oral rapamycin combined with aspirin has been used prophylactically in a newborn with bilateral face and significant leptomeningeal involvement, resulting in seizure freedom and notable lightening of the PWB after 10 sessions of pulsed dye laser therapy. Sun and co-authors [32]. reported that sirolimus effectively managed epilepsy in a small group of patients, achieving sustained remission for 26 months without additional antiepileptic drugs. Parents and caregivers should be informed about the risks of seizure clusters and encouraged to develop personalized emergency plans that include rescue benzodiazepine treatment. Some physicians recommend intermittent benzodiazepine use during febrile illnesses, similar to strategies used in Dravet syndrome. Low-dose aspirin (3-5 mg/kg/day) may be used alongside antiepileptic medications to reduce the frequency and sternness of headaches, seizures, and stroke like episodes in SWS patients. Aspirin has been shown to be safe and well abided in pediatric studies. Asymptomatic patients with anatomical brain abnormalities identified by imaging may benefit significantly from this therapy. There is speculation about the potential for aspirin to alleviate glaucoma through its anti-aggregate activity, but further research is needed. The use of cannabidiol in patients with SWS and rebellious epilepsy has also been documented.

8. PROSPECTS OF SWS RESEARCH

The search for biomarkers in SWS requires additional longitudinal and prospective data due to the disorder's considerable variability. Various studies have demonstrated that quantitative EEG power analysis is effective for transmission and observing SWS brain contribution. A pilot study on sirolimus recommended that q-EEG could detect therapeutic responses in individuals with a history of stroke-like events. Studies are currently underway to assess vascular markers in urine in SWS, with long-term urine marker data under analysis in conjunction with clinical results [33]. There are also efforts to use artificial intelligence with neuroimaging data to predict seizure onset age and clinical outcomes. More research is desired throughout acute decompensations and stroke like events to understand if patients recover spontaneously. A multi-center forward looking study is currently underway aiming to detect biomarkers from blood and imaging in patients with symptomatic SWS (NCT04717427 - ongoing longitudinal studies to discover biomarkers for SWS). Approximately 85% to 90% of individuals with SWS have a fundamental somatic R183-Q GNAQ mutation. Diagnosing this common somatic mutation does not reveal brain or ocular contribution and requires a facial skin sample; therefore, genetic testing is not yet a standard practice for most patients. Current studies have identified additional causal mutations, underscoring the need for genotype/phenotype investigations. As targeted therapies advance, the importance of gene sequencing is expected to increase [34].

9. CONCLUSION

SWS is a complicated disorder characterized by vascular malformations in the leptomeninges within the brain, a port wine birthmark, and irregular blood vessels in the eye. Given the typically progressive and sometimes severe nature of the condition, individuals are recommended to seek routine consultations with a specialized medical team focused on their particular symptoms. Although the R183-Q GNAQ mutation is the most well-known genetic link to SWS, recent research has also associated somatic mutations in GNA-11 and GNB-2 (p.Lys78Glu) with the disorder. Additional studies are required to enhance our knowledge of the genetic causes underlying SWS, its natural course through longitudinal research, and the creation of biomarkers and clinical outcome measures. Recent advancements in SWS treatment have been reported, with some facilities using low-dose aspirin, which may help reduce stroke-like events and seizures, though it is not universally adopted. Clinical trials of Sirolimus and cannabidiol have demonstrated enhancements in cognitive function and reductions in seizure frequency, correspondingly. Early use of low-dose aspirin and antiepileptic medications might delay the onset of seizures. Forthcoming research focusing on

multicenter drug trials and genetic models is expected to significantly enhance patient treatment and improve our understanding of SWS.

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Abbreviations

Sturge-Weber Syndrome (SWS)
magnetic resonance imaging (MRI)
Electroencephalography (EEG)
Port-wine birthmarks (pwbs)
computed tomography (CT)
Arterial spin-labeling (ASL)
sleep-wake states (SlWS)
G-protein alpha q subunit (GNAQ)
mammalian target of rapamycin (mTOR)
vascular endothelial growth factor (VEGF)
vascular endothelial growth factor receptors (VEGFR)
mammalian target of rapamycin (mTOR)

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