Sturge-Weber Syndrome Associated With Other Abnormalities

A Medical Record and Literature Review

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Objective: To develop hypotheses regarding the relationship between Sturge-Weber syndrome (SWS) and other abnormalities in a subset of patients.

Design: We retrospectively reviewed medical records in a group of 28 patients with SWS, noting the main features of SWS and accompanying unexpected abnormalities. We also conducted a literature review of abnormalities associated with SWS.

Results: Twenty-eight medical records of patients with SWS were reviewed. Of this number, we found 8 (29%, 2 female) patients who manifested other abnormalities. Our review of the literature uncovered 15 additional cases with associated abnormalities.

Conclusions: We hypothesize that the abnormalities associated with SWS suggest testable insights regarding pathogenesis and that chromosome 17p1-p13 may be a candidate region for genes involved with SWS. We also propose that some patients with SWS may have disorders of cholesterol biosynthesis or carbohydrate glycosylation.

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Sturge-Weber syndrome (SWS) is a sporadically occurring neurocutaneous disorder with vascular malformations of the brain, skin, and eye. Patients classically present with triad of port-wine stain in the distribution of the ophthalmologic division of the trigeminal nerve accompanied by ipsilateral leptomeningeal angiomatosis and glaucoma or other vascular eye abnormalities. Neurologically, seizures, stroke-like episodes, headaches, cognitive impairments, hemiparesis, and homonymous hemianopia may also occur. The cause of SWS is unknown; however, non-Mendelian genetic hypotheses, including chromosomal instability, have been suggested. We studied the dysmorphic features, structural abnormalities, and masses seen in patients with SWS.

PROPOSED SWS CAUSATION MODELS

Sturge-Weber syndrome occurs sporadically, with no known genetic, environmental, or prenatal factors. The simplest causation model involves spontaneous somatic mutation early in the first trimester of development. Mutation in a common progenitor cell line of dermal, neural, and ocular tissues during this period could result in genetic mosaicism of the affected areas. This hypothesis is supported by a report of 1 of 2 monozygotic twins with typical bilateral SWS.1

In 1987, Happle2 proposed the existence of a lethal mutation surviving through mosaicism as a mechanism for SWS and several similar neurocutaneous disorders. Happle revised the idea in 1993 with paradominance to explain a high frequency of familial cases of neurocutaneous disorders.3 According to this paradominance model, a homozygous lethal mutation might pass from generation to generation, leading to the disorder only when the partner chromatid undergoes isolated somatic mutation or loss during development. A variation on this 2-hit model involves multiple genes requiring simultaneous mutation, allowing for the possibility of both inherited and spontaneous factors leading to mosaicism. Sturge-Weber syndrome has been reported in a family with multiple members with port-wine stains,4 and we have encountered such families (unpublished data, 2004), suggesting that paradominance may have a role in this context.

Another possible factor may be nonspecific chromosomal instability. One
chromosomal analysis study of individuals with SWS revealed multiple chromosomal abnormalities in a mosaic pattern specific to the disease lesions. Cells from affected tissues (port-wine stain skin and angiomatous leptomeningeal vessels) contained higher proportions of inversions or dysplody aberrations compared with findings in blood or normal skin samples in the same patients. Results of further studies suggested specific genetic factors that may have a role in SWS. Comi and colleagues found significantly (P = .007) increased fibronectin gene expression in fibroblasts of port-wine stain tissue compared with those of normal skin samples in the same patients. Fibronectin's role in the regulation of vasculogenesis makes it a likely candidate for causing SWS. Analysis of 17 families with familial capillary malformation–arteriovenous malformation allowed identification of the RASA1 mutation, present on chromosome 17q, in 6 families. The gene product of RASA1 is p120-RasGAP, a negative regulator of the Ras–mitogen-activated protein kinase signaling pathway. The role of p120-RasGAP in cellular growth, differentiation, and proliferation makes it a candidate for involvement in the vascular abnormalities of SWS and hereditary port-wine stain.

SUMMARY OF PATIENTS WITH ADDITIONAL ANOMALIES

This study received expedited institutional review board approval and was granted exemption status. Twenty-eight medical records were reviewed (23 males and 5 females; age range, 1-35 years [mean age, 10.4 years]). We found that 8 (29%, 6 male and 2 female) of the patients with SWS manifested other abnormalities. Four male patients (14%) reported structural abnormalities of the genitalia, including congenital unilateral and bilateral inguinal hernias, congenital bilateral hydroceles, and hypospadias. These findings are summarized in Table 1. Table 2 summarizes the 15 cases of abnormalities associated with SWS reported in the literature. In our study and in the literature, a wide variety of associated abnormalities are reported. In a survey of 171 patients with SWS, 12% presented with dysmorphic features or additional symptoms not related to SWS. Our findings were closer to 30% (8 of 28 medical records reviewed). Two main themes emerged in our review: (1) masses and malignancies, and (2) malformations and dysmorphism. Abnormalities associated with vasculature, such as the case of the double inferior vena cava, have at least some superficial relationship with SWS, in which vascular development is abnormal.

NEW HYPOTHESES FOR SWS

We searched the Online Mendelian Inheritance in Man using key words related to any of the dysmorphic features, structural abnormalities, or masses described in patients with SWS. Our results revealed a number of genes in the 17p1-p13 region with links to the unexpected abnormalities we found. PMP22, the gene implicated in hereditary neuropathy with liability to pressure palsies, is located at 17p11.2, and the RAI1 gene often mutated in Li-Fraumeni syndrome and many other cancers is at 17p13.1. RAI1 is associated with Smith-Magenis syndrome, a disease caused by a deletion in chromosome 17p. One patient with Smith-Magenis syndrome, lacking a portion of 17p11.2, presented with cleft palate and genitourinary abnormalities. The HIC1 gene (17p13.3) may account for the dysmorphism accompanying Miller-Dieker lissencephaly and is associated with cancer in animal models. We found 3 genes in this chromosomal region (17p1-p13) with some link to retinitis pigmentosa, which was reported in 3 of our literature review cases. PEDF (17p13.1) is a candidate for involvement in retinitis pigmentosa, whereas CORD5 (17p13.12) is linked to progressive cone degeneration. PEDF (17p13.3), a pigment epithelium-derived factor, is a key player in retinal neuronal and vascular functions. We, therefore, suggest that region 17p1-p13 may be a candidate region for genes involved in SWS and the associated abnormalities as described.

Table 1. Features of Sturge-Weber Syndrome With Other Abnormalities

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Neurologic Features</th>
<th>Skin Features</th>
<th>Ophthalmologic Features</th>
<th>Unexpected Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/25</td>
<td>Left occipital leptomeningeal angioma</td>
<td>Left facial PWS (V1)</td>
<td>None</td>
<td>Bilateral inguinal hernias</td>
</tr>
<tr>
<td>2/M/4</td>
<td>Left TPO leptomeningeal angioma</td>
<td>Left facial PWS (V1)</td>
<td>Dense hemifield cut (right)</td>
<td>Bilateral hydrocele</td>
</tr>
<tr>
<td>3/M/6</td>
<td>Left diffuse leptomeningeal angioma</td>
<td>Left facial PWS (V1)</td>
<td>Glaucoma (left eye)</td>
<td>Hypospadias</td>
</tr>
<tr>
<td>4/M/2</td>
<td>Bilateral parieto-occipital leptomeningeal angioma</td>
<td>Left hemifacial PWS</td>
<td>Glaucoma (left eye), strabismus, ptosis</td>
<td>Maxillary juvenile ossifying fibroma</td>
</tr>
<tr>
<td>5/F/10</td>
<td>Right frontal leptomeningeal angioma</td>
<td>Left hemifacial PWS</td>
<td>None</td>
<td>Bilateral inverted nipples</td>
</tr>
<tr>
<td>6/M/23</td>
<td>Left TPO calcifications*</td>
<td>Left hemifacial PWS</td>
<td>None</td>
<td>Unilateral inguinal hernia</td>
</tr>
<tr>
<td>7/M/18</td>
<td>Right parieto-occipital leptomeningeal angioma</td>
<td>None</td>
<td>None</td>
<td>Hereditary neuropathy with liability to pressure palsies</td>
</tr>
<tr>
<td>8/F/4</td>
<td>Left diffuse leptomeningeal angioma</td>
<td>Left facial PWS</td>
<td>Glaucoma (left eye)</td>
<td>Cleft palate</td>
</tr>
</tbody>
</table>

Abbreviations: PWS, port-wine stain; TPO, temporal-parieto-occipital; V1, trigeminal nerve.

*Data obtained by computed tomography of the head.

Table 2. Summary of Patients With Additional Anomalies

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Other hypotheses are suggested by these observations. Some forms of human malformation, such as cleft palate, hypospadias, and limb anomalies, can be linked to insufficient cholesterol. Cholesterol is necessary for normal embryonic development, and decreased levels affect the activity of the hedgehog morphogen proteins, especially that of sonic hedgehog, which is responsible for midline patterning and limb formation, and has been shown to regulate capillary formation, and instruct arterial vs venous patterning. Decreased levels of cholesterol can also affect desert hedgehog, which controls genital development. Four of the 8 patients in our study are affected in the genital region, suggesting that patients with SWS may be more likely than unaffected individuals to have failures in a pathway affecting the hedgehog morphogens or cholesterol biosynthesis. Carbohydrate glycosylation disorders are another group of metabolic disorders with a wide variety of manifestations, including inverted nipples, syndactyly, and seizures. We hypothesize, therefore, that disorders of cholesterol biosynthesis or carbohydrate glycosylation may have a role in the pathogenesis of SWS, particularly in individuals with other associated dysmorphisms.

Data in this report were obtained from a retrospective medical record review in patients with SWS evaluated at The Johns Hopkins Hospital and The University of Texas Southwestern Medical Center at Dallas. Both of these institutions are tertiary care centers. Therefore, the data from this retrospective review are likely to be biased toward patients with more significant medical problems. Nevertheless, the findings from this study and literature review suggest new and testable hypotheses regarding the cause and pathogenesis of SWS. Although hydroceles and inguinal hernias together have a prevalence of 2.5% in a population of school-aged boys, the other abnormalities all have incidences far smaller than 1% in the general population, suggesting that these associations are not likely to be due to chance.

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**Table 2. Results of Literature Review of Abnormalities Reported in Association With Sturge-Weber Syndrome**

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age</th>
<th>Neurologic Features</th>
<th>Skin Features</th>
<th>Ophthalmologic Features</th>
<th>Unexpected Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/11 y 15/Mo/9 y</td>
<td>Bilateral cortical calcifications*</td>
<td>Bilateral facial PWS (V1, V2), PWS patches on neck, oral angioma</td>
<td>None</td>
<td>Several teeth absent congenitally</td>
</tr>
<tr>
<td>2/M/35 y 30/Mo/47 y</td>
<td>Grand mal epilepsy*</td>
<td>PWS on left frontal and malar region</td>
<td>Glaucoma (left eye)</td>
<td>Paranasal sinus enlargement</td>
</tr>
<tr>
<td>3/M/3 y 2/M/35 y</td>
<td>Right TPO cortical calcification, right cerebral atrophy*</td>
<td>Right facial PWS (V1, V2)</td>
<td>Glaucoma (right eye)</td>
<td>Bilateral congenital symmetrical syndactyly involving third and fourth digits</td>
</tr>
<tr>
<td>4/M/5 mo 4/M/53 y</td>
<td>Right diffuse cortical calcifications, bilateral cortical atrophy*</td>
<td>Extensive bilateral PWS of face, trunk, and extremities</td>
<td>None</td>
<td>Hypoplastic larynx and subglottic stenosis</td>
</tr>
<tr>
<td>5/M/28 y 5/M/53 y</td>
<td>Right parieto-occipital cortical calcifications*</td>
<td>Bilateral facial PWS (V1, V2, V3)</td>
<td>Glaucoma (right eye)</td>
<td>Retinitis pigmentosa, deafness (both bilateral)</td>
</tr>
<tr>
<td>6/M/35 y 7/M/52 y</td>
<td>None*</td>
<td>Left facial PWS</td>
<td>Glaucoma (left eye)</td>
<td>Retinitis pigmentosa</td>
</tr>
<tr>
<td>8/M/3½ y 9/F/13 y</td>
<td>Mild hydrocephalus and left focal seizures*</td>
<td>Extensive bilateral PWS of face, trunk, and extremities</td>
<td>Glaucoma (bilateral)</td>
<td>Renal hemangioma with perirenal hematoma, double inferior vena cava, Klippel-Trénaunay syndrome</td>
</tr>
<tr>
<td>10/M/11 y 11/M/14 y</td>
<td>Right diffuse leptomeningeal angioma</td>
<td>Right facial PWS</td>
<td>Right total vision loss (retinal detachment)</td>
<td>Pleomorphic xanthoastrocytoma (left temporal lobe)</td>
</tr>
<tr>
<td>12/F/30 y 13/F/24 y</td>
<td>Left parietal cortical calcifications*</td>
<td>Left facial PWS (V2)</td>
<td>Nystagmus</td>
<td>Giant meningioma of fourth ventricle</td>
</tr>
<tr>
<td>14/M/47 y 15/M/9 y</td>
<td>Seizures</td>
<td>Right facial PWS (V1)</td>
<td>Vision loss, glaucoma (right eye)</td>
<td>Cystic disease of lung, clubbing of fingers</td>
</tr>
<tr>
<td></td>
<td>Left parieto-occipital calcifications, right-sided hemiparesis*</td>
<td>None</td>
<td>None</td>
<td>Acral arteriovenous tumor within PWS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Congenital scalp aplasia</td>
</tr>
</tbody>
</table>

Abbreviations: PWS, port-wine stain; TPO, temporal-parietal-occipital; V1, first division of the trigeminal nerve; V2, second division of the trigeminal nerve; V3, third division of the trigeminal nerve.
*Data obtained by computed tomography of the head.
This study highlights evidence of a broader array of abnormalities occurring in conjunction with SWS than the previously described triad of vascular abnormalities of the brain, skin, and eye. Further research is needed in this area to determine whether the proposed link between dysmorphic features or masses with SWS is real and to evaluate candidate genes in the 17p11-p13 region. In addition, for patients with SWS and associated masses or dysmorphic features, it may be appropriate to ascertain karyotypes, perform subtelomeric fluorescence in situ hybridization and serum transferrin electrophoresis, and screen for cholesterol biosynthesis disorders.

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REFERENCES