HHS Public Access

Author manuscript

Pediatr Neurol. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Pediatr Neurol. 2018 July ; 84: 11–20. doi:10.1016/j.pediatrneurol.2018.04.005.

A Multidisciplinary Consensus for Clinical Care and Research Needs for Sturge-Weber Syndrome

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Abstract

Background and Rationale—Sturge-Weber syndrome (SWS) is a neurocutaneous disorder associated with port wine birthmark, leptomeningeal capillary malformations, and glaucoma. It is associated with an unpredictable clinical course. Due to its rarity and complexity, many physicians are unaware of the disease and its complications. A major focus moving ahead will be to turn knowledge gaps and unmet needs into new research directions.

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Methods—On October 1 to 3, 2017, the Sturge-Weber Foundation assembled clinicians from the Clinical Care Network with patients from the Patient Engagement Network of the Sturge-Weber Foundation to identify our current state of knowledge, knowledge gaps and unmet needs.

Results and Conclusions—One clear unmet need is a need for consensus guidelines on care and surveillance. It was strongly recommended that patients be followed by multidisciplinary clinical teams with life-long follow up for children and adults to monitor disease progression in the skin, eye, and brain. Standardized neuroimaging modalities at specified time points are needed together with a stronger clinicopathological understanding. Uniform tissue banking and clinical data acquisition strategies are needed with cross-center, longitudinal studies that will set the stage for new clinical trials. A better understanding of the pathogenic roles of cerebral calcifications and stroke-like symptoms is a clear unmet need with potentially devastating consequences. Biomarkers capable of predicting disease progression will be needed to advance new therapeutic strategies. Importantly, how to deal with the emotional and psychological effects of SWS and its impact on quality of life is a clear unmet need.

Keywords

Sturge-Weber syndrome; consensus statement; imaging; treatment

Introduction

Sturge-Weber syndrome (SWS) is a neurocutaneous disorder associated with facial port wine birthmark, leptomeningeal capillary malformations, and glaucoma. It is caused by somatic activating mutations in the *GNAQ* gene.[1] Although rare, SWS has been recognized for over a century.[2–4] Its natural history is poorly delineated, but there are prognostic indicators that can be utilized to predict its varied course. For example, forehead distribution of the port wine birthmark, delineated at its inferior border by a line joining the outer canthus of the eye to the top of the ear, including the upper eyelid portends adverse neurologic and ophthalmologic outcomes.[5] Seizures are common, and often devastating to the patient and their families. Seizures occur in 75% of unilateral cases and more than 90% among those with bilateral involvement.[6] Early seizure onset,[7] high seizure frequency,[8] and bilateral brain involvement[9] have been associated with poor cognitive outcomes, suggesting that seizure control or possibly prevention is critical. Currently, a major limitation of the treatment of SWS exists as there are no consensus guidelines for the care and surveillance of individuals affected with SWS nor a clear pathophysiological understanding of why the disease progresses.

The Sturge-Weber Foundation was established over 30 years ago by Kirk and Karen Ball, who united families across the world with the goal of improving the quality of life and care of individuals affected with SWS through collaborative education, advocacy, research and financial support. On October 1 to 3, 2017, the Foundation organized a nationwide conference in New Orleans, Louisiana, with the goals of developing a consensus of unmet needs, mechanisms for improving care from the initial diagnosis through the disease course based on these needs, and new research directions. Members of the Clinical Care Network (CCN) from 25 centers, consisting of specialists and researchers in neurology, epilepsy, neuroimaging, ophthalmology, dermatology, dentistry and pathology, met with patients from

the Patient Engagement Network (PEN) to address the following questions in each of these areas:

1. How does clinical symptomatology relate to disease pathogenesis?
2. What are the most important unmet needs in each area and how do these needs affect quality of life?
3. How can we use the CCN to optimize the use of data from registries, clinical datasets, imaging studies, genetics and tissue banking to address these needs?
4. How can we then use this data to develop new biomarkers and therapeutics?

The meeting was broken down into two parts. In the first part, a multidisciplinary overview of SWS was presented to highlight the current consensus on disease treatment, gaps in knowledge, and unmet needs of patients, specifically in the subspecialties of neurology, dermatology, ophthalmology, dentistry and pathology. There were two breakout sessions in the second part of the meeting. The first session focused on unmet clinical needs in neurology, dermatology and ophthalmology. The second breakout session focused on future research directions to explore disease progression. Groups in this session focused on neuroimaging, pathology (tissue banks)/genetics, and data integration. The discussions and recommendations of each breakout group are summarized below.

Neurology

One of the most challenging aspects of CNS manifestations of SWS is the highly variable and unpredictable neurological course. The syndrome is marked by neurologic abnormalities, including seizures, migraine headaches, fluctuating hemiparesis, developmental delay, and stroke-like episodes. Major downstream consequences include cognitive impairments and behavioral dysfunction with attention problems, learning disabilities, and mood fluctuations.[10] Neurologic symptoms are age-dependent. During infancy, initial neurologic symptoms include epilepsy, hemiparesis and stroke-like events. At school age other signs and symptoms can become more noticeable, including headaches, academic difficulties, and behavioral problems. In teenagers and adults, in addition to the previously mentioned symptoms, mental illness, including depression, can be significant. Epilepsy and stroke-like events can continue to occur throughout life. While there is considerable overlap, age-related consensus guidelines and surveillance recommendations will be needed to improve the neurologic care of individuals with SWS. The current state of knowledge of each of these neurological symptoms are described below by age and symptom.

Infancy and toddler age group

Seizures—Seizures in SWS often start in the first 2 years of life, occurring earlier in those with bilateral and/or extensive unilateral hemispheric disease.[10,11] Focal seizures, consisting of clonic motor movements, are the most commonly reported seizure type, followed by generalized seizures.[12,13] However, in SWS specifically, apneic seizures are more common and concerning due to the involvement of the perisylvian region and amygdala. Seizure clustering with intense bouts of seizures following a prolonged period of seizure freedom is

common in SWS, occurring in 40% of cases.[14,15] The underlying cause of these clusters remains unclear, but it may relate to underlying vascular or parenchymal changes, including dense calcifications near the leptomeningeal capillary malformations. Febrile illnesses tend to be an important trigger of seizures, and often lead to status epilepticus.[16] Electroencephalography (EEG) is an important test to perform for SWS patients with a febrile illness and altered mental status (unexplained confusion or unresponsiveness), as they are at risk for non-convulsive status epilepticus. Prolonged video EEG may be needed in some cases of episodic mental status changes. Myoclonic-astatic and gelastic seizures, and asymmetric epileptic spasms, have been described as well.[6]

It is currently advisable to warn parents and caregivers about the risk of seizure clusters and to encourage the development of individualized emergency plans that include the use of rescue benzodiazepine therapy. Some providers recommend the use of intermittent benzodiazepine therapy during febrile illnesses. A similar strategy, as used for the prevention of status epilepticus in Dravet syndrome,[17] may be considered as well. There is no clear treatment guideline for the drug of choice for chronic therapy of seizures in SWS.

Early seizure onset,[7] high seizure frequency,[8] and bilateral brain involvement[9] have been associated with poor cognitive outcomes in SWS, suggesting that during early stages of the disease, infants and toddlers, especially those with bilateral SWS and seizures, are the most vulnerable to the neurologic complications of SWS. Meeting attendees felt that this age group requires close surveillance that would allow for rapid interventions, including epilepsy surgery. Due to the high incidence of seizures in SWS and the potential deleterious effects of seizures in the developing brain during early life stages, the use of preventative anti-seizure treatment in SWS could be used as it has been for other disorders.

Stroke-like episodes—Stroke-like episodes are unique, but poorly understood. They commonly appear as transient episodes of hemiparesis or visual field defects and are often difficult to distinguish from ongoing seizure activity. The underlying mechanism behind stroke-like episodes is poorly understood, but some investigators believe that they may be due to transient ischemia of the cortex due to leptomeningeal capillary malformations. Recurrent thrombosis has also been postulated as a potential cause of stroke-like episodes in SWS.[18] Based on these suppositions, preventative treatment using low dose aspirin at 3–5 mg/kg/day has been proposed and used by many to limit or prevent stroke-like episodes and improve neurodevelopmental outcome.[19,20] However, there have been no prospective controlled trials to help determine whether aspirin actually prevents stroke-like episodes and if the side effects of aspirin therapy outweigh the potential benefits.

School age and teenage group

Headaches—Headache is perhaps the second most common symptom in SWS, effecting 30–45% of patients.[18] Headaches tend to be more prominent in older children and adults and can have a significantly detrimental impact on quality of life.[21] The prevalence of headache meeting the International Headache Society definition of migraine is roughly 28%, with the majority of SWS patients having onset before age 10 years and >50% with associated neurological deficits (focal weakness, visual loss and paresthesia) occurring during an acute

migraine attack.[22] In SWS, migraine with prolonged visual auras and with hemiplegic attacks have been frequently reported.[23–25] The underlying mechanism of migraine aura in SWS is unclear, but may be due to the altered cerebral vascular hemodynamics in SWS that trigger the phenomenon of cortical spreading depression[26] of the underlying brain region near the leptomeningeal capillary malformations and calcifications. Indeed, a single photon emission computed tomography (SPECT) study during an acute attack of headache associated with visual aura in SWS showed increased blood flow in the involved occipital cortex with LMA, which resolved during the convalescent stage but showed interval hypoperfusion, suggesting that the migraine aura in SWS could be due to focal hyperemia associated with vasogenic leakage in the brain under the vascular malformation.[27] Alternatively, these SPECT changes could also be consistent with an initial epileptic event followed by spreading depression.

Despite the high prevalence of headaches and migraines in SWS, there are no existing guidelines on its acute and preventative management in patients with SWS. However, some suggest that sleep, hydration, ibuprofen use and anti-emetics are effective.[28] There have not been any reports of serious side effects associated with the use of triptans in SWS, and many patients self-reported efficacy from its use.[21] For headache prophylaxis, the use of anti-seizure medications, including valproic acid, gabapentin and topiramate, have been suggested.[10] Mechanistically, this is supported if the stimulus of the migraine is a focal ictal event. Concerns about the use of topiramate due to the risk of glaucoma have been risen, although an earlier study on its use for seizure treatment in SWS did not show increased incidence of glaucoma.[29]

Neurocognitive and behavioral Issues—Intellectual disability is common in SWS, noted in 60% of patients, including 33% with a severe cognitive defect.[16] In a recent longitudinal study involving unilateral SWS, early-onset frequent seizures, frontal lobe involvement, and inter-ictal epileptiform EEG abnormalities were strong predictors of poor cognitive outcome.[7] Attention deficit hyperactivity disorder (ADHD) occurs in about 40% of patients with SWS.[30] In another study, stimulants were subjectively assessed to be effective ADHD treatments in SWS with minimal side effects.[30] Neuropsychological testing beginning at age 3 or 4 years can be helpful in identifying high-risk children[31] so that proper interventions, including early initiation of an individualized education plan and behavioral therapy, can be implemented.

Adulthood

Behavioral issues—While all of the above neurological symptoms can persist into adulthood, behavioral issues are an important concern and come up repeatedly in clinical care. Etiology of these are poorly understood and require further study including the ongoing psychological stigmata of the birthmark, role of changing developmental and cognitive abnormalities, seizures, or headaches. Psychological dysfunction may occur in 50% of adult SWS patients, including depression, anxiety, low self-esteem, shame, emotional outbursts and isolation.[32] There are several reports of paranoid disorder and pseudodementia.[33] A recent study showed that the presence of facial port wine stain (with or without associated syndromes) in adults significantly negatively affects their quality of life,

with anxiety and depression as the most commonly reported morbidities.[34] Although mental illness can be a significant issue in SWS in adulthood, there are a lack of detailed studies or proven therapeutic strategies, including a lack of studies on the efficacy and safety of psychopharmacologic medications.

Unmet needs and next steps for neurological symptoms

A major limitation in our ability to establish recommendations for surveillance and develop new treatments stems from a lack of understanding of the natural history of the disease. For this reason, a multicenter standardized surveillance data collection approach is required with detailed, longitudinal clinical data, neuroimaging, and when available, de-identified pathological samples. Standardized surveillance data would allow us to understand how clinical disease manifestations relate to underlying brain pathology, including stroke-like events and noticeable focal neurologic deficits. A major unmet need is to improve our understanding of why some patients with SWS develop clusters of headaches, seizures and stroke-like episodes, especially in young infants during febrile illnesses. Natural history studies are also needed to assess the benefit of potential future therapies.

A considerable amount of discussion at the meeting focused on the pathophysiology of the neurologic manifestations. SWS disease progression remains unclear. Longitudinal studies are needed to measure any changes in cortical draining veins,[35] evidence of cortical ischemia, and growth of intra-parenchymal calcifications. There was discussion of the potential negative effects of these dense calcifications. Recent longitudinal imaging studies demonstrate a possible link between progression of calcifications and early epilepsy.[36] The possibility of targeting therapeutically targeting calcifications in SWS could potentially be supported by earlier studies of treatment of other calcified brain disorders using disodium etidronate.[37] Developing guidelines and evidence-based studies on the use of seizure medications and aspirin is a clear unmet need. The establishment of predictive clinical biomarkers of disease progression that can be used to shorten and increase the number and lower the cost of clinical trials is also an important unmet need.

Epilepsy remains perhaps the most life-altering SWS symptom, affecting up to four of every five patients with SWS. Because of the high prevalence of epileptic symptoms in SWS patients, more clinical trials are required to address the best treatment approach with current medications, as well as to establish the development of disease modifying treatments to prevent or reduce disease burden. There is not currently consensus on how early in life anti-seizure medications should be started and whether there is any preference between the many anticonvulsants available. Ville et al. preformed a study treating pre-symptomatic patients,[38] showing a possible window of optimal opportunity to intervene and, perhaps, improve neuro-cognitive outcome. Studies of alternative treatments, including the use of cannabinoids, are recommended, as earlier studies have shown a potential role of cannabinoids in SWS treatment.

Although considerably more information is needed for an extensive clinical consensus, some recommendations at the meeting were made:

Lastly, the psychological ramifications of SWS are vastly underexplored, and no clear diagnostic or treatment guidelines exist. To the surprise of many clinicians at the meeting, this was the most important unmet need from the PEN. Surveillance, patient registries, and detailed, longitudinal neuropsychological testing are needed, as psychological symptoms are likely underreported. Neuropsychological testing must be include a formal evaluation of psychotherapy versus medication treatment. Support groups with professional facilitators and leaders could be potentially helpful in using online systems to bring patients and their families with this rare disorder together.

Dermatology

Protocols for the timing of evaluation and treatment of high risk capillary malformations on the face vary by institution. According to the International Society for the Study of Vascular Anomalies (ISSVA) classification, SWS falls under the category of capillary malformations with central nervous system and/or ocular anomalies. Dermatologic diagnosis of high risk facial capillary malformations is often used as a predictive tool for estimating risk of neurological problems or glaucoma. As shown by Waechli et al., the location of capillary malformation, or a port-wine stain, could potentially predict a patient's risk for glaucoma. If the port-wine stain involves the forehead (delineated at its inferior border by a line joining the outer canthus of the eye to the top of the ear, and including the upper eyelid), patients have a significantly higher possibility of having an abnormal MRI, epilepsy, poor neurocognitive outcome, and glaucoma, compared with lesions not affecting the forehead.[5]

The importance of treating dermatologic lesions is not only for aesthetic reasons, but also to improve psychosocial outcomes. There have been previous discussions of the potential neurotoxicity of exposing pediatric patients to repetitive anesthetics for laser treatments. However, in a recent study, Terushkin et al. demonstrated no increment in the risk for neurodevelopmental disorders in patients who received multiple laser procedures under general anesthesia compared to the general population.[39]

Although pulsed dye laser is the most common first-line treatment, several different dermatologic treatment options currently exist for patients with SWS, including the use of other visible light lasers, fractionated lasers and devices, photodynamic therapy, and a combination of those modalities. Many practices have patients undergo multiple laser treatments under general anesthesia, while other practices perform all laser treatments without general anesthesia. As exposure to anesthesia remains controversial in pediatrics, an open discussion of timing, benefits and risks of laser therapy with and without general anesthesia should be discussed with patients and families prior to initiating therapy.

Unmet Needs and Next Steps for Dermatological Symptoms

While the dermatological manifestations of SWS do not lead to the same developmental and cognitive deficits as seizures and neurological manifestations, the stigmata and psychological trauma is not adequately discussed. Standardized treatment approaches and clinical trials to optimize psychological and dermatologic treatments and whether generalized anesthesia should be used for these are current unmet needs. The use of the

extent of the port wine birthmark could be a potential biomarker to warrant neuroimaging and glaucoma surveillance studies.

Ophthalmology

An ophthalmic exam is indicated for all newborn babies with a port wine mark affecting the eyelids. When involving the eye, SWS is associated with periocular cutaneous vascular malformations and intraocular findings which include episcleral or choroidal hemangiomas and iris heterochromia.[40] The most common ocular complication associated with SWS is glaucoma, which occurs in 30–70% of patients.[41–43] Glaucoma is characterized by optic nerve damage associated with elevated intraocular pressure that can result in complete, irreversible blindness if untreated.[44] The onset of glaucoma is thought to be bimodal, with 60% of patients developing glaucoma in infancy and the remaining 40% developing glaucoma in childhood or early adulthood.[45] As children with SWS have a life-long risk of glaucoma, there is a need for periodic ocular examinations with or without the use of general anesthesia, depending on the age and cooperation of the child.

Currently, little is known about the mechanism of glaucoma development in SWS. It is thought to be related to both congenital anterior chamber vascular malformations as well as high episcleral venous pressure (EVP). Increased EVP causes a resistance to outflow from the anterior chamber and could have other implications on proper treatment and disease management.[46] Currently, the first line of treatment consists of topically applied medications to target: (1) reduction in aqueous humor production (beta-blockers and carbonic anhydrase inhibitors); (2) increase in the rate of aqueous humor outflow (prostaglandin analogs); or (3) both decrease aqueous humor production and increase outflow (alpha agonists). Despite all these, the pharmaceutical agents currently available to treat glaucoma do not reduce EVP.

Given the rare nature of this condition, only small case series exist regarding the management of patients with SWS. As SWS is associated with anatomic abnormalities of the anterior chamber, medical therapies to lower the intraocular pressure are often ineffective.[46] Therefore, surgical interventions such as goniotomy and trabeculotomy are the preferred treatments.[47,48] However, patients with SWS tend to have lower surgical success rates[49,50] and greater numbers of intra- and post-operative complications following glaucoma surgery.[51,52] As many as 60% of eyes treated with angle surgery require additional angle surgery and 40% require post-operative medications after 3–5 years.[53] Future randomized prospective studies would be helpful in determining a definitive treatment course, however are unlikely to be performed given the rare nature of the condition.

The critical barrier in developing better intervention strategies is the need for better understanding of physiological processes in the diseased state. Currently, lowering the intraocular pressure (IOP) is the only proven strategy for protecting the optic nerve from glaucomatous optic neuropathy. Many aspects are still unknown as far as the molecular mechanisms by which trabecular meshwork (TM) cells sense the fluid flow fluctuations in the extracellular matrix and how cell shape and motility varies TM pore size, thus regulating the passing of fluid through TM. The Bhattacharya lab is currently working towards elucidating biomarkers for lipid entities that make the TM more elastic in the pathologic

state, thus making it more “normal” like.[54] There is also research on neurotrophic factor intraocular implants,[55] as well as efforts towards discovering lipid entities capable of neuronal regeneration.[56]

The development of IOP-independent strategies is needed to address the underlying pathology in glaucoma. For instance, when elevated IOP occurs because of elevated episcleral venous pressure, it can be very challenging to decrease the IOP without treating the primary cause of the raised episcleral venous pressure. Therefore, the role of episcleral venous pressure should be better explored as a potential target for medical interventions.

Unmet needs for Ophthalmological Symptoms

In order to make meaningful progress in SWS, a better understanding of the mechanisms of glaucoma is needed. A key advantage of the eye is that, unlike the brain, lesions can be visualized and followed without the need for neuroimaging. Clinical studies of optimized treatments and surveillance recommendations will need to be established. Further mechanistic studies in SWS ophthalmology research are needed, which include cell culture, tissue banking, animal models and more extensive collaborative efforts between researchers and clinicians.

Radiology

Neuroimaging provides critical diagnostic information to establish and monitor presence, extent and severity of brain involvement in SWS. Goals and methods of neuroimaging in SWS should be tailored based on the patient’s age, symptoms and disease stage. MRI is the primary imaging modality recommended for clinical practice. Other imaging modalities (CT, PET, SPECT) have a more limited role and may be used in select cases to address specific clinical or research questions.

MRI in various stages of SWS

MRI is preferably performed on 3 Tesla (T) field strength, but 1.5T is acceptable to establish diagnosis when no 3T magnet is available. MRI performed and interpreted in specialized pediatric centers is recommended due to the availability of experienced radiologists who can provide dedicated facilities and protocols to assess the spectrum of imaging features associated with SWS. Targeted imaging should be performed based on patient age, clinical history and symptoms. Recommended basic and optional advanced sequences are listed in Table 2. The potential specific diagnostic values of each MRI sequence for detection of SWS-related abnormalities are listed in Table 3.

1. Children with high-risk port-wine birthmark (PWB) but no clinical evidence of brain involvement—These children are usually very young (often infants) whose facial PWB involves the forehead and therefore concerning for brain involvement. When PWB is observed in the nursery, no immediate neuroimaging (including acute CT scan) is necessary, unless there are clinical signs of brain involvement (seizures and/or neurological deficit). Parents should be aware of potential false negative imaging findings, especially before 1 year of age when myelination is largely incomplete.[57] The goal of MRI, if performed, is to

evaluate for brain abnormalities consistent with SWS necessitating greater clinical vigilance. Pre-symptomatic diagnosis of brain involvement may support the use of preventive anti-seizure medication or aspirin, and/or enrollment in a drug trial. Concerns regarding MRI in young children include the potential long-term cognitive effects of sedation and general anesthesia, as well as repeated gadolinium contrast administration with systemic deposition in various tissues, including brain and bone marrow.[58] To minimize these risks, one could choose a fast, non-sedated, non-contrast screening MRI in young pre-symptomatic children, including axial T1, T2 (or FLAIR), DWI and SWI. This approach is also useful in symptomatic patients with known contrast allergy. These non-contrast images may be able to detect early venous vascular abnormalities (such as absence of cortical veins, pial angiomatosis, engorgement of deep medullary/ependymal veins and choroid plexus), accelerated myelination, focal encephalomalacia, atrophy, and cortical calcification.[59–61] Alternatively, parents and physicians may decide to perform a full diagnostic MRI with contrast administration in the presymptomatic phase (recommended MRI details in next section); however, delaying such an MRI to after 1 year of age is preferred in children who are asymptomatic or in whom no preventive therapy is planned. The comparative effectiveness of these two approaches has not been established; collecting such data will require a multi-center effort.

2. Children shortly after onset of first neurological symptoms (early post-symptomatic phase, e.g., seizure(s) or stroke-like episode(s)—Children with new-onset seizure(s) and/or other neurological symptoms concerning for SWS brain involvement will require at least one optimized, high-quality MRI with contrast. Optimal timing is not established, but most clinicians will order this shortly after the first clinical symptom(s) (often during initial hospitalization). If the MRI appears negative for venous vascular abnormalities diagnostic of SWS, a follow-up imaging can be considered after 1–2 years of age if no additional or progressive clinical symptoms occur. The recommended MRI approach includes 3-D pre- and post-contrast sequences, requiring sedation or anesthesia for optimal good image quality. High-resolution volumetric sequences are recommended to optimize detection of subtle parenchymal changes, cortical malformations. SWI is very sensitive for venous abnormalities, and can be reconstructed into minimal intensity projections (minIP) for optimal visualization.[60,62,63] Phase maps from SWI can also be utilized to assess diamagnetic phase shift from cortical calcifications, typically (but not always) a late finding in SWS that is related to progressive venous ischemia.[64,65] Post-contrast MRI is recommended to evaluate for optimal evaluation of pial angiomatosis. Anatomic and/or vascular imaging may demonstrate the absence of normal cortical veins, with the characteristic pial angiomatosis of SWS best visualized on post-contrast T1 and/or FLAIR images. The radiologist should also assess for extracerebral changes associated with SWS, including choroidal angiomas and soft tissue/bone overgrowth.

Of note, post-symptomatic MRI following prolonged seizures, status epilepticus, seizure clusters, or stroke-like episodes may detect transient abnormalities, such as diffusion/perfusion changes and pial vascular engorgement.[66,67] In this scenario, repeat MRI following resolution of symptoms may be advisable to more accurately assess the extent and severity of SWS involvement.

3. Follow-up MRI in symptomatic SWS children—Routine follow-up MRIs are not recommended in SWS children with stable clinical symptoms, controlled seizures, and no neuro-cognitive decline, due to the potential risks delineated above. Repeat MRI may be indicated in select patients with known SWS, e.g., in the case of new or progressive neurological symptom(s), uncontrolled or worsening seizures, change in seizure semiology, new stroke-like symptoms with prolonged neurological deficit, new-onset migraine, or other clinical issues that may arise from progressive changes in brain structure and/or function. Follow-up MRI should include basic pre-contrast (T1, T2/FLAIR, DWI, SWI) sequences comparable to those used for baseline imaging. These sequences are sufficient to evaluate progression, such as progressive atrophy, calcification, enlarged deep medullary veins and/or ischemic brain abnormalities.[59,60,63] Routine use of contrast-enhanced MRI for follow-up should be avoided, due to the potential risks of from repeated sedations and gadolinium tissue deposition; decision regarding contrast injection has to be made on individual basis.

4. MRI in children with SWS-associated drug-resistant epilepsy undergoing pre-surgical evaluation—The primary goal of pre-surgical MRI in children with drug-resistant epilepsy is to determine the extent and severity of brain involvement (frontal lobes, eloquent cortical areas, unilateral versus bilateral involvement). These results can assist in clinical assessment and surgical planning for various epilepsy surgeries including focal cortical resection, posterior disconnection, partial or complete callosotomy, and hemispherectomy. Advanced imaging techniques may include DTI for fiber tractography, [68–70] and functional MRI (fMRI) in older co-operative subjects to localize eloquent cortical regions (motor, language, visual, auditory). Pre-surgical imaging may include additional imaging, such as PET, as detailed below.

5. MRI for clinical research and biomarker development—MRI examinations performed for clinical research or trials including biomarker development should be tailored to the specific research question(s). Emphasis should be made on limitation of potential risks from sedation/anesthesia and gadolinium administration. For biomarker development, advanced MRI parameters that are objective, quantifiable and replicable are preferred, especially when applied in longitudinal studies. Most advanced MRI techniques require further validation in prospective patient cohorts and should be acquired with as similar parameters as possible for multi-center studies. Examples include anatomic morphometry (including cortical thickness, gray and white matter volumes,[71] extent of calcifications[65]), diffusion-weighted ADC and FA values,[60] structural connectivity from DTI, functional connectivity from resting-state fMRI,[72] perfusion parameters from DCE/DSC/ASL MRI, and various brain metabolites on MRS[73,74] (Table 2).

Additional imaging modalities in SWS

1. Computed tomography (CT)—Repeated use of CT scanning in the diagnosis and follow-up of SWS is not generally recommended, due to limited overall sensitivity and risk of ionizing radiation. Sometimes, SWS may be suspected or diagnosed on CT performed in a child with no port-wine stain without prior clinical suspicion of SWS. CT is sensitive for brain calcifications, which can be progressive and a late finding of SWS. However, MRI with SWI can provide comparable if not greater accuracy, being sensitive to

microhemorrhages/microcalcifications, and is preferred due to the non-ionizing technique. CT is also the gold standard for cortical bone imaging, and may be indicated for patients with craniofacial overgrowth when such abnormalities are suspected to cause clinical symptoms.[75]

2. Positron emission tomography (PET) and single-photon emission tomography (SPECT)—Nuclear medicine imaging modalities expose the patient to radiation, and their use is typically confined to select patients requiring pre-surgical evaluation for drug-resistant epilepsy. FDG-PET can be used to evaluate the extent and severity of hypometabolic abnormalities in the affected hemisphere, as well as the functional integrity of the opposite hemisphere (in unilateral SWS).[60,76] In addition to hypometabolic changes, affected cortical regions in young children with SWS may show inter-ictal hypermetabolism that may precede evolution to decreased metabolism subsequently (if PET is repeated without interval surgery).[77] FDG-PET can also be applied as an imaging biomarker of disease progression and neurocognitive function.[78,79] Ictal and inter-ictal SPECT[80] may be used to lateralize and/or localize the epileptogenic area in cases where clinical semiology, EEG and other imaging modalities are non-concordant. Optimal SPECT image analysis includes the application of SISCOM (Subtraction Ictal SPECT Co-registered to MRI) with statistical methods such as statistical parametric mapping.[81]

Tissue Banking

By involving the skin, the eye, and the brain, SWS produces disease manifestations that yield biopsies and resections of these tissues. Given that one of our major limitations is relating clinical symptoms to the underlying pathophysiology, tissue banking and detailed analyses of these invaluable samples could be instrumental in moving this understanding forward. The Tissue Banking Group of the 2015 SWS Workshop concluded that a paucity of available tissues from SWS patients for research is a significant impediment to progress and can be alleviated by further development of a centralized tissue banking system.[82] Several limitations currently exist in the procurement of tissue samples, which inhibit research progress. Investigators who have to date made important advances in understanding the underlying biology of SWS have necessity relied on very limited “private” archives of often haphazardly collected and inconsistently preserved affected tissues (skin and brain).

Affected tissue has also been obtained from other NIH-funded brain and tissue banks, where affected tissue is at least theoretically more consistently collected, but it is rarely paired with blood or unaffected adjacent tissue from the donating patients and there is generally very limited clinical information to form clinicopathological associations. The establishment of a centralized tissue banking system and tissue collection and processing protocol would allow researchers to specify the types of tissue and tissue preservation tactics which would further research. Participating locations must be able to efficiently, accurately, and systematically process incoming samples—particularly under time constraints—and provide basic banking services (sealing, monitoring freezers, secure documentation, and technical support).

Specifically, the Tissue Banking Group of the 2017 SWS Workshop called for tissue samples from the eyes (including the aqueous humor, choroid angioma, and the whole eye), brain,

skin (unaffected and affected areas), and oral regions of SWS patients. Further, researchers expressed a need for blood and/or adjacent unaffected tissue from donating patients that is important for genetic studies of mosaic mutations. Importantly, there must also be a variety of tissue processing methods to accommodate differences in researcher needs: (a) retrospective and prospective collection of paraffin-embedded blocks from well-characterized SWS patients from multiple collaborating institutions; (b) quality snap-frozen tissues for molecular and proteomic studies; and (c) fresh (unfixed/unfrozen) “live” tissue to perform in vitro tissue explant and cell culture studies and from which to prepare various SWS cell lines which will become important once techniques for isolating and perpetuating cells with the mutation are established. Development of a process is needed for requesting and choosing optimal samples for individual study protocols and for determining appropriate aliquot sizes for any given study (to maximize availability of tissue from any given donor for multiple SWS studies). Potential users of the Bank’s tissue archives would be required to register, in order to facilitate thoughtful and fair stewardship of the bank’s limited stores, to be overseen by a multipartisan utilization committee empowered to prioritize and audit usage in order to help govern sustainable and fair distribution practices.

The value of each tissue specimen goes up exponentially with the quality and detail of associated clinical and imaging data. Having neuroimaging studies precisely linked to each brain tissue sample could be instrumental in developing non-invasive biomarkers. Knowing the clinical stories of each patient linked to tissue samples can provide important clues to disease progression and underlying pathogenesis. Therefore, it is critical that any centralized tissue collection be linked to ongoing efforts of clinical data collection.

The Tissue Banking Group of the 2017 SWS Workshop proposed the funded utilization of the resources of one or more pre-existing, high-quality biobanks already affiliated with SWS investigators and active vascular anomalies centers, forming a closely coordinated “central” SWS bank network that would store SWS tissue originating from those central network facilities as well as tissue shipped in from other hospitals that do not have viable local banking options. Such a network of collaborating biobanks focused on SWS/PWB tissue would together form a multisite SWS/PWB bank with standardized collection, shipping, storage, and quality control protocols. The component primary “physical” banks of such a system, joined by other collaborating banks, could together create a “virtual” bank of specimens and associated clinical data available for use by a defined—hopefully large—group of registered users with web-based access. Universal identifiers for each sample, individual, or cell line would be recorded to retain important linkages.

The Tissue Banking Group of the 2017 SWS Workshop outlined steps toward the development of the centralized tissue banking system: designation of a central administrative facilitator; identification of 2–5 primary banking sites and PIs as well as recruitment of key clinicians, surgeons, pathologists, and administrative staff at each site into the process; the establishment of a workgroup between the sites to develop guidelines and protocols for collection and dissemination of samples and scheduling of telemeetings towards these goals; compilation of a “starter set” of archived SWS tissues; pursuance of funding; and development of a centralized IRB protocol. These are lofty goals with lots of hurdles, but the knowledge to be gained would greater outshadow the potential pitfalls along the way.

Data Integration

Our long-term goal is to develop both clinical recommendations, novel biomarkers, and new therapeutics for SWS. To achieve this, we need to be able to link what we know clinically about symptoms to underlying pathophysiology. Key to success of these linkages are integrating all of the various types of data at a single web-based, de-identified site. Achieving data integration requires alignment of IRB protocols and then bringing together different databases with different types of data including patient registries, clinical data, imaging, tissue/histology, and genetic data onto a single platform. While this is a lofty goal, it is achievable and has recently been done for neocortical epilepsy patients yielding important new insights and potential biomarkers.[83–87]

Conclusions

The meeting recognized that creation of evidence-based guidelines in the care and surveillance of individuals affected with SWS would be of great value to patients and their care givers. To achieve these goals, initial guidelines should be suggested based on currently available evidence. Creation of a multicenter, integrated and standardized dataset linking clinical presentations, neuroimaging, genetics and pathology are needed to develop new biomarkers of disease and therapeutics that could be tested through the Sturge-Weber Foundation Clinical Care Network. While a major focus has been on the medical manifestations of the skin, eye, and brain, it is important not to neglect important emotional and psychological manifestations of SWS.

Acknowledgments

We greatly acknowledge the participation and important suggestions from the Patient Engagement network of the Sturge-Weber Foundation. Without them, and all the patients with Sturge-Weber Syndrome, this work would not have been possible. We would also like to acknowledge the support from Patient-Centered Outcomes Research Institute (PCORI) and National Institutes of Health grants (NS041922 for Juhász, C.) and the Brain Vascular Malformation Consortium: Predictor's of Clinical Course (U54NS065705 Pilot project for Loeb, JA).

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Table 1

Clinical recommendations in Neurology

Recommendations in Neurology	
1.	We recommend that all patients with SWS and epilepsy should have an individualized or personalized seizure action plan.
2.	For patients with a history of seizure clusters or status epilepticus, we recommend to consider intermittent benzodiazepine therapy during the patient's febrile illnesses.
3.	Electroencephalography (EEG) is an important test to perform for SWS patients with a febrile illness and altered mental status (unexplained confusion or unresponsiveness) as they are at risk for non-convulsive status epilepticus.

Table 2

Recommended MRI sequences at various disease stages in Sturge-Weber syndrome. + indicates established basic sequences recommended at various disease stages, mostly to provide qualitative information for practical clinical diagnosis and evaluation. (+) indicates optional sequences at each stage including advanced MRI enabling potential disease quantification for clinical research and biomarker development.

	non-contrast MRI										post-contrast MRI		
	T1	**T2/FLAIR**	**SW**	**3D-T1**	**3D-T2/FLAIR**	**DWI/ADC**	**DTI**	**MRS**	**ASL**	**fMRI**	**DSC/DCE**	**T1/FLAIR**	**TOF/TRMRA/MRV**
Pre-symptomatic	+	+	+	(+)	(+)	+						(+)	
Early/first post-symptomatic	(+)	(+)	+	+	+	+	(+)		(+)		(+)	+	(+)
Follow-up post-symptomatic	+	+	+	(+)	(+)	+	(+)		(+)		(+)	(+)	(+)
Presurgical evaluation			+	+	+	+	(+)	(+)	(+)	(+)	(+)	+	+
Research, biomarker development	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)

ADC=apparent diffusion coefficient; ASL=arterial spin labeling; DCE=dynamic contrast-enhanced; DSC=dynamic susceptibility contrast; DTI=diffusion tensor imaging; DWI=diffusion-weighted imaging; FLAIR=fluid-attenuated inversion recovery; fMRI = functional magnetic resonance imaging; MRA=magnetic resonance angiography; MRV=magnetic resonance venography; MRS=magnetic resonance spectroscopy; SWI=susceptibility-weighted imaging; TOF=time-of-flight; TR=time-resolved

Table 3

Potential diagnostic value of various MRI sequences in evaluation of SWS patients. Advanced sequences where clinical value has not been fully established should be candidates for utilization in clinical research, validation studies, and biomarker development.

MRI sequence	Applications, target structure/function	Main pathology detected in SWS
Pre-contrast sequences		
T1	Anatomic structure, myelination, volumetry (if 3D)	Cortical/white matter atrophy Encephalomalacia
		Cortical developmental malformation
T2/FLAIR	Anatomic structure, myelination, white matter signal, volumetry (if 3D)	Accelerated myelination (infants)
		White matter injury and atrophy
		Cortical developmental malformations
SWI	Calcification, venous abnormalities	Cortical/subcortical calcification
		Enlarged medullary and ependymal veins
DWI/ADC	Brain diffusivity	White mater injury (ischemic)
		Post-seizure effects
DTI	Brain microstructure	White matter microstructural damage
	White matter structural connectivity	Damaged/reorganized fiber tracts
MRS	Metabolite concentrations	Decreased NAA, increased choline in normal-appearing white matter
ASL	Evaluation of absolute cerebral blood flow (CBF)	Decreased/increased CBF in affected hemisphere
fMRI - activation	Blood flow changes during task (motor, language)	Localization of eloquent (motor and language) cortex for presurgical evaluation
- resting-state	Evaluation of brain functional connectivity and networks without activation	Extent/severity of altered functional connectivity
Post-contrast sequences		
Perfusion MRI (DSC/DCE)	Evaluation of relative contrast kinetics (with post-processing)	Decreased/increased relative cerebral blood volume and CBF in affected hemisphere
T1/FLAIR	Identification of superficial and deep cerebral veins.	Leptomeningeal pial angiomatosis, enlarged choroid plexus, enlarged deep medullary and ependymal veins
		Choroidal angioma
MRA/MRV	Dedicated vascular evaluation	Arterial and venous flow abnormalities

Table 4

Critical goals which must be achieved for the successful development of a centralized tissue bank

Goals for a successful Tissue Bank	
1.	Enlist key clinicians, surgeons, and pathologists at primary (later secondary) participating institutions to promote timely salvage and banking of excess tissue from medically necessary tissue resections
2.	Procure NIH or other nonpartisan funding to fund both centralized and local facilitators, storage, shipping, and processing fees
3.	Development of inclusion criteria for each IRB-consented donor is needed, which would include clinical documentation and verification of diagnosis
4.	Develop a shared, multi-institutional IRB protocol to facilitate sample acquisition using standardized instructions and kits for collection, handling, portioning, processing, shipping, and storage of fresh, snap frozen, and fixed paraffin-embedded tissue samples
5.	Standardized forms must be developed for collection of pertinent clinical information from each consented donor and input of that data into a centralized, web-accessed database cataloging all banked specimens from all participating institutions
6.	Consent protocols will require a standardized banking consent form and assignment of a unique SWS identifier (preferably pre-assigned before scheduled surgery to each specimen, regardless of storage location)
7.	The establishment of a dbGaP project (database of Genotypes and Phenotypes) is needed to archive and distribute the results of studies that have investigated the interaction of genotype and phenotype and to store SWS/PWB sequence data
8.	Must determine a cost/subsidy structure for infra-structural development, maintenance, and usage
9.	System of outcomes or publication tracking should be developed.