Sturge-Weber Syndrome

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Sturge-Weber syndrome is a sporadic neurocutaneous disease characterized by facial port-wine stain, ocular abnormalities (glaucoma and choroidal hemangioma) and leptomeningeal angioma. Although the precise pathogenesis is unknown, available data regarding genetics, embryogenesis, and pathologic features are briefly reviewed. Clinical features vary from mild incomplete forms to full-blown disease with facial stain, seizures, and glaucoma. Frequencies of associated complications are reviewed. To plan treatment and further follow-up, diagnosis of glaucoma and intracranial involvement, even if asymptomatic, is fundamental in children at risk. Early neuroimaging features are important to recognize. Management of patients with Sturge-Weber syndrome is focused on treating associated neurologic and ocular abnormalities. © 2004 Elsevier Inc. All rights reserved.

Sturge-Weber syndrome is a sporadic neurocutaneous disorder characterized by a facial capillary malformation, ipsilateral leptomeningeal angioma and vascular eye abnormalities. However, many incomplete forms, lacking one feature of this triad, exist. The clinical features of this syndrome were first described by Sturge in 1879, and Parkes Weber described the cortical calcifications on X-rays in 1922. The facial capillary malformation in SWS has often been referred to as facial port-wine stain (PWS), due to the characteristic dark red color similar to the Portuguese liquor. The facial PWS typically involves the forehead and upper eyelid, in a distribution that resembles the area innervated by the first branch (ophthalmic branch) of the trigeminal nerve (V1).

PATHOGENESIS

It has been suggested that SWS results from failure of the primitive cephalic venous plexus to regress during the first trimester of pregnancy. At this stage in embryogenesis, the close proximity of the ectoderm destined to form the facial skin to the portion of the neural tube destined to form the parietooccipital area of the brain may explain the association of a facial PWS and leptomeningeal angioma. Other authors suggest that there is either a failure of superficial cortical veins to develop or early thrombosis of these veins. As a result, there is redirection of blood to the developing leptomeninges and into the deep venous system. Despite this redirection there is insufficient venous drainage, leading to progressive venous stasis and vessel dilatation producing chronic hipoxia.

The pathogenesis of PWS remains controversial. It seems clear that there is only dilatation of blood vessels without proliferation. The cause of blood vessels ectasia does not seem to be secondary to a defective vessel wall (see Histopathology section) but may be related to a deficiency in sympathetic innervation of the vessel and failure to regulate vasoconstriction.

GENETICS

SWS occurs sporadically with equal frequency in boys and girls. There are only a couple of familial cases reported in the literature; a father and son both affected by SWS and a mother with PWS in the distribution of the third branch of the trigeminal nerve, whose son had SWS. It has been proposed that SWS is the result of a somatic mutation in the affected areas. Discordance in monozygotic twins is consistent with this hypothesis. Chromosomal rearrangement and trisomies in chromosomes 4 and 10 have been detected in the affected skin of 2 patients with SWS who lacked these findings in normal skin and blood.

Familial occurrence of capillary malformations in an autosomal dominant manner has been described in the literature. The locus for this hereditary form has been mapped on chromosome 5q, and a candidate gene has been identified. However, in these familial cases, capillary malformations are multiple, small, pink to red patches that are not restricted to the face and are clinically different from PWS of SWS.
HISTOPATHOLOGY

On histopathologic examination of skin biopsies of PWS in SWS, dilated and ectatic thin-walled vessels in the superficial vascular plexus are observed. There is no increase in the number of vessels. In some cases, there is an underlying “cavernous hemangioma” with proliferation and ectasia of thin-walled vessels in the deeper dermis, subcutaneous adipose tissue, and skeletal muscle. The cobblestoned, roughened surface of older lesions is due to progressive ectasia of blood vessels. In some cases, small angiomatosus nodules may appear that usually represent pyogenic granulomas. In a few instances, the angiomatosus nodules correspond to acral arteriovenous tumors. Vessel morphology is typical of capillaries, postcapillary venules and small veins. There is no decrease in the components of the vessel wall (fibronectin, factor VIII, or type IV collagen) to explain decreased support and secondary dilatation. Immunohistochemical analysis with monoclonal antibodies specific for endothelium (PAL-E, anti-Factor VIII related antigen, anti-ICAM-1 and anti-ELAM-1) show no substantial differences from normal blood vessels. In one study, S-100 immunoperoxidase staining revealed a significant decrease in nerve density in the wall of blood vessels, which may explain dilatation.

Histological studies of leptomeningeal angiomas has revealed thickened leptomeninges with tortuous blood vessels. The underlying brain may be atrophic, with intense gliosis and calcifications both in the cortex and white matter. Calcium deposits are seen initially only in the vessel wall and later on in perivascular tissue or rarely within the neurons. Focal cortical dysgenesis has been found in some cases.

Histological studies of trabeculectomy specimens in patients with SWS have shown abnormal collagen deposition and abundant vessels in the intra-trabecular spaces, as well as morphological abnormalities in the Schlemm canal. The presence of hemangiomas in the trabecular meshwork is a highly characteristic finding of SWS and is never associated with congenital glaucoma of other etiologies.

CLINICAL MANIFESTATIONS

There are a number of reviews of SWS that address clinical manifestations and frequencies of different complications. Clinical manifestations can be divided into cutaneous, neurologic, or ocular manifestations.

Cutaneous Manifestations

Port-wine stains or nevus flammeus in SWS are well-demarcated red macular stains present at birth. With increasing age, the stain darkens in color and becomes raised and thickened. Sometimes multiple, small, red to purple nodules develop on the surface that confer a cobblestone pattern to the lesions. In a few instances, larger nodules develop representing pyogenic granulomas or acral arteriovenous tumors.

Facial port-wine stains, whether or not associated with SWS, usually have a sharp midline demarcation, although some extension over the midline may be observed. The pattern of the cutaneous PWS, although repetitive from patient to patient, does not conform exactly to any known dermatomal or vascular distribution and does not reproduce the embryological facial prominences. However, in the literature the distribution of the facial nevus has always been correlated to the branch of the trigeminal nerve that innervates most of the involved skin. Following this convention, PWS in patients with SWS always involve the skin innervated by the first arch of the trigeminal nerve (V1, forehead and upper eyelid). Involvement of V1 alone is uncommon (2%-4% in patients without SWS, and up to 20% in patients with SWS). In many patients, there is additional involvement of V2 or V2 and V3 (2%-23%). Bilateral lesions can be seen in 10% to 30% of the patients (Fig 4). Extrafacial involvement in patients with facial
PWS may be seen and is much more common when the lower face is involved or with bilateral lesions.43

Soft tissue hypertrophy and facial bone overgrowth may occur, especially when the maxillary and mandibular areas are involved.44-46 In these cases, there is often gum hyperplasia and maleruption of teeth that may cause periodontal and dental problems.47,48 Phenytoin-induced gum hyperplasia may aggravate the symptoms.

Overall, the risk of associated ocular and/or neurologic manifestations in patients with involvement of V1 varies from 32% to 65%.32,33,38 The risk increases with extensive and bilateral lesions. However, some authors have not found a correlation between the size of facial PWS and the
size of pial angioma.\textsuperscript{10,49} Glaucoma and neurologic manifestations (23%-38%) occur more commonly than either glaucoma alone (3%-8%) or neurologic manifestation alone (5%-19%).\textsuperscript{33,38} The inconsistencies in the reported frequencies can be explained by differences in the modes of ascertainment and by the age distribution of the study populations.

**Neurologic Manifestations**

Seizures are the most common neurologic manifestations and have been reported to occur in 23% to 83% of patients with SWS.\textsuperscript{10,36,37,50,51} Again, such differing prevalences are probably due to variations in the age of patients in different studies. Seizures are an early manifestation of SWS and may first present anywhere between birth to adolescence. However, in the majority of patients, they develop before 2 years of age.\textsuperscript{37} Seizures occur either on the contralateral side of the PWS or are generalized. Focal motor seizures predominate but secondary generalization may develop. Generalized seizures are primarily tonic-clonic seizures, but atonic seizures and absence seizures may also occur. Infantile spasms may be the first epileptic manifestation in infants.\textsuperscript{10,40} In many patients, the seizures begin during febrile episodes. With advancing age seizures tend to become more severe, frequent, and complex. Status epilepticus may also be observed.

Certain subsets of patients may have more severe neurologic involvement. Patients with bilateral leptomeningeal angiomatosis, which occur in 7% to 26% of patients, have more severe seizures, developmental delay and focal deficits.\textsuperscript{10,32} Early onset of seizures may correlate with poorer prognosis and difficult epilepsy control.\textsuperscript{10,37} However, Arzimanoglou at al, in their series, found that late onset was associated with a greater degree of intractability.\textsuperscript{31}

Developmental delay and progressive mental retardation are reported in half of the patients with SWS.\textsuperscript{36,37} Children with SWS may need some special education but only one third of patients may be severely mentally handicapped.\textsuperscript{10} There is a direct correlation between age of onset of seizures and degree of intellectual impairment. Children without epilepsy or with onset of seizures after 48 months of age have normal development and intelligence.\textsuperscript{36} The occurrence of prolonged seizures, lasting for more than 1 hour, correlates with further severe epilepsy, motor deficits and mental deterioration.\textsuperscript{49}

Recurrent headaches are another common manifestation present in one third to one half of the patients.\textsuperscript{36,53} Additional neurologic manifestations include contralateral hemiparesis, hemiplegia and hemianopsia (Table 1).\textsuperscript{10,37} In many instances, neurologic deficits follow prolonged seizures. Acute hemiparesis not associated with an obvious seizure may occur in a few patients and have been related to vessel thromboses.\textsuperscript{54}

**Ocular Manifestations**

Glaucoma is the most common ocular manifestation, and develops in as much as one third of the patients.\textsuperscript{53-57} Sujansky et al found an even higher incidence of 60% in their cohort of 52 adult patients with SWS.\textsuperscript{36} Glaucoma is usually ipsilateral to the facial PWS, although bilateral glaucoma with unilateral PWS stain may be seen.\textsuperscript{58} The age of onset ranges from birth to 41 years with a median of 5 years.\textsuperscript{36} Glaucoma in SWS develops insidiously, with a chronic or subacute increase in ocular pressure. There is a single case report with acute glaucoma in SWS.\textsuperscript{59} Increases in the episcleral venous pressure and developmental anomalies in the anterior chamber angle have been considered to be the main causal factors for the glaucoma associated with SWS.\textsuperscript{29,30,57}

Diffuse choroidal hemangioma ipsilateral to the PWS is another characteristic feature of SWS that may be found in up to 71% of SWS cases.\textsuperscript{57} It is usually seen as a red, flat to moderately elevated mass producing a classic “tomato ketchup” appearance on fundoscopic examination. This image is in contrast to choroidal hemangiomas not associated with SWS that are discrete and raised. With time, choroidal hemangiomas produce sec-

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<td><strong>Neurologic</strong></td>
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ndary changes in the overlying retina such as retinal pigment epithelium degeneration, fibrous metaplasia and cystic retinal degeneration leading to visual loss and visual field defects. Continuing exudation of the hemangioma may cause retinal detachment. Choroidal hemangiomas are almost always associated with leptomeningeal hemangiomas; therefore, neuroimaging is mandatory when fundoscopic evaluation reveals a choroidal hemangioma. Only 2 cases of choroidal hemangioma without intracranial involvement have been reported.  

Other ocular abnormalities that have been reported in SWS include dilatation and tortuosity of conjunctival and episcleral vessels, (Fig 5) buphthalmos, iris heterochromia, optic disc coloboma and cataract. Nevus of Ota may coexist in patients with SWS. Visual loss in patients with SWS is secondary to glaucoma or from damage to the retrogeniculate pathways by the angiomatous lesions. Optic neuropathy may develop rarely and contribute to progressive visual loss. Homonymous hemianopsia may also be secondary to occipital lobe involvement. Central vein occlusion has been reported in young adults with SWS without any other predisposing factors other than high intraocular pressure.

**Atypical Forms and Variants of Sturge-Weber Syndrome**

Leptomeningeal angioma without facial nevus has been reported and is considered a variant of SWS. In 3 reported cases the leptomeningeal angioma was present in an unusual frontoparietal temporal location sparing the occipital lobe. Glaucma has not been reported in patients lacking facial PWS.

In SWS, leptomeningeal angioma and choroidal hemangiomas are typically ipsilateral to the facial PWS. Leptomeningeal angioma contralateral to facial PWS, unilateral leptomeningeal angioma with bilateral facial PWS, and bilateral choroidal hemangioma with unilateral PWS have been reported rarely.

Patients with SWS may have other vascular abnormalities (Klippel-Trenaunay syndrome) or other neurocutaneous syndromes, including phakomatosis pigmentovascularis. Intracranial manifestations of SWS have been described in patients with Klippel-Trenaunay syndrome. In fact, some authors consider SWS and Klippel-Trenaunay syndrome to be the same disorder differing only in severity and location. A patient with hypomelanosis of Ito with pial angiomatosis has been reported.  

**NEUROIMAGING STUDIES**

Radiologically, a leptomeningeal (pial) vascular malformation, commonly located in the parieto-occipital area, cerebral atrophy and calcifications may be seen. Neuroradiologic data in SWS has been reviewed extensively. Cerebral lesions in SWS are ipsilateral to the facial PWS. Bilateral intracranial involvement is uncommon even in patients with bilateral PWS.

On CT scans, homolateral cortical atrophy may be seen, which may be associated with a compensatory hypertrophy of the frontal bone and frontal sinus. Cortical and intracranial calcifications underneath the leptomeningeal angiomas are best seen on CT-scans. They have a characteristic gyriform or “s” shape. They may be found at the cortex as well as at the meningeal arteries, cortical, and subcortical veins. They are commonly associated with cortical atrophy in the same area. Atrophy and calcifications are considered to be an indirect consequence of chronic ischemia of the cortex due to vascular stasis in the
area of leptomeningeal angioma. In severe forms they may develop rapidly. Calcifications may be seen at birth, but in many instances they may not be visible until an older age.87 Direct visualization of the pial malformation after contrast injection may be difficult on CT scans.93 Areas of contrast enhancement may differ in successive CT scans and may even disappear. It has been shown that cortical enhancement is usually present if performed shortly after an episode of severe seizures or hemiplegia but is absent or considerably less marked if performed later.87 An ipsilateral prominent choroid plexus may be seen on contrast-CT, with or without calcifications. Sometimes this is the only sign of Sturge-Weber on CT scans.87,88,92 CT scan may also show thickening of the ocular globe as a manifestation of choroidal disease, especially in unilateral cases where the opposite side can be used for comparison.52,93 However, in bilateral cases, CT is less useful because it is difficult to distinguish between enhancement and beam-hardening effects. CT scan after contrast injection may demonstrate dilatation of the deep venous structures.91

MRI, especially after contrast injection, is the preferred and most sensitive imaging technique for diagnosis and evaluation of SWS. MRI without contrast may show cerebral atrophy both in T1 and T2 sequences, diploic prominence, and enlarged choroid plexus (Fig 7). Calcifications may be seen in T2, especially, in gradient-echo images, as areas of low signal.89,90,94 Accelerated myelination may produce the areas of hypointensity in T2, and this may be the earliest sign of SWS in children under 6 months of age. In others, hyperintensity on T2 representing areas of gliosis may be seen.

After injection of gadolinium, there is diffuse pial enhancement seen in T1 weighted images. This is the single most reliable criterion for diagnosis of SWS. Contrast enhanced fluid-attenuated inversion recovery (FLAIR) sequences improve the detection of leptomeningeal angiomatosis because they suppress the signal intensity of normal vascular structures.95 There are 2 patients reported in the literature with SWS without pial enhancement on MRI.51,96 They were older children of 11 and 14 years of age. The lack of leptomeningeal enhancement might be due to progressive obliteration of leptomeningeal vessels, a well-documented phenomenon in SWS.96

Enlargement of the choroid plexus of the affected side is another characteristic feature of SWS and is best seen on contrast MRI.52,72,87,93 The size of the choroid plexus seems to correlate with the extent of leptomeningeal involvement.72 For some authors, the choroid plexus is enlarged because there is a choroidal hemangioma while for others it represents dilatation due to impaired drainage by the engorged deep venous system.93 Abnormalities in the draining venous system with dilatation of deep venous system can be in both contrast enhanced and non-contrast MRI.91,97 Diffuse choroidal hemangioma can be identified more easily with contrast MRI than with CT scans or non-contrast MRI.52,93 Fat suppression images are very useful when evaluating the orbits.

Cerebral angiography, although usually not performed, demonstrates the venous anomalies of SWS including a lack of superficial cortical veins, non-filling superior sagittal sinus and thickening and tortuosity of the deep subependimal and deep medullary veins.10,98 Intracranial arteries appear of smaller size in the affected hemisphere secondary to cerebral atrophy.

Skull radiographs are no longer obtained for evaluation and early diagnosis of SWS (Fig 8). However, if obtained a typical pattern of calcification resembling a “railroad track” may be seen, and is usually demonstrable at a mean age of 7 years.50 Other indirect signs that may be demonstrated on skull radiographs include cranial asymmetry, thickening of the cranial diploe and increased sinus sizes on the side of the PWS.

Functional neuroimaging studies of glucose metabolism by position emission tomography (PET) or cerebral perfusion by SPEC, have been introduced recently in the evaluation of SWS and may show disturbances before clinical symptoms appear.86,99 In initial stages, they show a transient...
hypermetabolism (PET) in the affected cortex second- 
ary to hyperperfusion (SPEC). At advanced 
stages there is hypometabolism and hypoperfu-
sion. These studies are not performed routinely 
for diagnostic purposes although they may poten-
tially give some insight into the pathogenesis of 
SWS and information regarding the functional re-
percussion of the pial angiomatosis.100-102

ELECTROENCEPHALOGRAPHY

EEG (electroencephalography) in patients with 
SWS shows asymmetry of the background ampli-
tude in the waking record involving the affected 
hemisphere. This asymmetry may be detected 
early but becomes more pronounced as cerebral 
atrophy becomes more severe. Epileptiform activ-
ity can be obtained in patients having clinical sei-
zures.

DIAGNOSIS AND WORK-UP

Diagnosis of SWS can be made on clinical 
grounds by the association of facial nevus and 
neurological features and/or glaucoma. However, 
because glaucoma should be treated before symp-
toms manifest, newborns at risk with a facial PWS 
in the V1 distribution should have an eye exam 
with fundoscopy and measurements of intraocu-
lar pressure (Fig 9). Glaucoma may not develop 
until late childhood; therefore, lifelong assess-
ment of eye pressure is mandatory. Choroidal 
hemangioma is also important to diagnose in chil-
dren with SWS, because it may predispose to reti-
nal detachment and to choroidal hemorrhage 
during or after surgery for glaucoma. Choroidal 
hemangioma may be difficult to diagnose clini-
cally on fundoscopic examination. Contrast-MRI 
is the most sensitive way to demonstrate the cres-
centric enhancement in the posterior wall of the 
ocular wall. Eye ultrasonography is a noninvasive 
technique that may demonstrate choroidal thick-
ening with or without associated retinal detach-
ment.

Infants at risk, should also have neuroimaging 
strong studies, even if asymptomatic, because there is a 
potential role for prophylactic antiepileptic treat-
ment if extensive intracranial involvement is de-
tected (Fig 9). Contrast-MRI is the optimal and
most sensitive neuroimaging technique for the screening in infants at risk for SWS. CT scan is not sensitive enough in infants as cortical calcifications and atrophy appear later. In the neonatal period, pial angiogmatosis may be difficult to identify even after contrast-MRI. Accelerated myelination in the involved hemisphere, with areas of white matter hyperintensity on T2 may be an early diagnostic feature before 6 months of age. If this early neuroradiological evaluation is negative, it is recommended to obtain a MRI with contrast later in the course as progressive dilatation of meningeal vessels with increasing age leads to better recognition of a leptomeningeal angiomia.

**TREATMENT**

Control of epilepsy is the major goal in treatment of SWS patients. Medical treatment with carbamazepine, sodium valproate, phenobarbitol, or phenytoin have all been tried. Vigabatrin may also be useful. Epilepsy control in SWS is difficult and usually requires the administration of more than one drug. Poor control correlates with progressive mental deterioration and motor deficits. Ideally, treatment should prevent first seizures. There are no prospective randomized studies about the prophylactic use of anticonvulsants. In a non-randomized study, seizures that started later were less severe and cognitive function was better in the prophylactically treated group. Although no general recommendation regarding prophylactic treatment can be made it may worth considering it in children at higher risk, ie, those with large leptomeningeal angiomia.

For children with refractory unihemispheric seizures, hemispherectomy has been proposed as a form of therapy. In reviewing surgical outcomes in 32 patients with SWS who underwent hemispherectomies, 81% were seizure-free after surgery. Hemiparesis was not more severe than before surgery. Cognitive deterioration may even improve after surgery. Therefore, surgery should be considered early, before mental status deterioration, if it becomes clear that epilepsy is untreatable. Some authors have proposed venous thrombosis as a cause for clinical deterioration in patients with SWS, and aspirin therapy has been advocated.

Control of glaucoma may be achieved with medical treatment alone (beta-blockers and carbonic anhydrase inhibitors) and should be considered the initial treatment of choice. In patients not responding to medical treatment, different surgical procedures have been performed including cyclocryotherapy, YAG laser goniometry, surgical goniometry, and trabeculotomy. Choroidal effusion and hemorrhage are common complications of surgery. Late postoperative complications as a result of persistent hypotony may result in loss of vision. Molteno or Ahmed implants may be necessary if these fail or even at first intervention. Retinal detachment secondary to choroidal hemangiomia is usually treated with external beam radiation. Recently photodynamic therapy has been used.

Facial port wine stain can be treated with pulsed dye laser in the same way that is treated in children without SWS. Facial PWS in V1 respond better than in other locations. Both local anesthesia and general anesthesia may be used. Anesthesia should be planned to avoid increases in ocular pressure or intracranial pressure.

**REFERENCES**

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