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Current Therapeutic Options in Sturge-Weber Syndrome

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Abstract

Sturge-Weber syndrome is a vascular malformation syndrome consisting of a facial port-wine birthmark associated with malformed leptomeningeal blood vessels and a choroid “angioma” of the eye. It is a rare neurocutaneous disorder that occurs sporadically, is not inherited, and is caused by a somatic mosaic mutation in *GNAQ*. In patients with Sturge-Weber syndrome, brain involvement typically presents in infancy with seizures, strokes, and stroke-like episodes, and a range of neurologic impairments. Standard treatment includes laser therapy for the birthmark, control of glaucoma through eyedrops or surgery, and the use of anticonvulsants. Increasingly low-dose aspirin is offered. Treatment with propranolol has been tried generally without the dramatic results seen in hemangiomas. Treatment with an anticonvulsant or low-dose aspirin or both before the onset of seizures is an option. Surgical resection may be offered to those whose seizures are medically refractory. Endocrine, medical rehabilitation and cognitive comorbidities are important to manage. In the future, new therapeutic options are likely to be offered stemming from preclinical studies and small pilot clinical trials currently ongoing. Discovery of the causative somatic mosaic mutation suggests new insights into the pathophysiology of this vascular malformation disorder, and potential novel treatment strategies for future study. The mutation results in constitutive overactivation of the Ras-Raf-MEK-ERK and the HIPPO-YAP pathways and inhibitors of these pathways may in the future prove useful in the treatment of Sturge-Weber syndrome.

Introduction

Sturge-Weber syndrome is a vascular malformation involving the brain, skin, and eye. In Sturge-Weber syndrome a facial port-wine birthmark (PWB), a capillary malformation (Fig. 1), is associated with abnormal blood vessels in the brain leptomeningeal “angioma” (Fig. 2) and the eye (choroid “angioma”). The vascular malformation in the brain results in epilepsy and neurologic impairments such as intellectual disability, hemiparesis, visual impairments, and severe migraines. Eye involvement with the vascular malformation produces glaucoma and can lead to vision loss. Sturge-Weber syndrome is a condition with a spectrum of clinical manifestations, which can range from isolated brain involvement (in approximately

10% of the cases), isolated eye involvement, eye and skin or eye and brain involvement, to birthmark associated with both brain and skin involvement.

The isolated birthmark is not usually referred to as Sturge-Weber syndrome, but rather it is generally called a facial PWB. Usually Sturge-Weber syndrome brain involvement is most frequently required to make the diagnosis; however the small subset of patients with the birthmark and eye involvement may sometimes be considered to have Sturge-Weber syndrome. If children with a facial PWB are older than 1 year and their contrast-enhanced magnetic resonance imaging (MRI) is normal, then they are very unlikely to have Sturge-Weber syndrome brain involvement.

A child, boy or girl, born with a PWB on the forehead or the upper eyelid, has a 10%–35% risk of brain involvement. When the PWB involves both the upper and the lower eyelid, the risk of glaucoma is approximately 50%.¹ No population-based studies have been done; the estimates of prevalence range between 1 in 2000 and 1 in 50,000 live births. Isolated PWBs are very common; approximately 1 in 300 infants are born with it, most often located on the face, head, and neck.² The somatic mosaic mutation causing Sturge-Weber syndrome is an activating mutation in *GNAQ*.³ Unexpectedly, the same R183Q mutation in *GNAQ* underlies a form of uveal melanoma.⁴ It has been hypothesized that the mutation occurring at a different time in development accounts for its resulting in a vascular malformation rather than a cancer. Furthermore, the timing of the mutation during fetal development probably determines the extent of Sturge-Weber syndrome involvement.⁵ The role of this *GNAQ* mutation is beginning to be understood, partly from extrapolation of data from the cancer literature.

In this article, we review the presentation, diagnosis, pathophysiology, and current treatment of Sturge-Weber syndrome, with a focus on therapeutic options both conventional and more controversial.⁶ The available treatment literature reviewed is primarily clinical cohort series; there are results from a few anonymous surveys. There have not been any randomized, placebo-controlled drug trials yet for Sturge-Weber syndrome. Although a couple of prospective open-label studies are currently ongoing, published drug studies to date are limited to retrospective open-label trials.

Diagnosis

The PWB is present at birth and may initially be confused with a bruise. However, the “bruise” does not resolve and should be evaluated by a dermatologist or other vascular specialists so that it can be appropriately identified. The presence of a facial PWB should result in referral for treatment of the birthmark, as well as consultation with a neurologist and ophthalmologist for appropriate evaluation and treatment of brain or eye (or both) involvement, if necessary.

The diagnosis of Sturge-Weber syndrome brain involvement requires a contrast-enhanced MRI (Fig. 2). Susceptibility-weighted imaging and postcontrast flair sequences may increase the sensitivity. Contrast-enhanced MRI has decreased sensitivity in young infants and therefore neuroimaging must be repeated after a year of age.^{7,8} The diagnosis of Sturge-

Weber syndrome brain involvement is made by visualizing the enhancing leptomeningeal vessels. Noncontrast susceptibility-weighted imaging (or blood oxygenation level dependent magnetic resonance venography) may be helpful in visualizing deep transmedullary veins. A recommended approach is to evaluate newborns with a history, an examination, and an electroencephalogram (EEG), and do an early MRI only if an abnormality is noted. Also, imaging newborns with a large facial PWB and an increased risk of brain involvement is a reasonable approach.

Infants with Sturge-Weber syndrome brain involvement usually present with seizures; approximately 75% of patients do so by 1 year of age and 90% within the first 2 years of life.⁹ A subset of patients develop early handedness or a visual gaze preference before onset of their seizures. Most often, however, infants acutely develop hemiparesis and focal deficits with the onset of their seizures, which are usually, but not always, focal and complex partial in nature. Neurologic, cognitive, and seizure control outcomes correlate with the extent of brain involvement and the age of seizure onset.¹⁰

Eye involvement in infancy presents with increased vascularity of the conjunctiva, buphthalmos (eye enlargement), or increased tearing.¹¹ A child with a PWB of both the upper and the lower eyelid is at high risk of glaucoma. Screening for glaucoma every few months in infancy and early childhood is required to detect glaucoma and initiate treatment.¹² Annual ophthalmologic examinations for life are recommended even if early evaluations do not detect glaucoma or evidence of eye involvement.

At this time the role for *GNAQ* testing in diagnosis remains to be established. It has been shown that the gene mutation is rarely, if ever, present in the blood of affected individuals. Skin or other abnormal tissue is required for testing. Therefore, development of a prenatal test is not a straightforward task. Furthermore, testing skin tissue would not distinguish an infant with an isolated birthmark from the one who has brain or eye involvement; the same mutation is found in both the syndrome and the isolated birthmark. There are a few other capillary malformations with phenotypic overlap that are sometimes confused with Sturge-Weber syndrome (ie, capillary malformation-macrocephaly syndrome). In these cases, testing may be helpful, especially in the future if gene-targeted therapy is available.

Pathophysiology

GNAQ codes for Gα_q, an alpha subunit of a heterotrimeric guanosine-5'-triphosphate-binding protein coupled to Gβ and Gγ subunits and known to couple with several GPCRs (including certain serotonin and glutamate receptors, and endothelin-1, angiotensin 2 receptor type I, alpha-1 adrenergic receptors, and vasopressin type 1 and type B) which are important to vascular development and function. The mutation is predicted to decrease efficiency of the autohydrolysis and results in constitutive overactivation of downstream pathways.

In Sturge-Weber syndrome, histologic studies have reported an increased number of leptomeningeal vessels,¹³ and atrophy and calcification of the cortex particularly around blood vessels.¹⁴ Numbers of cortical vessels are decreased, however, as the brain atrophy

develops over time with gliosis and neuronal loss; most likely this is secondary to tissue loss. Calcification, neuronal loss, and gliosis are secondary to brain injury from venous stasis and impaired brain perfusion. Several of the G protein-coupled receptors linked to Gαq are critical to blood vessel development and function, and their abnormal signaling may result in the vascular malformations.¹⁵ Cortical dysgenesis has been reported in surgical brain samples and suggests that Sturge-Weber syndrome brain involvement can include dysgenesis of cortical development, like focal cortical dysplasia (FCD) type IIa near the region of leptomeningeal angiomatosis, cortical dysplasia, and polymicrogyria.^{14–16} It is possible that the somatic mutation affects the developing cortex itself, although available data to date suggest that cortical dysgenesis probably results either from impaired perfusion during brain development or because of the abnormal vascular development having indirect effects on cortical development ongoing at the same time.

PWBs and the abnormal Sturge-Weber blood vessels of the brain have demonstrated abnormal vascular innervation,^{17–21} malformed cortical vessels lacking the normal cholinergic and sensory fibers.¹⁹ The vasoactive responses to temperature changes or seizures are also abnormal. Ictal spect (blood flow studies) in patients with Sturge-Weber syndrome have shown that during a seizure, blood flow can decrease to ischemic levels.^{22–24} The normal response to a seizure is for blood flow to increase but this may not occur in Sturge-Weber syndrome and a stroke may result. Perfusion imaging has demonstrated impaired venous drainage resulting in impaired blood flow to affected brain regions, and abnormal automatic regulation of blood flow during seizures in patients with Sturge-Weber syndrome probably contributes to their stroke-like episodes. It is possible that the somatic mutation directly affects vascular innervation.

Research has also shown evidence of ongoing vascular remodeling,²⁵ probably in response to chronic ischemia. Subjects with Sturge-Weber syndrome are more likely to have vascular factors, such as MMPs, in their urine than normal controls.²⁶ Immunohistochemistry in Sturge-Weber syndrome tissue has demonstrated increased VEGF expression in cortical neurons and glia underlying the abnormal leptomeningeal vessels. Also, increased VEGFR-1, VEGFR-2, HIF-1α, and HIF-2α expressions in endothelial cells of the abnormal leptomeningeal vessels have been seen, suggesting that chronic tissue hypoxia and VEGF may drive ongoing vascular remodeling.²⁵ The Ras-Raf-MEK-ERK-mTOR pathway can increase both VEGF²⁷ and HIF activities,²⁸ and the somatic mutation in *GNAQ* may also contribute to the vascular remodeling.

Di Trapani et al²⁹ hypothesized that a putative vascular factor secreted by the vessel connective tissue contributed to the formation of the calcifications. This putative “vascular factor” may be the constitutive hyperactivation of GPCR-Gαq-ERK-mTOR pathways. Further study is required to identify additional important factors in this cascade and others affected by the R183Q mutation in *GNAQ*.

Current Treatment Options

The PWB is treated with laser procedures beginning in infancy when the flat, pink birthmark responds best and the birthmark is smaller.³⁰ Early laser treatment may lessen later

progression of the birthmark, which can consist of tissue hypertrophy, blebs, and complications affecting vision, airway, and swallowing. A variety of lasers have been developed over the years and are used, depending on color of the skin and color, thickness, and size of the birthmark; the lasers heat the hemoglobin within the blood vessels and destroy them, sparing surrounding skin structures. A series of laser treatments are required until no further lightening of the birthmark is seen. The treatments are painful and another controversial aspect of care is whether to do the laser treatments with sedation or anesthesia or with just a topical numbing agent. The trend seems to be moving away from putting infants to sleep for this as it may be done as often as monthly; however, there are a range of practices seen and little data to support an approach over any other. The PWB frequently recurs over time, requiring maintenance treatments.

Glaucoma (increased eye pressure) threatens vision as it can cause ischemic injury to the optical nerve. The increased intraocular pressure is treated with eyedrops, such as timolol and lantaprost, which decrease fluid production in the eye.³¹ The glaucoma can be difficult to control even with combinations of ophthalmic medications. When medical management is unsuccessful, various surgical approaches have been tried to drain fluid from the eye and relieve the excessive pressure. All too frequently, medical management fails or the glaucoma is fulminant (particularly in infants) and surgery is required with shunt placement or other means of relieving ophthalmic pressure.³² Theoretically, low-dose aspirin may relieve glaucoma due in part to venous hypertension; however, this requires further study. The major complication of surgical intervention for Sturge-Weber syndrome-related glaucoma stems from the risks of relieving the eye pressure too quickly; this can result in retinal hemorrhage and further sudden vision loss. There have been recent anecdotal reports using beta-blockers for Sturge-Weber syndrome; the results have been mixed and so do not appear to be generally successful. Antiangiogenic ophthalmic treatments have also been anecdotally reported; however, this treatment needs to be more extensively studied. Laser therapy around the eye does not appear to adversely affect eye pressure.

The mainstay of neurologic treatment is the use of anticonvulsants to reduce seizures.

Epilepsy in Sturge-Weber syndrome can be difficult to control, occurring in clusters of seizures and episodes of status epilepticus.³³ Although generalized seizures are seen, most seizures in patients with Sturge-Weber syndrome are focal motor with or without impaired consciousness. The most commonly used anticonvulsants in infants include oxcarbazepine, leviteracetam, and phenobarbital. A few patients develop infantile spasms, which may respond to steroids, topiramate, vigabatrin, or ketogenic diet.³⁴ Another small percentage of patients, taking anticonvulsants such as oxcarbazepine, carbamazepine, or lamotrigine, develop a generalized spike and wave pattern on EEG associated with myoclonic seizures³⁵; these patients are usually switched from these anticonvulsants to others that cover both focal and generalized seizures, such as valproate, leviteracetam, or topiramate. Most patients attain reasonable seizure control on 1 or 2 anticonvulsants plus low-dose aspirin.³⁶ Prolonged seizures, particularly in infants and young children, can result in stroke,²³ and therefore aggressive antiepileptic management is warranted. Other patients, however, do not get a reasonable seizure control or develop intolerable side effects from medications. Many of them, with medically refractory seizures, also have a significant hemiparesis and visual-field

cut, as well as intellectual impairments. In these situations, hemispherectomy or other surgical interventions are usually considered.

Low-dose aspirin (3–5 mg/kg/day) is also a therapeutic consideration although not all groups use it. There is published evidence that it decreases the frequency and severity of stroke-like episodes and seizures.^{37–40} Side effects include increased bruising, nosebleeds, and gum bleeds; rarely allergic reactions and more seriously bleeding can occur. Lance et al³⁶ reported the clinical experience over the past decade in 60 children with Sturge-Weber syndrome, and showed that low-dose aspirin was safely given to infants as young as 1 month of age. Subdural and subgaleal hematomas are rarely reported both on and off low-dose aspirin.^{41,42}

As infants are increasingly being diagnosed before the onset of seizures, an important therapeutic question is what could be done to delay seizure onset and improve long-term neurologic and cognitive outcome. Those diagnosed with Sturge-Weber brain involvement presymptomatically can be offered treatment with anticonvulsants or low-dose aspirin or both. However, data demonstrating clear benefit of presymptomatic treatment are lacking. A study reported that phenobarbital was administered presymptomatically in infants with Sturge-Weber syndrome and a trend noted for improved cognitive outcome. However, the study groups were not randomized and the infants given presymptomatic phenobarbital had less brain involvement compared with those not presymptomatically treated; therefore the trend for their better outcome could relate to their less severe brain involvement.⁴³ Infants with extensive bilateral brain involvement should perhaps be offered presymptomatic treatment with both an anticonvulsant and low-dose aspirin as they are at the highest risk for poor outcome and ischemic global cerebral injury, and they are not good surgical candidates.

However, for those patients whose seizures are refractory to medical management with anticonvulsants, additional treatment options include hemispherectomy or hemispherotomy, focal resection, the ketogenic or the Atkins diet,⁴⁴ and the vagal nerve stimulator. For unilaterally involved patients, surgery should be considered for those who have failed 2 or more anticonvulsants combined with low-dose aspirin.^{45,46} The decision to proceed with surgery is easier in those patients who, in addition to the impairment and medically refractory seizures, also have hemiparesis and a significant visual-field deficit. Surgery should also be seriously considered in patients whose cognitive development is progressively falling behind normal, even if their seizures and other neurologic symptoms are not very severe. The most common scenario where surgery is pursued, in my experience, is children with frequent seizures or clusters of severe seizures, a significant hemiparesis, and visual-field deficits. For them, the need for surgery is obvious and the risk-benefit ratio greatly supports having the surgery.

Experience supports the conclusion that seizure control results in the best chance of optimal cognitive and neurologic development whether medically or surgically managed. When medical management fails, surgery should be considered especially when hemiparesis and visual deficits are already present. A couple of published series of approximately 20 patients with Sturge-Weber syndrome demonstrate that hemispherectomy is very successful (approximately 90% effective) in eliminating seizures in most cases. Focal resections is

significantly less effective.⁴⁶ The extensively bilaterally affected children with Sturge-Weber syndrome and severe brain involvement have the highest risk of very poor neurologic and cognitive outcome. Essentially most of their cortex is at risk for ischemic brain injury, atrophy, and calcification. For these infants, very aggressive treatment with anticonvulsants and low-dose aspirin is warranted. They are generally not considered good surgical candidates; hemispherectomy has been recommended only in bilaterally affected children with very severe disabling seizures primarily coming from 1 hemisphere and the surgery is considered palliative rather than potentially curative.⁴⁷

In patients with Sturge-Weber syndrome, headaches, and particularly migraines, commonly begin at a young age, can worsen over time, and are frequently associated with their seizures. Sleep deprivation is a common trigger. Anticonvulsants that also prevent migraines, such as topiramate or valproate, can be helpful. Triptan medications have been safely used and are helpful for some patients,⁴⁸ but most require a prophylactic agent.

Strokes and stroke-like episodes are common, particularly in infants and toddlers, and often associated with seizures or migraines or both. Stroke-like episodes can be defined as a focal neurologic deficit lasting longer than 24 hours; these impairments resolve over a period of days to weeks. Neurologic impairment that does not fully resolve but persists may be referred to as a stroke. Many children gradually acquire a hemiparesis in a stepwise fashion such that stroke events are not recognized; other children have clear acute onset of focal neurologic deficit. During a stroke-like episode the EEG often demonstrates focal slowing. Single-photon emission computed tomography studies show perfusion deficits.²¹ High apparent diffusion coefficient values are seen on MRI, and decreased N-acetylaspartate and choline peaks are found on proton magnetic resonance spectroscopy.⁴⁹ Patients who are seizure free for a year or more demonstrate recovery of glucose hypometabolism and neurologic improvement.⁵⁰

Endocrine abnormalities in Sturge-Weber syndrome require screening and treatment if present. These patients have an increased risk of hypothyroidism (commonly central) and growth hormone (GH) deficiency.^{51,52} GH deficiency is suspected when young childrens' growth rate decreases and they are not following the percentile predicted by midparental height and bone age. In this case a serum insulin-like growth factor-1 level test should be performed to screen for GH deficiency, and if it is low then formal GH testing should be done. Central hypothyroidism or primary hypothyroidism also occurs with greater frequency in these patients than in the general population,^{52,53} usually associated with anticonvulsants' use. Patients with symptoms such as excessive weight gain, dry skin, sleepiness, and constipation should have free T4 by equilibrium dialysis tested. If hypothyroidism is confirmed, treatment with synthroid relieves their symptoms.

Future Treatment Options

Research efforts for the future would increasingly be centered around targeted therapies. This is already being seen to some extent in the Phase I-II treatment trials studying the use of mechanistic target of rapamycin inhibitors for the treatment of PWB,⁵⁴ and of medically refractory seizures in Sturge-Weber syndrome (<https://clinicaltrials.gov/ct2/show/>

[NCT01997255?term=sturge-weber&rank=4](https://clinicaltrials.gov/ct2/show/NCT01997255?term=sturge-weber&rank=4)). Another ongoing Phase I-II clinical trial of cannabidiol may in part target Gαq hyperactivation (<https://clinicaltrials.gov/ct2/show/NCT02332655?term=sturge-weber&rank=1>).

The current goal is to develop new treatments, which both ameliorate or reverse the symptoms of those patients already affected by the disease, and to prevent the symptoms of those who have yet to manifest clinical course progression. To achieve this goal the following efforts are needed: (1) to continue to create safe screening methods to detect presymptomatic brain and eye involvement, (2) to develop genetic in vitro and animal models of Sturge-Weber syndrome for screening of novel drug treatments, and (3) to perform new Phase I-II clinical trials to study the safety and possible efficacy of the new treatment strategies based on our growing understanding of the pathophysiology.

MEK and ERK inhibitors are now of interest and under discussion and inhibitors of the HIPPO-YAP pathway have also been proposed (Fig. 3). Safe use of these compounds is an important goal. It is expected that, within the next few years, patients would have the opportunity to participate in additional clinical drug trials as preclinical studies and screening programs bring forward additional targets and lead compounds for the treatment of Sturge-Weber syndrome.

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Figure 1. Child with Sturge-Weber syndrome, right-sided facial port-wine birthmark and right eye involvement. (Color version of figure is available online.)

Figure 2. Sturge-Weber syndrome brain involvement. (A) T1-weighted postcontrast enhanced axial MRI 3-T demonstrating increased leptomeningeal enhancement of the left parietal-occipital lobes (arrow). Enhancement (arrow) in the left hemisphere also seen on coronal images (B) of this child with Sturge-Weber syndrome.

Figure 3.

Potential Treatment by inhibition of constitutive activation of Hippo-YAP and Ras-Raf-MEK-ERK-mTOR pathway: somatic mutation in GNAQ results in impaired autohydrolysis of Gαq with constitutive overactivation of downstream pathways, including increased mTOR activity. Treatment with mTOR inhibitors is currently being studied. mTOR, mechanistic target of rapamycin. (Color version of figure is available online.)