Chapter 5
Sturge-Weber Syndrome

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Contents

Introduction

Sturge-Weber syndrome occurs in an estimated 1 in every 20,000–50,000 live births, while facial capillary malformations (*PWB*) occur in 3 in 1000 lives births [1]. It occurs in all ethnic and racial backgrounds and in both males and females. Familial inheritance of *SWS* has never been documented. Identical twins have been reported in which one twin was affected and the other twin was not [2, 3].

As predicted [4], the cause of SWS was determined to be a somatic mosaic mutation (see Chap. 1). An activating R183Q somatic mosaic mutation in *GNAQ* was originally reported [5] and accounts for about 90–95% of cases so far studied. Since then other less common GNAQ somatic mutations have been described, and mutations in the paralogue GNA11 have been reported to cause phakomatosis pigmentovascularis and extensive dermal melanocytosis [6] and to much less commonly underlie SWS [7, 8] (see Chap. 1).

GNAQ codes for the protein Gαq [5]. Gαq is an alpha subunit of a heterotrimeric GTP-binding protein that interacts with a subset of seven transmembrane-spanning

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G protein-coupled receptors. It is known to couple with several GCPRs (including certain serotonin and glutamate receptors, and endothelin-1, angiotensin 2 receptor type I, alpha-1 adrenergic receptors, vasopressin types 1A and 1B) important to vascular development and function. The R183Q SWS mutation is predicted to impair the ability of the guanine nucleotide protein to return to the deactivated state and complex with its GPCR [9]; the mutation therefore likely results in constitutive overactivation of downstream pathways, although any cellular compensatory responses to this hyperactivation are not understood. When mutant constructs were transfected into HEK 293T cells, increased phosphorylated ERK was noted compared to cells transfected with wild-type construct [5]. The downstream effectors of Gαq include p38, ERK, JNK, and Trio [10, 11] which regulate gene expression important in many cell functions, including cell proliferation and differentiation. Studies to date point to the endothelial cells being enriched in the GNAQ mutation [12, 13]; however these results are from cell sorting experiments and depend upon the mutant cells expressing typical cell markers. There is evidence of expression in multiple other cell types as well [14].

Clinical Characteristics

Skin Involvement

Port-wine birthmarks are the most common early identifier of *Sturge-Weber* syndrome [15, 16]. When a baby is born and has a port-wine birthmark that is on the forehead, temple region, and/or on the upper or lower eyelids [17–19] (Fig. 5.1), it is recommended that the infant be checked for Sturge-Weber brain and eye involvement. Depending on whether the birthmark is on one side or both, and how large the birthmark is (*larger, segmental birthmark has higher risk*), the chance that a child

Fig. 5.1 *Panel A.* Male infant with a port-wine birthmark on the left forehead. He began having seizures at 7 months of age and was found to have left-sided brain involvement. *Panel B.* A 13-year-old female with bilateral Sturge-Weber brain involvement and bilateral facial port-wine birthmark. *Panel C.* Same female child soon after receiving laser treatment for her birthmark

has SWS with a port-wine birthmark varies from 10% to about 50% [1, 20]. At birth the birthmark is flat and red [21] and can be mistaken for a bruise related to birth. Over the next few months, it can fade somewhat to a pink color. A port-wine birthmark grows commensurate with the child and does not spread; it also does not usually resolve without treatment. Soft and bony hypertrophy can develop later in adolescence and adulthood to varying degrees and is associated with larger birthmarks, particularly those affecting the lips and central face [22, 23].

Eye Involvement

Glaucoma, the most common ophthalmologic issue, occurs in 30–70% of SWS patients [15, 21]. The dilation of abnormal venous vessels in the eye contributes to the impaired venous drainage and glaucoma which can cause blindness and pain. Dilation of the venous vessels can cause increased intraocular pressure and, combined with the anterior chamber irregularities, may interfere with the proper draining of the eye [24, 25]. Eye pressure should be monitored in patients with *Sturge-Weber* syndrome beginning at birth, for glaucoma can begin any time, and early treatment may prevent vision loss (see Chap. 47). Treatments include various eye drops to decrease fluid and pressure in the eye, and if this is unsuccessful, then surgical interventions are carried out to improve eye drainage and reduce eye pressure [26]. In addition to glaucoma, patients with choroidal involvement are at risk for retinal detachment, either associated with surgery or as a spontaneous consequence of their eye involvement [27].

Brain Involvement

Patients with *Sturge-Weber* syndrome often have seizures; they occur in 72–97% of SWS patients [28–30]. Most seizures are focal motor seizures and begin in infancy [30] (see Chap. 50). These seizures may be hard for parents to spot, for they don't generally present as generalized convulsions or fulfill the usual perception of what a seizure is; anticipatory education is therefore helpful. These seizures present as focal rhythmic twitching or tapping, eyes deviated or jerking to a side, or other subtle signs such as staring and twitching of one side of the mouth. Other types of seizures *SWS* patients tend to have are partial seizures with impaired consciousness or more rarely infantile spasms or drop seizures [31]. Seizures are thought to exacerbate neurological deficits, so aggressive treatment is highly recommended [32]. Seizures can be triggered by everyday factors such as sleep deprivation, illness, or stress but also by migraines or stroke-like episodes. During prolonged or repetitive seizures, there is a significant decrease of blood flow to the side of the brain that's seizing; this seems to be correlated to worsening of brain function in patients with

SWS and probably harms the brain by contributing to strokes and brain atrophy and calcification [32] (see Chap. 4).

The neurological symptoms in *Sturge-Weber* syndrome such as seizures or migraines can evolve as the patient ages [28, 33, 34]. There is a relationship between seizures and migraines, with seizures triggering migraines and migraines triggering seizures. Another severe neurological symptom is stroke-like episodes [35], which, unlike a Todd's paralysis after a seizure, lasts days to weeks after an event. Afterward the patient's weakness may be temporary or permanent; if the hemiparesis is permanent, then the patient is said to have had a stroke, rather than a stroke-like episode. Stroke-like episodes are more common in young children and infants with Sturge-Weber syndrome [36]. Other less obvious impairments can include a visual gaze preference or early handedness.

Chronic functional disability can develop over time. Patients with hemiparesis are of a higher likelihood to have cognitive deficits [37]. Referral for a medical rehabilitation evaluation of the young infant or child is important so that physical, occupational, and speech/language therapy services can be provided if warranted [38, 39]. Around 67% of patients have psychomotor deficits, while 30–50% suffer from mental disability. Common behavioral signs are aggression, depression, and attention deficit disorders [40]. Neuropsychological testing is suggested at the ages of 3–4 years, particularly if they have some degree of hemiparesis, for this evaluation will help bring to light any other impairments not found previously [37]. A recent study in England noted autism spectrum disorder and social impairments to be very common in SWS [41]; it is not clear that this is the case in every population.

Endocrine Involvement

There are hormonal imbalances associated with SW syndrome including growth hormone deficiency [42] and central hypothyroidism [43, 44]. The rate of growth hormone deficiency in patients with *SWS*, while still low, is 18 times greater than in the general population [42]. While the cause of the deficiency is unknown, nevertheless it is important to make the diagnosis where present as it is treatable. Treatment should be pursued with caution as in some patients it has resulted in seizure relapse [45]. Untreated growth hormone deficiency in adults may result in depression and organ dysfunction; therefore even in adult patients it is important to make the diagnosis of growth hormone deficiency and offer treatment where present. Central hypothyroidism is also more prevalent in patients with *SWS* than in the average population: we noted a 2.4% prevalence at our *SWS* Center, compared to a 0.0002–0.0005% of the general population [43]. While anticonvulsant medications may contribute to the risk of central hypothyroidism, *Sturge-Weber* patients are also at additional risk of central hypothyroidism because of the disruptions in their central nervous system, which could cause hypothalamic-pituitary issues. Testing for central hypothyroidism is extremely important and must be done by testing free T4 by equilibrium dialysis method [44], and if patients have low thyroxine hormones,

they should be started on levothyroxine. Partial hypopituitarism has also been described; therefore cortisol and estrogen/testosterone levels should also be evaluated where concerns exist [46].

Pathology (See Chap. 4)

Brain involvement in SW syndrome consists of abnormal leptomeningeal vessels (Fig. 5.2) and dilated deep venous vessels, resulting in impaired venous drainage of the brain [47–49]. This impaired drainage creates compromised arterial perfusion. Injury to various brain cells can cause the calcification seen in *Sturge-Weber* patients; this is particularly seen around blood vessels on the cortex [50, 51]. The cortex can be atrophied and numbers of cortical draining vessels are decreased; calcification becomes apparent as the hemisphere atrophies. Therefore, calcification, neuronal loss, and gliosis are also probably secondary to brain injury due to impaired brain perfusion. Cortical dysgenesis has been noted in surgical brain samples [52], including focal cortical dysplasia (FCD) type IIa near the region of leptomeningeal angiomatosis, *cortical dysplasia*, and *polymicrogyria* [53]. Modestly increased proliferative index within the leptomeningeal blood vessels suggests ongoing vascular remodeling [54]. Increased VEGF expression in cortical neurons and glia underlying the abnormal leptomeningeal vessels and increased VEGFR-1, VEGFR-2, HIF-1α, and HIF-2α expression in endothelial cells of the abnormal leptomeningeal vessels suggest that chronic tissue hypoxia and VEGF may drive ongoing vascular remodeling [54]. The Ra-Raf-MEK-ERK pathway can increase both VEGF [55] and HIF activity [54]; therefore the *SWS* somatic mutation in *GNAQ* may contribute to the vascular remodeling. Indeed, increased p-ERK expression has been noted in abnormal leptomeningeal vessels of surgical brain samples from patients with SWS [56].

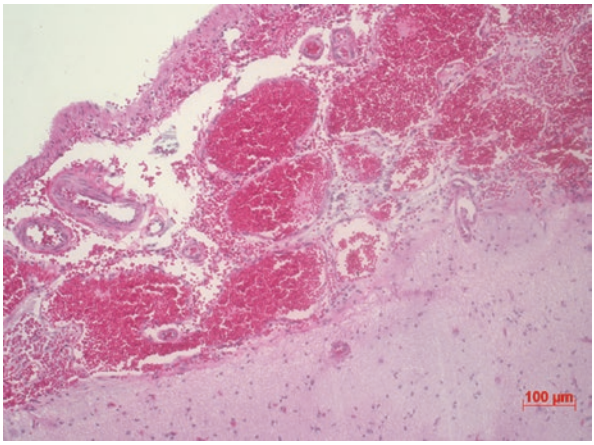

Fig. 5.2 Hematoxylin and eosin-stained, formalin-fixed brain section from a patient with Sturge-Weber syndrome removed at surgery for epilepsy. Note increased number of leptomeningeal blood vessels in the thickened leptomeninges

Diagnosis

Sturge-Weber syndrome is a spectrum disorder ranging from brain involvement alone to skin involvement only; the full presentation consists of typical brain, skin, and eye involvement; however individuals on the spectrum can include those who have only brain and skin involvement or those who have only skin and eye involvement. The precise manifestation of the spectrum likely depends on when in fetal development the somatic mutation occurs. Diagnosis of a *SWS* port-wine birthmark is usually straightforward; it is present at birth, unlike a hemangioma, and is usually off midline, unlike a nevus flammeus nuchae (angel's kiss, stork bite) birthmark. On occasion the port-wine birthmark is located midline forehead, and this has been associated with more severe neurologic prognosis [57]; it is differentiated in this case from the nevus flammeus nuchae by not being associated with symmetric upper eyelid involvement typically seen with the other benign birthmark. Occasionally the diagnosis is unclear and requires the input of a dermatologist or expert.

Diagnosis of *Sturge-Weber* syndrome brain involvement is made by MRI with and without contrast (Fig. 5.3); post-contrast flair [58] and susceptibility-weighted imaging (SWI) [59] and quantitative ADC analysis [60] can help increase the sensitivity of the imaging, yet MRI can have low sensitivity in early infancy or under the age of 1 [17]. Contrast is required to reveal the leptomeningeal angiomatosis, atrophy may be seen if injury has occurred, and susceptibility-weighted imaging (SWI) may demonstrate an increase in abnormal deep draining vessels. Calcification is best demonstrated on CT [61] (Fig. 5.4) but may also be seen on MRI if extensive (see Chap. 3). A scan that is negative for SWS brain involvement in an infant under the age of 1 does not rule out the possibility that the child has Sturge-Weber; a study

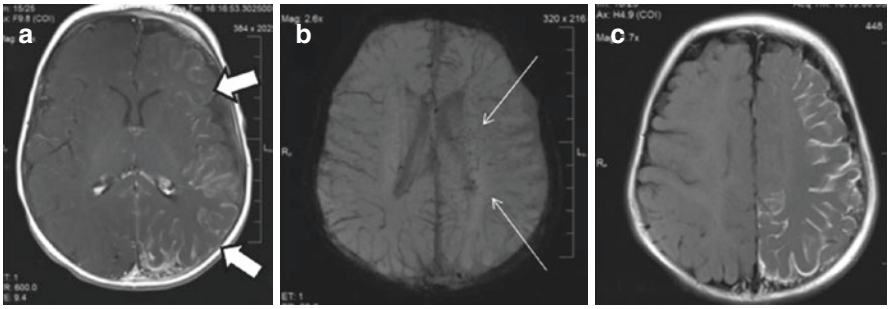

Fig. 5.3 Neuroimaging demonstrating typical features of Sturge-Weber syndrome brain involvement. A 4-month-old female with left-sided brain, skin, and eye Sturge-Weber syndrome involvement and recent onset of seizures. *Panel A:* T1-weighted contrast-enhanced MRI showing extensive leptomeningeal enhancement and mild brain atrophy involving the left hemisphere (bold arrows). *Panel B:* Susceptibility-weighted imaging showing increased number of small deep draining vessels within the left hemisphere. *Panel C:* Post-contrast flair imaging: leptomeningeal enhancement is even more prominent

demonstrated that early MRI only has a sensitivity of about 25% [17]. Imaging should be repeated after a year of age both to exclude brain involvement and, if the brain is involved, to determine the full extent of brain involvement. Other evaluations which can be helpful in the first year of life include a careful history, repeated exams, EEG looking for slowing, decreased amplitude, frequent sharps or spikes [62], and quantitative EEG evaluating [16] for a decrease in power on the affected side (see Chap. 50). Examinations should be performed as soon as possible after birth to evaluate for eye involvement and glaucoma risk and should be repeated every few months for the first few years of life and then at least yearly thereafter.

Indications for DNA testing are evolving. The most common genotype in published cases is R183Q GNAQ [63]; however the phenotype spectrum has been reported with other mutations in GNAQ [6, 63] and with GNA11 mutations [7, 8]. Capillary malformation and glaucoma can also be seen with PIK3CA mutations [64]. These other mutations can have implications for tumor risk, tissue overgrowth, and other vascular anomalies. Genetic testing can begin with blood particularly in patients with multiple birthmarks; however frequently skin or other abnormal tissue is required for testing; this situation does not lend itself to prenatal testing. Since the same mutation is found in both, DNA testing of skin tissue from the port-wine birthmark will not distinguish an infant with an isolated birthmark from one who has SWS brain and/or eye involvement (see Chap. 1).

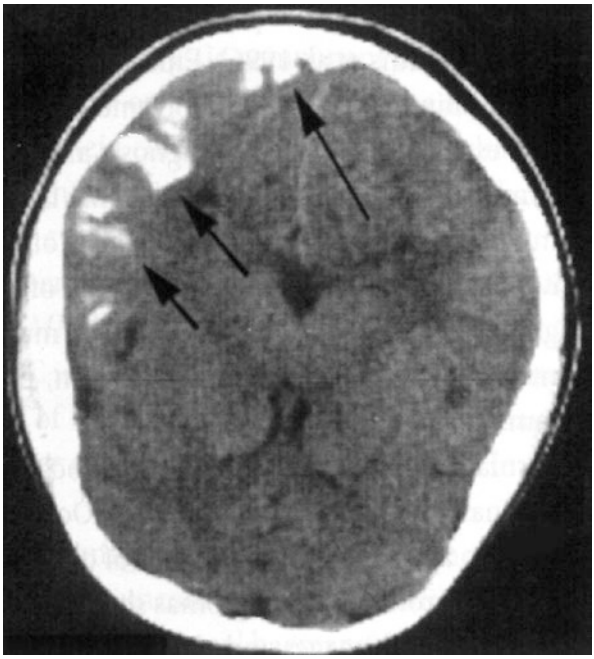

Fig. 5.4 Axial CT image of a young woman with Sturge-Weber shows coarse cortical calcifications (arrows)

Therapy

The gold standard treatment for port-wine birthmarks is *flashlamp-pumped* pulse dye laser treatment, often in combination with other older laser technologies. This will often lighten the birthmark and may also reduce the effects of physical impairments from the birthmark, as well as the risk of hypertrophy. It is recommended that treatments begin in infancy as the birthmark responds best to treatment while still flat and pink and small infants tolerate the treatments well without the need for general anesthesia [65, 66]. Six to 12 treatments are generally required to maximally lighten the port-wine birthmark, periodic maintenance treatments are usually required, and some birthmarks are resistant to laser treatment. Most birthmarks are not fully cleared with current treatment. Treatments, although brief, are painful, and the question of how best to manage this aspect ranges from topical anesthetics to oral sedation and to treatments done under anesthesia; the ethics of this are controversial. As a result, new treatment approaches are being researched and developed including topical and oral anti-angiogenesis treatments currently being studied in combination with laser treatment [67], and current practice emphasizes early, frequent treatment which usually obtains good results [65, 66] (see Chap. 50).

The *goal of glaucoma treatment* is control of intraocular pressure (IOP) to prevent optic nerve injury. This can sometimes be achieved with the following agents: beta-antagonist eye drops and carbonic anhydrase inhibitors which are both used to decrease the production of aqueous fluid and adrenergic eye drops and miotic eye drops which are used to promote drainage of aqueous fluid from the eye and thereby reduce eye pressure. However, for some patients surgery may be needed to reduce the eye pressure. There are many different types of surgeries which can be applied including goniotomy, trabeculotomy, trabeculectomy, and argon laser trabeculoplasty [68–70] (see Chap. 47). Choroidal involvement can lead to retinal detachment, which if symptomatic may be treated with photodynamic therapy or external beam radiotherapy [71].

The primary treatment for seizures in *Sturge-Weber* syndrome comprises the use of anticonvulsants [72] (see Chap. 50). These medications provide seizure control in about 50% of patients [73, 74]. However, if treatment with different anticonvulsants has been found unsuccessful, a patient may require surgery. First-line anticonvulsants, typically oxcarbazepine and levetiracetam [72], should be given aggressively at the first focal seizure. Other commonly used anticonvulsants include topiramate, phenobarbital, and carbamazepine [72]. These may be added if a single treatment has been unsuccessful. After a patient with *Sturge-Weber* has passed 3 months of age, parents are instructed to give rectal diazepam to abort seizures lasting longer than 3–5 min or clusters of seizures [45] (see Chap. 50).

Low-dose aspirin is becoming more accepted and used in the treatment of *SWS* but remains controversial, and further studies are needed. In a recent investigation of 58 patients with brain involvement, 49 children (84%) had no significant side effects to the aspirin. Six of the nine patients who reported side effects had minor complications [75]. Also, according to an online survey, low-dose aspirin significantly decreased the frequency of stroke-like episodes and seizures [76]. This

corresponds with *Udani's* results of fewer seizures and stroke-like episodes of six *SWS* patients after starting low-dose aspirin [77] and Maria's data of 14 patients, 65% of which had reduced stroke-like episodes on low-dose aspirin [61]. The modified Atkins diet and the ketogenic diet are also prescribed to patients with *SWS* to help prevent seizures. This diet consists of low daily carbohydrates but calls for high-protein and high (*unsaturated*)-fat foods. The modified Atkins diet is much less restrictive than the ketogenic diet, which also regulates calories and fluids. These diets are successful in around 50% of subjects with SWS [78] but are very difficult to maintain except in infants.

Hemispherectomies and focal brain resections are surgical options for many patients with unilateral *Sturge-Weber* syndrome. Candidates for surgery are the patients who have tried multiple anticonvulsants (and often low-dose aspirin), been on treatment for 6 months prior to surgery, don't have bilateral brain involvement, and have frequent seizures and classical SWS symptoms. It may yield more successful results to perform the hemispherectomy earlier on in childhood, but this is controversial and not all studies bear out this hypothesis [79–82]; surgery under a year of age increases the risk of inappropriately attempting surgery in a patient thought to be unilaterally involved, but who in fact is bilaterally involved and may have a higher risk of morbidity (see Chap. 48). Hemispherectomies are riskier, but more patients have fewer seizures after this type of surgery than with focal resection surgery. One study of 32 hemispherectomies performed worldwide found that 81% of subjects didn't have a decline in their motor function and were without seizures [81]. For unilaterally involved patients, surgery should be considered for those who have failed two or more anticonvulsants combined with low-dose aspirin [80, 81]. The decision to proceed with surgery is easier in those patients who also have hemiparesis and a significant visual field deficit in addition to impairing, medically refractory seizures. Surgery should also be seriously considered in patients whose cognitive development is progressively falling behind normal. The extensively bilaterally affected child with *Sturge-Weber* syndrome and severe brain involvement has the highest risk of very poor neurologic and cognitive outcome. For these infants, very aggressive treatment with anticonvulsants and low-dose aspirin is warranted. Hemispherectomy has only been recommended in bilaterally affected children with very severe disabling seizures primarily coming from one hemisphere, and the surgery is considered palliative rather than potentially curative [83] (see Chap. 48).

Headaches frequently start at an early age in patients with SWS and can be very severe. Headaches frequently happen along with seizures; other triggers include minor blows to the head [84]. Medications such as topiramate, gabapentin, and valproate may provide both seizure and migraine prevention. Migraine treatment can be an essential part of seizure management since migraines can trigger seizures [33]. Over-the-counter anti-inflammatory medications and triptans are common abortive migraine medications helpful to these patients [33]. The greater cognitive impairment a child has, the higher likelihood of behavioral problems. Stimulants may be used to treat attention deficit disorders with high success in patients with *Sturge-Weber* syndrome [85]. Individualized or special educational classes or programs can also be beneficial, along with behavioral psychology therapy.

Prognosis

There is an extremely wide range of outcomes in patients with *Sturge-Weber* syndrome. Predictive variables include their age of onset and controllability of seizures and unilateral vs. bilateral brain involvement. Genetic predisposition to seizures, strokes, and migraines likely plays an important, though undefined, role as well; a family history of epilepsy is associated with early onset of seizures in *SWS* [86], which in turn is associated with worse neurologic outcome. Therefore, each patient is unique and prognosis is difficult to predict. *Sturge-Weber* syndrome is progressive, in the usual sense, in some, but not in all, patients. Some patients can attend regular mainstream schooling, and some receive extra assistance in school; many of these patients are able to move on to higher education and can complete college and beyond. Other patients require special education services, while a subset are trainable or require full care. Many patients with *SWS* receive some sort of school accommodation. Some patients live with their parents and families of origin into adulthood, while others can live independently and start families of their own. Need for assistance with transportation is common because of epilepsy and vision issues.

Recent Treatment Trials and Future Prospects

It is to be hoped that with the discovery of the underlying somatic mosaic mutation and a new understanding of the *pathogenesis* of *Sturge-Weber* syndrome in the not too distant future, target treatment options will become available which will effectively treat the vascular basis of *SWS* and effectively alleviate its neurologic, ophthalmologic, dermatologic, and endocrine manifestations. Early progress has been made recently in the publication of the first prospective treatment trials of Sturge-Weber syndrome which have pioneered the application of several outcome measures and suggested the usefulness of cannabidiol (Epidiolex) [87] and rapamycin (mTOR inhibitor/sirolimus) [88] for the neurologic treatment of Sturge-Weber syndrome. Furthermore, because seizures exacerbate blood flow impairments in SW syndrome and increase the risk of venous hypertension, stroke, and brain injury particularly in infants and young children, presymptomatic treatment (prior to the onset of seizures) is gradually being evaluated [89–91].

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