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Original Article

Neurological Complications of Sturge-Weber Syndrome: Current Status and Unmet Needs

Aimee F. Luat, MD [a, b], Csaba Juhász, MD, PhD [a, b], Jeffrey A. Loeb, MD, PhD [c], Harry T. Chugani, MD [d], Stephen J. Falchek, MD [e, f], Badal Jain, MD [e, f], Carol Greene-Roethke, BSN, RN [e, f], Catherine Amlie-Lefond, MD [g], Karen L. Ball, BS [h], Amy Davis, BSN, RN [i], Anna Pinto, MD, PhD [j, *]

[a] Department of Pediatrics, Wayne State University Children's Hospital of Michigan, Detroit, Michigan
[b] Department of Neurology, Wayne State University Children's Hospital of Michigan, Detroit, Michigan
[c] Department of Neurology and Rehabilitation, University of Illinois, Chicago, Illinois
[d] Department of Neurology, New York University School of Medicine, New York, New York
[e] Department of Neurology, Nemours duPont Hospital for Children, Wilmington, Delaware
[f] Thomas Jefferson University, Philadelphia, Pennsylvania
[g] Department of Neurology, Seattle's Children's Hospital, Seattle, Washington
[h] The Sturge-Weber Foundation, Houston, Texas
[i] Department of Neurosciences, Cook Children's Healthcare System, Forth Worth, Texas
[j] Department of Neurology, Harvard Medical School, Children's Hospital Boston, Boston, Massachusetts

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ABSTRACT

Objective: We aimed to identify the current status and major unmet needs in the management of neurological complications in Sturge-Weber syndrome.
Methods: An expert panel consisting of neurologists convened during the Sturge-Weber Foundation Clinical Care Network conference in September 2018. Literature regarding current treatment strategies for neurological complications was reviewed.
Results: Although strong evidence-based standards are lacking, the implementation of consensus-based standards of care and outcome measures to be shared across all Sturge-Weber Foundation Clinical Care Network Centers are needed. Each patient with Sturge-Weber syndrome should have an individualized seizure action plan. There is a need to determine the appropriate abortive and preventive treatment of migraine headaches in Sturge-Weber syndrome. Likewise, a better understanding and better diagnostic modalities and treatments are needed for stroke-like episodes. As behavioral problems are common, the appropriate screening tools for mental illnesses and the timing for screening should be established. Brain magnetic resonance imaging (MRI) preferably done after age one year is the primary imaging modality of choice to establish the diagnosis, although advances in MRI techniques can improve presymptomatic diagnosis to identify patients eligible for preventive drug trials.
Conclusion: We identified the unmet needs in the management of neurological complications in Sturge-Weber syndrome. We define a minimum standard brain MRI protocol to be used by Sturge-Weber syndrome centers. Future multicenter clinical trials on specific treatments of Sturge-Weber syndrome-associated neurological complications are needed. An improved national clinical database is critically needed to understand its natural course, and for retrospective and prospective measures of treatment efficacy.

Introduction

Sturge-Weber syndrome (SWS) is a rare neurocutaneous disorder associated with facial cutaneous capillary or venous malformations (port-wine birthmark), leptomeningeal vascular

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* Communications should be addressed to: Pinto; Department of Neurology; Harvard Medical School; Children's Hospital Boston; 300 Longwood Avenue, Boston, MA 02115.
E-mail address: Anna.Pinto@childrens.harvard.edu (A. Pinto).

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malformations, and ocular abnormalities including glaucoma and choroidal venous malformations. Both SWS and isolated capillary malformation or port-wine birthmark are now known to be caused by an activating somatic mutation of the *GNAQ* gene (R183Q), which encodes the α-subunit of the guanine nucleotide-binding protein (G-protein) called Gαq[1] (Fig). G-protein-coupled receptors are membrane receptors that transmit external signals to the inside of the cell.[2] The R183q mutation in *GNAQ* results in a protein with impaired autohydrolysis of activated Gαq leading to its impaired inactivation, and, as a result, overactivation of multiple downstream pathways[3] (Fig). Somatic *GNAQ* gene mutation has been demonstrated in the SWS-affected skin capillary malformations, brain structures, and endothelial cells.[4-6] Recently, a computational modeling study has shown that the mutation results in destabilization of the inactive guanosine diphosphate-bound form of *GNAQ* by abolishing the hydrogen bonds between R183 residue and guanosine diphosphate molecule.[7] The timing of the mutation during postconceptual fetal development determines the extent of involvement; the earlier the somatic mosaic mutation in progenitor cells, the greater the impact and the number of structures involved (brain, skin, and eye). When the somatic mutation occurs later in fetal development, after the structures have separated, a more limited involvement might occur as in isolated nonsyndromic port-wine birthmarks[8] or isolated brain involvement without skin manifestation.[9] Studies on disease pathogenesis could inform treatment strategies that specifically target the imbalance of the downstream signaling pathways hyperactivated by the *GNAQ* mutation.[3]

The neurological complications of SWS include epilepsy, stroke-like episodes, migraine, learning, and behavioral difficulties affecting every aspect of the affected individual's life. The exact mechanisms by which the SWS extra-axial vascular abnormality leads to brain injury and neurological complications remain to be fully understood, but venous stasis likely plays a role. Efforts have been made to predict who is at greatest risk for these symptoms. The strongest predictors of neurological complications include both distribution (involvement of the forehead and upper eyelid) and size of the port-wine birthmark[10] and the magnetic resonance imaging (MRI) findings (unilateral versus bilateral brain involvement).[11]

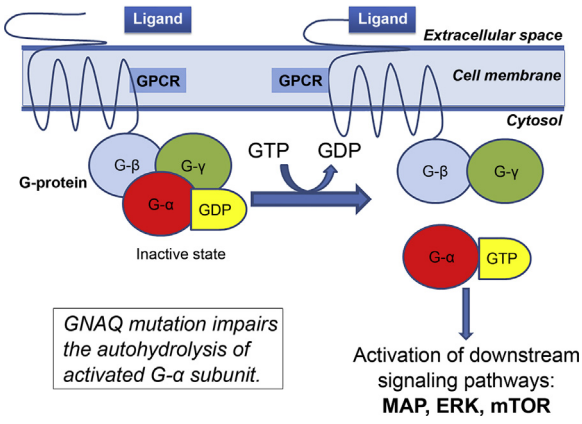

FIGURE. A simplified scheme of the Gαq signaling pathway. G-protein-coupled receptors (GPCRs) are key transducers of signals from the extracellular milieu to the inside of the cell. GPCR is linked to a membrane-bound heterotrimeric G-protein composed of three subunits: α, β, and γ. The G-α subunit has a guanosine triphosphatase (GTPase) domain and is capable of hydrolyzing guanosine triphosphate (GTP) to guanosine diphosphate (GDP). When bound to GDP, the complex is inactive because the α subunit is tightly bound with the β and γ subunits. Upon binding of an extracellular ligand to the GPCR, conformational changes occur that release the GDP, allowing GTP to bind to the G-α subunit, thus activating the complex and resulting in the dissociation of G-α from the G-β and G-γ subunits. The G-α subunit then proceeds to interact with downstream pathways including mitogen-activated protein (MAP) kinase, extracellular signal-regulated kinase (ERK) also known as Ras-Raf-MEK-ERK pathway, as well as the mammalian target of rapamycin (mTOR) pathway. R183q mutation in GNAQ results in a protein with impaired autohydrolysis of the activated G-α leading to impaired inactivation and, as a result, hyperactivation of the downstream pathways. The color version of this figure is available in the online edition.

We have limited understanding of the pathophysiology of symptoms in SWS, and the literature regarding the optimal management and surveillance of the neurological complications in SWS is largely confined to retrospective studies (Table). The Sturge-Weber Foundation Clinical Care Network (CCN) convened on September 21 and 22, 2018, at the A. I. duPont Hospital for Children, Wilmington, DE, to discuss the current status and unmet needs in the management of the neurological issues in SWS. A panel of neurologists, epileptologists, neuroradiologists, and researchers reviewed and discussed the literature in regard to the optimum management of the neurological complications in SWS. A major goal of these proceedings was to identify major unmet needs and translate these into future clinical studies to improve the neurological outcome of individuals with SWS. Below, we summarize these for each of the major neurological complications and discuss a standardized imaging approach that could be applied in a serial manner to understand, identify potential treatments, and develop biomarkers for future clinical trials.

Seizures

Epilepsy is very common in SWS, occurring in approximately 70% of those with unilateral leptomeningeal capillary malformation and 90% of those with bilateral disease[11] with most seizures presenting in the first two years of life.[8,29] In a study of 171 patients, 75% of those with seizures became symptomatic during the first year of life, 11% during the second year, and only 14% after the second year.[30] This finding suggested that if a child stayed seizure-free during the first two years of life, the subsequent risk of developing seizure would decrease significantly, although adult onset of seizures has been rarely reported.[31] The predominant seizure type is focal, especially focal motor clonic seizures.[32,33] In infants, a characteristic pattern of seizure clustering, defined by Kossoff et al.[12] as multiple seizures over a 24-hour period (or three or more in 24 hours[34]) or a prolonged seizure ≥30 minutes at least once in their lifetime followed by prolonged seizure-free periods, is common.[12] This suggests the need to evaluate the impact of the use of aggressive rescue medication with benzodiazepines during seizure clustering.[12] Thus, intermittent benzodiazepine therapy during febrile illnesses and an individualized seizure action plan is encouraged in the recently published multidisciplinary consensus on SWS.[35]

Recent studies have shown that seizure-related factors including early age of seizure onset, frequent seizures, and abnormal epileptiform discharges on electroencephalography contribute to poor cognitive and motor outcome in SWS.[26,36] The largest impact has been shown in young children with seizure onset before age one year, suggesting that delay or prevention of seizure onset, e.g., with the use of prophylactic antiseizure medication in children younger than one year, may have a positive effect on their cognitive and motor outcome.[36] Hence, investigators have explored the use of presymptomatic treatment with aspirin and antiseizure medications to delay the onset of seizures in SWS.[14,15] In the most recent retrospective study reported by Day et al.,[14] seizure scores were significantly less in presymptomatically treated infants compared with carefully matched postsymptomatically treated infants, and a higher age of seizure onset was noted in the presymptomatically treated group.

TABLE.
Summary of Studies That Address the Diagnostic Evaluation and Treatment of the Key Neurological Complications in Sturge-Weber Syndrome

Neurological Considerations	Key Studies	Study Design	No. of Subjects	Diagnostic or Therapeutic Intervention Involved	Main Conclusions	Suggested Research Avenues
Seizures						
Seizure clustering	Kossoff et al.[12]	Retrospective	77	None	A characteristic pattern of seizure clustering followed by seizure-free periods was noted in 39%	Intermittent BZP therapy in patients with risk of having seizure clustering
Seizure frequency	Juhasz et al.[13]	Retrospective	10	MR spectroscopic imaging	Affected hemisphere with high GLU/ Cr compared with the unaffected side; high GLU ratios correlated with high seizure frequency	Prospective study on the effect of anti-GLU ASD on seizures
Presymptomatic treatment	Day et al.[14]	Retrospective with matched controls	15	LEV + aspirin	Seizure scores were significantly less in presymptomatically treated subjects than in postsymptomatically treated infants	Prospective multicenter trial with ASD and/or aspirin
	Ville et al.[15]	Prospective, nonrandomized	37	Phenobarbital	Mental retardation was less frequent in the group treated prophylactically (43.7% versus 76.2%, $P < 0.05$)	
Postsymptomatic ASD treatment	Kaplan et al.[16]	Retrospective	108	ASD comparative efficacy on seizure control	CBZ/OXC with better seizure control than LEV in initial therapy	Prospective randomized controlled trial to compare the efficacy, tolerability, and neuropsychologic effects of ASD
	Kaplan et al.[17]	Prospective, open label	5	CBD treatment (side effects)	CBD well tolerated	Prospective evaluation of CBD efficacy (NCT02332655 trial active, not yet recruiting)
Epilepsy surgery	Bourgeois et al.[18]	Retrospective	27	Evaluation of surgical outcome with regard to seizure control and neuropsychologic development	Adequate resection or disconnection of diseased hemisphere is an important factor in achieving early seizure control	Systematic review of all studies that assessed the outcomes of epilepsy surgery including focal resection and hemispherectomy
	Kossoff et al.[19]	Retrospective parent survey	32	Evaluation of early hemispherectomy	81% seizure-free, 53% off ASD Hemispherectomy type did not influence the outcome. Postoperative hemiparesis was not more severe following surgery	Collection of multicenter surgical data for seizure and neurocognitive outcome
	Arzimanoglou et al.[20]	Retrospective	20	Postoperative outcome after 14 cortical resections, 5 hemispherectomies, 1 callosotomy	13 of 20 became seizure-free, most benefited	
Headache	Kossoff et al.[21]	Retrospective Internet-based survey	104	Prevalence and treatment patterns of migraine in SWS	74 had migraine; both triptans and daily preventative medications were effective	Prospective, randomized controlled trial to test the efficacy of available abortive and preventive migraine therapies
	Gallop et al.[22]	Retrospective	20	Tolerance and possible efficacy of flunarizine in headache prophylaxis	Flunarizine was found to reduce frequency and severity of SWS-related headaches and vascular events	Prospective, randomized controlled trial
Stroke-like episodes, aspirin	Bay et al.[23]	Retrospective Internet-based survey	98	Association of seizure frequency, stroke-like episodes, and complications	Lower frequency of self-reported seizures and stroke-like episodes in aspirin users; 39% mild side effects while on aspirin (bruising, gum or nose bleeding).	Prospective, randomized controlled multicenter trial with aspirin
	Lance et al.[24]	Retrospective chart review	58	Symptoms of aspirin users	Low incidence of severe neurocognitive symptoms No significant side effects in the majority of aspirin users	
Cognitive and behavioral issues	Day et al.[25]	Retrospective, multicenter survey	277	Identification of prognostic factors	Bilateral brain involvement was associated with learning and intellectual disorders, whereas the extent of port-wine birth mark was associated with occurrence of epilepsy and glaucoma	Prospective longitudinal study to determine the prognostic indicators in childhood that could predict the outcome in adulthood
	Bosnyak et al.[26]	Retrospective, longitudinal	33	Neuropsychology evaluation	Early onset, frequent seizures, and frequent IED on EEG associated with poor IQ	Prospective multicenter trial with preventive AED to improve neurocognitive outcome
	Pilli et al.[27]	Retrospective, longitudinal	15	Calcification on MRI and neuropsychology	Calcification is progressive, associated with worse IQ	Evaluation of calcium chelators

(*continued on next page*)

TABLE. (*continued*)

Neurological Considerations	Key Studies	Study Design	No. of Subjects	Diagnostic or Therapeutic Intervention Involved	Main Conclusions	Suggested Research Avenues
	Lance et al.[28]	Retrospective	12	Stimulant use for ADHD	Well tolerated, 11 of 12 reported subjective benefit	Prospective evaluation of ADHD treatment

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Antiseizure drugs
BZP = Benzodiazepines
CBD = Cannabidiol
CBZ = Carbamazepine
Cr = Creatine
EEG = Electroencephalography
Glu = Glutamate
IED = Interictal epileptiform discharges
IQ = Intelligence quotient
LEV = Levetiracetam
OXC = Oxcarbazepine
MR = Magnetic resonance
MRI = Magnetic resonance imaging

The pathophysiology of epileptogenesis and other neurological symptoms in SWS is poorly understood. As cerebrovascular insufficiency and epileptogenesis are known to be linked,[37] the role of chronic ischemia on epileptogenesis in SWS has been proposed.[38-40] Studies have suggested that the impaired cerebral venous flow underlying the leptomeningeal vascular malformation results in brain tissue damage from long-standing ischemia leading to neuronal loss, atrophy, and calcifications, which can be demonstrated on neuroimaging.[41] Brain calcification is a common feature of SWS-affected brain structures; its role in the etiopathogenesis of epilepsy in SWS is also supported by studies demonstrating a positive relationship between the severity of brain calcifications and seizure severity.[42] Furthermore, owing to their simultaneous evolution, abnormal vascular development can lead to abnormal cortical development.[8] This is supported by the presence of associated cortical malformations, focal cortical dysgenesis, and white matter neurons seen in surgical specimens from patients with SWS.[32,43-45] Cortical malformations in SWS have been speculated to be due to ischemia from the presence of leptomeningeal capillary malformation during the second trimester of brain development.[38,43] Although there is no direct evidence for this, it has been postulated that the somatic mutation may affect the developing cortex itself.[46]

A major unanswered question is whether suppression of seizures by aggressive treatment with antiepileptic drugs or resective surgery early in development would prevent future neurological symptoms and cognitive decline. The efficacy of antiepileptic drugs in SWS-related epilepsy has been studied by Kaplan et al.[16] In this large, single-center cohort of 108 subjects with SWS-related epilepsy (76% with unilateral SWS), both oxcarbazepine or carbamazepine and levetiracetam were commonly used alone or in combination, but subjects using oxcarbazepine or carbamazepine had better seizure control when compared with those subjects not using these medications and with subjects using levetiracetam. Oxcarbazepine was also associated with fewer side effects. Thus the investigators recommended starting with oxcarbazepine unless features of generalized seizure are present. Oxcarbazepine can be associated with thyroid insufficiency, which may exacerbate hypothalamic-pituitary dysfunction associated with SWS.[47] The use of topiramate did not appear to cause new onset or exacerbation of existing glaucoma in their subjects, whereas the reported side effects of valproic acid were in line with its known side effects, suggesting that these medications may be an option for those with comorbid epilepsy and migraine. The same group of investigators has explored the use of cannabidiol in five subjects with SWS-related intractable epilepsy.[17] In this very small study, three subjects had 64%, 83%, and 100% decrease in baseline seizure frequency.

Although seizures in the majority of patients with SWS are reasonably well controlled with one or two antiseizure medications,[29] in patients whose seizures fail to respond to medications, other treatment options include disconnection of the diseased hemisphere, resective surgery, placement of a vagus nerve stimulator, and a ketogenic diet.[8] Successful surgical outcome depends on the completeness of resection or disconnection of the diseased cortex, and early surgery is more likely to improve developmental outcome.[18] In some patients with unilateral SWS, complete resection of the pial capillary malformations and underlying cortex may be sufficient to provide seizure control.[20] The timing of surgery can be guided by the severity of epilepsy and neurocognitive decline. Some advocate early surgery to attain seizure freedom and maximize developmental progress,[19,48] whereas others advise surgery in those whose seizures are frequent and after adequate period of medication treatment trial.

In children with intractable epilepsy associated with hemiparesis and visual field deficits, involving the nondominant hemisphere, a decision to proceed with surgery may be more feasible if language is supported bilaterally or is lateralized in the other hemisphere because hemiparesis after surgery is a potential complication. Surgery should also be considered for patients with cognitive decline even if seizures and other neurological deficits are not so severe.[8] The decision to proceed with surgery may be difficult for patients with mild deficits and without apparent cognitive decline. In such cases, the postoperative functional consequences of surgical disconnection or anatomic resection should be a prominent point of discussion in family counseling, before any such procedure.

Actionable recommendations

- Parents and caregivers of patients with SWS at risk for seizure clustering, including those younger than three years and with young age of seizure onset, should be counseled for the risk, and the option of intermittent benzodiazepine therapy during febrile illnesses should be offered.
- Prospective preventive antiepileptic drug trials as well as further blinded studies to determine the efficacy and safety of cannabidiol for SWS-related epilepsies.

- Collection and analysis of long-term surgical outcome data, including neurocognitive outcome, from multiple centers may help determine the optimal conditions and timing of SWS epilepsy surgery.

Stroke-like episodes

Perhaps the most devastating and fearful symptoms in patients with SWS are stroke-like episodes that are functionally defined as development of a new neurological deficit, occurring with or without ongoing seizures, and lasting longer than 24 hours.[49] In some patients, neurological deficits may present as a hemiplegic migraine[50] after prolonged visual auras.[51] The etiology of these phenomena in SWS is unclear, but several possibilities have been proposed, including focal seizures,[52] blood flow disturbances, and vasogenic leakage under the leptomeningeal capillary malformations.[51] Aspirin at a dose of 3 to 5 mg/kg/day was associated with a lowered frequency and severity of stroke-like episodes in retrospective studies[23,24,53] without significant side effects noted.[24]

Mild head trauma can result in transient hemiplegia in children with SWS[54]; this is relatively common in toddlers and preschool-aged children with SWS. When this occurs, the patients are very likely to receive brain imaging. However, in a study from a single center, no radiological evidence of acute injury was noted in a cohort of patients with SWS following mild head trauma.[55]

Adequate differentiation between epileptic and ischemic causes of the stroke-like episodes is necessary, because management differs between the two causes. Along with meticulous history taking, clinicians will typically perform diagnostic MRI and video- electroencephalography monitoring. Some investigators have used advanced MRI techniques including perfusion-weighted imaging which may show decreased cerebral blood flow and volume with prolonged mean transit time,[56] whereas others have used single-photon emission computed tomography that may show reduced blood flow in the affected hemisphere.[57] Magnetic resonance spectroscopy has been explored in SWS owing to the premise that excessive glutamate release from chronic hypoxia and seizure activity is present in the diseased hemisphere.[13] In the study of Juhász and colleagues, the affected hemisphere showed increased glutamate/creatine ratio when compared with the unaffected side in children with unilateral SWS.[13] It would be interesting to know if during the stroke-like episodes these metabolic changes are more pronounced. Comparison of baseline studies with studies performed in the setting of a stroke-like episode using a number of imaging approaches may shed further understanding regarding its pathophysiology and help design better preventative and symptomatic treatments to minimize neurological damage.

Actionable recommendations

- Address the efficacy of aspirin in the prevention of stroke-like episodes in SWS in a prospective randomized trial.
- Comparison of baseline neuroimaging studies with studies performed during stroke-like episodes.

Headaches

Headache is a major neurological feature of individuals with SWS and can have moderate to severe impact on their quality of life.[21] A study performed in 71 patients with SWS showed that the prevalence of recurrent headache was 44%, including migraine in 28%; headache related to glaucoma in 8%; chronic and episodic tension-type headaches in 4% and 1%, respectively; and unclassified headache in 3%.[58] Unlike migraine in the general population, migraine in individuals with SWS exhibits no gender difference and becomes symptomatic earlier (less than 10 years). Clinical manifestations in young children may include episodes of vertigo, asthenia, and sleepiness.[59] Late-onset hemiplegic migraine has also been reported.[50]

The pathophysiology of focal neurological deficits associated with SWS-related migraine is unclear. It can be hypothesized that the vasomotor disturbance within and around the vascular malformations may lead to oligemia that can trigger cortical spreading depression. The most commonly used abortive treatment for SWS-related migraine includes ibuprofen and acetaminophen, although some patients have used sumatriptan without significant side effects.[21] A single study explored the use of flunarizine as preventive and abortive treatment for migraine with promising results.[22] Currently, no clear consensus exists for the therapeutic approach to SWS-related headache, so treatment remains empirical and based on clinical experience.

Actionable recommendations

- A longitudinal, retrospective study from the CCN centers to identify the efficacy of preventive and abortive migraine treatments that could lead to future randomized trials.

Learning and behavioral disorders

Studies have shown that learning and behavioral problems are common in children with SWS.[25,30,60-63] A recent multicenter study in 277 patients with SWS using survey questionnaires showed the prevalence of learning disorder at 42%, attention-deficit/hyperactivity disorder (ADHD) and attention deficit disorder at 14%, behavioral disorder at 11%, and mood disorder and autism at 8%.[25] The prevalence of these comorbidities was much higher in patients older than six years, suggesting the need for continued surveillance because many of the symptoms of these disorders may not be recognized or diagnosed until school age.[25] Most recently, however, the prevalence of autism spectrum disorder and social communication disorder in SWS was much higher and reported to be 24% and 45%, respectively, with autism more common in patients who had bilateral and more extensive leptomeningeal vascular malformations without association with epilepsy variables.[63]

The study by Raches et al. showed that children with SWS and seizures were referred for special education services 10-times more often than children with SWS without seizures.[61] Similarly, among the 171 individuals studied by Sujansky and Conradi ascertained through the Sturge-Weber Foundation, almost 60% had developmental delay and required special education classes, and those who developed seizures during the first year of life had 83% and 84% incidence of early developmental delay and special education requirements, respectively.[29] The same study showed a decreasing likelihood of mental retardation with an increasing age of seizure onset, and, in the children without seizures, only 6% had developmental delay and 11% required special education classes.

There is no doubt that the underlying pathophysiology as well as the effects of seizures and stroke-like episodes during development plays an important role in neurobehavioral outcome. Neuroimaging studies have also shown an association between brain calcification and lower intelligence quotient.[27] With the clinical availability of calcium chelators, exploration of their effect on the SWS-associated brain calcifications and patient outcome can be a research opportunity to explore. Owing to the high prevalence of attention-deficit/hyperactivity disorder in SWS[62] and its negative impact, clinicians often question the safety of prescribing stimulants in these children. Only one study has evaluated the efficacy and safety of stimulants in SWS.[28] In that study, subjective benefit was found in

11 of 12 patients and side effects were minor, but one adult patient reported impaired sleep and had a seizure and subsequent stroke-like event that resolved with stopping of the medication.

Given the high prevalence of neurocognitive and behavioral comorbidities in children with SWS, screening of their developmental and neuropsychiatric status is critical to initiate early interventions, especially because parents may not always recognize subtle developmental delays. The American Academy of Pediatrics recommends surveillance of children at all well-child visits, combined with standardized screening for developmental delays at ages nine, 18, and 30 (or 24) months, as well as in every well-child visit when developmental delay is suspected.[64] A number of developmental screening tools are available varying from broad general developmental screening (e.g., Bayley Infant Neurodevelopmental Screen or) to others that focus on specific areas (communication or motor skills). Health care professionals can choose the best fit for their patients, preferably those that are practical and easy to use in the office setting. If the screening results are concerning, the child should be scheduled for more comprehensive developmental and neuropsychologic evaluations. It will also be important to monitor the patients as they get older and during adulthood to evaluate for behavioral, emotional problems, learning disabilities, and mood disorders.

Actionable recommendations

- Screening of patients for comorbid cognitive and psychiatric issues.
- Collection of detailed neurobehavioral data in a multicenter database to facilitate further research on this issue.

Neuroimaging studies

Neuroimaging in SWS helps to establish the diagnosis, assess the severity, and follow the progression of brain involvement. Brain MRI, preferably utilizing a 3-T field strength imaging unit, is the primary imaging modality recommended for clinical practice in SWS.[35] The recommended MRI sequence following the onset of first neurological symptoms (early postsymptomatic phase) includes three-dimensional pre-and postcontrast axial T1 and T2 (or fluid-attenuated inversion recovery) imaging, susceptibility-weighted imaging (SWI), and diffusion-weighted imaging. SWI has been shown to be very sensitive in demonstrating venous abnormalities including deep transmedullary veins and enlarged periventricular veins as well as cortical calcifications.[41]

Postcontrast MRI is used to evaluate for the presence and extent of leptomeningeal pial vascular malformations, enlarged choroid plexus, and enlarged deep medullary and ependymal veins. After prolonged seizures, status epilepticus, or stroke-like episodes, MRI may demonstrate transient diffusion abnormalities,[65] hence a follow-up MRI is needed to more accurately assess potential progressive changes from the baseline extent of brain involvement. One unanswered question is whether the rarely observed diffusion restriction during stroke-like episodes results from true ischemia or from ongoing clinical or subclinical seizures that can produce a similar pattern.[65]

It should be noted that contrast-enhanced MRI can be false-negative in newborns and young infants. Thus, when a port-wine birthmark is seen in the nursery, no immediate neuroimaging (including computed tomographic [CT] scan) is necessary, unless there are clinical signs of brain involvement (focal neurological deficits or seizures) or for the purpose of presymptomatic diagnosis for preventive treatment. Otherwise MRI is often delayed until after age one year,[35] although a recent study reported that leptomeningeal enhancement or indirect signs of SWS brain involvement on clinical MRI performed before age three months could identify SWS in the presymptomatic stage with high sensitivity (100% [confidence interval: 75% to 100%]) and specificity (94% [confidence interval: 71% to 100%]).[66] The use of SWI may further improve this accuracy. Furthermore, it has been suggested that if the child is past age one year and the contrast-enhanced brain MRI is normal, the child is very unlikely to develop SWS with brain involvement[8] and no further follow-up imaging is necessary.

In a recent study of 35 patients with SWS who presented to an emergency department with acute neurological symptoms, a total of 89 urgent neuroimaging studies were done during 136 encounters, but none showed acute hemorrhagic or ischemic strokes.[55] The study suggests that urgent imaging in those who present with breakthrough seizures does not result in a significant change of clinical management. This study does not support the routine use of urgent imaging with CT or MRI with contrast in established patients due to limited overall sensitivity, the risk of ionizing radiation of head CT, and the risk of gadolinium contrast deposition systemically with MRI with contrast. Anecdotally, many children and adults with SWS are not evaluated in centers with a deep knowledge and understanding of the disease, thus leading to potential imaging studies that may not be needed.

Advanced neuroimaging techniques including diffusion tensor imaging for fiber tractography and functional MRI to localize the eloquent cortex (motor, language, visual, and auditory areas) as well as nuclear imaging modalities like positron emission tomography and single-photon emission tomography are typically reserved for patients requiring presurgical evaluation for drug-resistant epilepsy.[35] Recently, quantitative apparent diffusion coefficient mapping has been explored by Pinto and colleagues to identify young children who are at high risk for developing seizures.[67] The investigators demonstrated that larger regions of decreased apparent diffusion coefficient in the affected hemispheres, when compared with maps of an age-matched control group, were associated with later onset of seizures.

With regard to clinical MRI research and clinical trials including biomarker development, the recently published multidisciplinary consensus article[34] discussed that MRI performed for this purpose should be tailored to the specific research question(s). Advanced MRI parameters for biomarker development should be objective, quantifiable, and replicable, especially when applied in longitudinal studies, whereas emphasis should always be laid on minimizing potential risks from sedation or anesthesia and gadolinium administration.

At present, there is a need to compare MRI protocols across Sturge-Weber Foundation CCN centers to establish a minimum standard protocol necessary to make the diagnosis of brain involvement in SWS as well as to evaluate for the presence of complications. Recently, a standardized SWS MRI protocol has been proposed that, if used by all centers, could both improve evaluation of acute symptoms and be important to develop a better longitudinal understanding of the disease in the brain.[35] Standardized imaging protocols will also be crucial for using imaging biomarkers in therapeutic and preventive clinical trials.

Actionable recommendations

- Identification and application of MRI protocols across Sturge-Weber Foundation CCN centers to establish the minimum standard sequences necessary to make the diagnosis of brain involvement in SWS and to evaluate for the presence of complications followed by implementation of standard MRI sequences to be used in all CCN centers.

- Validation of safe and accurate MRI protocols, preferably with no contrast administration and no sedation, to screen for pre-symptomatic SWS brain involvement.

Limitations

Most reviewed studies had major limitations. The majority of the published studies were retrospective, and several studies had a limited sample size (Table). Therefore, truly evidence-based guidelines cannot be developed based on the available data. In addition, several studies had specific limitations that could affect the interpretation of the results. For example, in the study Kossoff et al.[12] the incidence of seizure clustering may have been underestimated because the data were obtained only during the initial clinic visit and follow-up information was incomplete. The study of Ville et al. on prophylactic antiepileptic treatment in SWS[15] lacked randomization of the treated and nontreated groups. The beneficial effect of preventing the occurrence of epilepsy in their treated group may also be because patients in the nontreated group, but not those in the prophylactically treated group, had been referred for epilepsy and the size of the angioma was smaller in the non-treated group, which may have contributed to bias. Most of such limitations could be overcome by well-designed, prospective, multicenter clinical trials in the future.

Conclusions

The neurology of SWS presents us with many unanswered challenges and unmet needs. Evidence-based standards of care, as well as retrospective and prospective outcome measures shared across all Sturge-Weber Foundation CCN centers, are much needed. Longitudinal, standardized studies will be important to understand disease pathogenesis and will give important clues to treatment strategies. The current state of knowledge and divergent clinical practices in SWS mandate clinical trials and the creation of evidence-based guidelines for antiepileptic drug usage and aspirin therapy, especially in asymptomatic patients. Better preventive and abortive treatment guidelines for stroke-like episodes and SWS-related headaches are also needed. As the underlying somatic mutation in SWS and its signaling pathway has been identified, research that explores the use of drugs that target the G-protein signaling is warranted. In addition, further studies are needed to explore how the mutated endothelial cells affect the brain parenchyma and lead to seizures, stroke-like episodes, headaches, and developmental and behavioral symptoms.

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