Port-wine stains and Sturge-Weber syndrome: comparison of risk stratification models

ABSTRACT

Controversy exists over the management strategy of pediatric patients with facial port wine stains (PWS) referred to pediatric dermatologists. A unifying and clinically manageable guideline recommending neuroimaging and ophthalmological screening for select patients with facial PWS enables potential prophylactic management in appropriate candidates while confidently minimizing the concerns of patients without risk. Recent attempts have been made to enhance the strength of risk prediction by identifying PWS distributions with new topographic maps and unique high risk areas.[1,2] The primary aim of this study was to compare multiple proposed "high risk" areas of facial PWS used as potential screening tools for identifying patients at risk of developing Sturge-Weber Syndrome (SWS). This data encourages further research to support a unified dermatological model used to guide management of young pediatric patients who present with asymptomatic facial PWS.

INTRODUCTION

Port-wine stains are congenital, facial capillary malformations that present at birth in unique topographic patterns with distinct margins. This subgroup of nevus flammeus, seen in 0.3% of all live births with a 1:1 sex ratio, has a broad scope of clinical impact, from tolerable cosmetic abnormalities to SWS.[3,4] The congenital, sporadic neurocutaneous disorder SWS, also called encephalotrigeminal angiomatosis, was described by Sturge in 1879 and later radialogically by Weber in 1922.[5,6,7] As in non-syndromic PWS, the syndrome presents at birth with a facial PWS. An estimated 8% of all PWS patients will eventually manifest syndromic disease, classically associated with an ipsilateral leptomeningeal angioma and ocular involvement.[8,9] Correlating topographic facial PWS distribution and eventual SWS development has been of peak research interest, with the ultimate goal of developing triage guidelines so screening and prophylaxis can be allocated to those patients with the highest risk of disease progression.

The classic trigeminal dermatome model with V1 involvement indicating increased risk of SWS has been used for decades in the assessment of PWS.[22] This model has come into question following recent studies that suggest a lack of connection between dermatomes and PWS development. In response to these discoveries, new models for risk stratification have been proposed.[1,2,9] Soon after the benchmark study identifying V1 by Enjorlas and colleagues, Tallman added the upper and lower eyelid and more of the trigeminal nerve distribution as areas of concern.[9] More recently, Dutkiewicz and colleagues identified six distinct facial PWS patterns, two of which were correlated with significantly increased risk of SWS.[1] Based on the vascular pathology central to PWS, Waelchli and colleagues identified the forehead with boarders dictated by embryonic development as the strongest clinical predictor of SWS.[2]

The primary aim of this study was to compare the classic trigeminal dermatome distribution model with Dutkiewicz' six pattern, Waelchli's vascular forehead area and the upper and lower eyelid. Through retrospective chart analysis of pediatric patients with records at Rady Children's Hospital from January 1st, 2000—June 29th, 2015, the sensitivity of each prediction model was assessed. Presence of a PWS on more than 50% of the upper eyelid or anywhere in the V1 dermatome were the most sensitive in identifying pediatric patients with PWS who develop SWS. In conclusion, more data on a larger scale would be required before we would support replacing the V1 dermatome method as a clinical decision making tool.

METHODS

Data on pediatric patients with diagnosed facial PWS and SWS that presented to Rady Children's Hospital Pediatric Dermatology Department between January 1st, 2000—June 29th, 2015. Patients met all of the following criteria: facial PWS located anywhere above the mandible, at least 2 years of age and/or have at least 2 years of follow-up, adequate images or detailed description of the PWS distribution sufficient to allow mapping of the stain, clinical signs or symptoms of ocular SWS or neurologic SWS and/or MRI or other imaging consistent with SWS. Patients with images insufficient to allow mapping of the facial PWS, no signs of SWS, under 2 years of age without 2 year follow-up and/or subsequent

change of diagnosis to hemangioma or other vascular anomaly were excluded. As the project entailed a retrospective chart review that excluded identifying information, the University of California, San Diego Institutional Review Board (IRB) approved exemption.

Specific information was collected on each patient – age, birthday, sex, visit date and clinician, facial PWS diagnosis, facial PWS distribution description and/or image, comorbidities, neurological symptoms (seizure, epilepsy, mental retardation, hemiparesis, MRI or other neuroimaging) and ophthalmological symptoms (glaucoma, choroidal hemangioma, increased intraocular pressure).

A total of 27 patients with a diagnosis consistent with SWS and PWS were identified within the timeframe approved by the IRB. Of these patients, eight had never visited the dermatology department at Rady Children's Hospital and therefore did not have photographic or descriptive data that enabled PWS mapping and three additional patients did not meet criteria for inclusion. A total of sixteen patients with facial PWS and evidence of SWS met all criteria described above. Of those sixteen patients, ten patients had imaging that was accessible at Rady Children's Hospital and was utilized for data analysis. The remaining six patients had sufficient descriptions in their chart history to enable adequate mapping of their facial PWS.

Each patient's facial PWS was mapped onto 4 standard face contours, each containing high risk areas outlined by the literature: V1 dermatome, pattern 5 and 6 described by Dutkiewicz et al., and "forehead" described by Waelchli et al. (see Figure 1). Patients were then categorized based on their unique dermatomal distribution with ≥ 50% coverage of the "high risk" area being recorded as positive distribution in all areas except the "forehead" and where the criteria outlined by Waelchli et al. was followed (any presence of PWS in the "forehead" area).[2] An additional area with any involvement in V1 was also included.

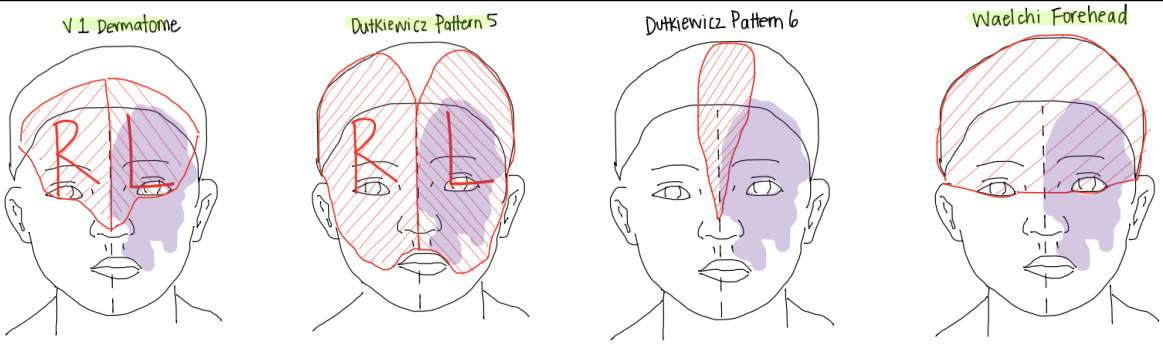


Figure 1: Example of individual PWS map with each topographic high-risk area described above. (Left to right) V1 dermatome, pattern 5 and pattern 6 described by Dutkiewicz et al., and "forehead" described by Waelchli et al.[2] (Green highlights "positive" distribution). Illustration adapted from Dutkiewicz et al.[1]

Each patient was categorization into the different topographic model categories, and the number of patients with "positive" PWS distribution in each topographic area who developed SWS was quantified. By calculating total patients with and without a PWS in each high-risk area, the sensitivity of predicting SWS based on clinical phenotype was quantified [sensitivity = true positive / (true positive + false negative)]. Additionally, within all patients with SWS, the sensitivity and specificity of each high-risk area in predicting glaucoma or seizure was quantified [specificity = true negative / (true negative + false positive)].

RESULTS

Sixteen patients with both facial PWS and ophthalmic and/or neurological signs of SWS were analyzed. Of these sixteen patients, fourteen had signs of glaucoma and ten had signs of seizure. These findings were documented by an ophthalmological visit with increased intraocular pressure noted and clinical report of seizure activity with electroencephalogram and/or magnetic resonance imaging confirmation, respectively. The following number of patients had PWS that were considered positive in the following high risk areas – V1 with any involvement (V1 any, 16 patients), V1 with >50% involvement (V1 >50%, 12 patients), Dutkiewicz area 5 (D5, 13 patients), Dutkiewicz area 6 (D6, 3 patients), "forehead"

(FH, 15 patients), upper eyelid (UL, 16 patients) and lower eyelid (LL, 14 patients). These findings resulted in the sensitivity values outlined in Table 1.

Table 1 Sensitivity of individual high-risk areas for predicting SWS.

	# of "+" Patients	SWS Sensitivity
V1 (any)	16	100.00%
V1 (>50%)	12	75.00%
D5	13	85.71%
D6	3	21.43%
FH	15	92.86%
UL	16	100.00%
LL	14	87.50%

The upper eyelid and any V1 involvement had the highest sensitivity (100.00%, specificity unknown) for predicting SWS in patients with facial PWS, followed by the forehead, the lower eyelid, Dutkiewicz area 5, and V1 >50%. Dutkiewicz area 6 had a much lower sensitivity than all the other areas assessed. Among all patients with SWS, the sensitivity and specificity of each high-risk area as a predictor of glaucoma and seizure were both assessed (listed in Table 2 (a) and (b), respectively).

Table 2 Sensitivity and specificity of high-risk areas for predicting (a) glaucoma and (b) seizure in patients with SWS.

(a) Glaucoma			**(b) Seizure**		
	Sensitivity	**Specificity**		**Sensitivity**	**Specificity**
V1 (any)	100.00%	0.00%	**V1 (any)**	100.00%	0.00%
V1 (>50%)	78.57%	50.00%	**V1 (>50%)**	90.00%	50.00%
D5	85.71%	50.00%	**D5**	90.00%	33.33%
D6	21.43%	100.00%	**D6**	42.86%	100.00%
FH	92.86%	0.00%	**FH**	100.00%	16.67%
UL	100.00%	0.00%	**UL**	100.00%	0.00%
LL	92.86%	50.00%	**LL**	80.00%	0.00%

This studies points out the drastic difference in sensitivity of current topographic prediction models in the literature used to assess facial PWS and allocate screening. Greater than 50% involvement of the upper eyelid and any involvement in V1 were the most sensitive areas in predicting SWS. Although this is valuable and should guide future research, a much larger population study including patients with facial PWS regardless of the SWS phenotype would enable statistical analysis and quantification of not just sensitivity, but additionally specificity, positive predictive value and negative predictive value.

The present study originally assessed seventy patients with facial PWS in an attempt to accomplish this; however, only three patients with signs or symptoms of SWS were identified among this population. Notably, this number of SWS was approximately half the reported incidence of SWS among patients with facial PWS.[8,9] This means a significantly larger number of total patients would need to be analyzed to identify sufficient SWS patients to make analysis meaningful. By searching our patient database for patients with SWS as a diagnosis, a significantly larger population of affected patients was identified. Therefore, this study was conducted as a preliminary analysis of the sensitivities of the proposed high-risk areas in patients with both facial PWS and SWS.

DISCUSSION

The pathophysiological understanding of PWS and their development has evolved tremendously over the last fifty years. Neurological presentations range from asymptomatic leptomeningeal hemangiomas seen on neuroimaging to seizure, hemiparesis, developmental delay and mental retardation; whereas, glaucoma and diffuse choroidal hemangioma are the most common ocular

manifestations. In a study of 171 patients with SWS, Sujansky and Conradi found that 95% of seizures, which occurred in 136 of the 171 patients, had an onset before 5 years of age. In all but one case, seizures were associated with PWS in V1 alone or V1 and V2 trigeminal dermatomes. Notably, later seizure onset was associated with decreased developmental delay – highlighting the importance of potential seizure prophylaxis and aggressive fever treatment in high-risk cases. Glaucoma was only present in 82 of the 171 patients, with 72% presenting by five years of age. Every patient with glaucoma had PWS in both V1 and V2 (92%) or V1 only (8%).[10] This data strongly supports the importance of V1 involvement as a risk factor for syndromic disease.

Early histological studies documented ectatic, dilated capillaries with uniformity throughout the lesion that progressed over time but did not demonstrate a proliferative process. Additionally, immunohistochemical analysis using antibodies against S-100 found in Schwamm cells demonstrated significantly less staining in PWS compared to normal tissue, indicating decrease innervation.[11] This decreased sympathetic innervation led Rosen and Smoller to logically theorize that the ectasia seen in PWS was the result of reduced sympathetic innervation that, if present, would normally induce capillary vasoconstriction.[12] Although detailed pathogysiology remains elusive and controversial, it is generally accepted that maldevelopment occurs early, when cells destined to become facial, meningeal and orbital tissue exist in close proximity.

Neurocutaneous syndromes have mystified medical and scientific fields for decades. From a distance, these disorders appear to have scattered phenotypic distribution without logical connection; however, abnormal tissues likely exist in close proximity when traced to their embryological origin. With recent intellectual gains following breakthroughs in both embryology and genetics, the early theory that altered ectoderm gave rise to pathology seen in diverse tissues involved in SWS has come into question. Furthermore, leaders in the field of embryology predict that the trilaminar model in its entirety with ectodermal, mesodermal and endodermal precursors all destined to differentiate into specific adult tissues will one day serve as merely an anecdotal reference. For example, following closure of the neural tube, a transient population of adjacent cells labeled neural crest cells (NCC) divide and migrate to form tissues originally presumed to be of ectodermal and mesodermal origin.[12]

"Neurocristopathies," a term coined by Bolande in 1974, historically included disease known to originate from NCC such as pheochromocytoma, neurofibromatosis, Hirschsprung disease and multiple endocrine neoplasia.[14] Recent data supports NCC as the multipotent precursors of atypical tissues involved in SWS, and perhaps all congenital neurocutaneous syndromes.[15] The broadening scope of neurocristopathies may soon include primary neurocutaneous syndromes. Unlike the mesodermal vasculature of the body, cephalic NCCs give rise to the "mesectoderm".[16] NCCs only differentiate once reaching their final destination and form the meninges, globe and facial dermis and vasculature – all distinct cellular populations disrupted in SWS. The recent discovery of a somatic *GNAQ* mutation on chromosome 9q21 points to genetic mosaicism as the root of PWS and SWS pathology. Specifically, a single nucleotide variant changing glutamine to arginine was found in 88% and 92% of phenotypically affected tissue in patients with SWS and non-syndromic PWS, respectively.[17] The variant was not found in normal tissue in the same patients and these results have been replicated.[18] Encoding the q polypeptide of a G-protein, this gain of function mutation alters numerous downstream effects through the RAS effector pathway and will scaffold future research.

Given the significant evidence supporting an early embryologic mutation, altered downstream expression could manifest as distinct populations of analogous abnormal tissue. The final location and extent of pathology thus depends on the number of precursor cells affected and their final destination. Pathology would logically exist in physiologic patterns laid by embryological NCC migration. These streams of cellular growth are uniquely visible on the skin and were described by German dermatologist Dr. Alfred Blaschko in 1901 based on over 150 patients with epidermal and sebaceous nevi. Lines of Blaschko, although invisible in normal phenotype individuals, are strikingly distinct in cutaneous mosaicism, with sharp contrast between normal and abnormal skin. Through years of research, Happle identified four additional patterns of cutaneous mosaicism that were later outlined by Molho-Pessach and Schaffer (Figure 2).[19-21] The "blocklike" pattern (Figure 2, Type 2) has been described in a number of cutaneous mosaic phenotypes affecting mesodermal tissues, such as blood vessels, neural tissues, fibroblasts and melanocytes. Molho-Pessach and Schaffer place PWS in this category, with its squares

of affected tissue and frequent sharp midline demarcation. A variant without midline delineation (Figure 2, Type 4) may represent bilateral PWS. These hypotheses encourage further study and may yield a unified map based on understanding of the true pathophysiological mechanism behind PWS and SWS.

Type 1a: thin lines of Blaschko
Type 1b: thick lines of Blaschko
Type 2: "blocklike,"
Type 3: "phylloid"
Type 4: large patches without midline
Type 5: lateralization

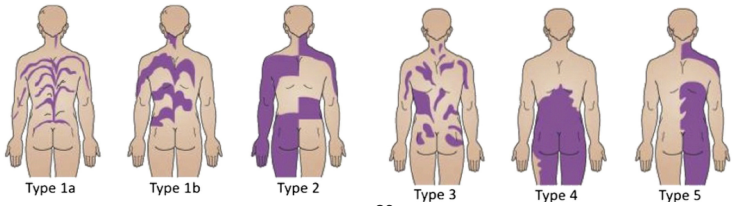


Figure 2: Happle's patterns of cutaneous mosaicism or "Blaschko lines"[20]

Several studies have identified relationships between different topographic patterns of facial PWS and SWS.[1,2,9,22-26] Whereas older studies have focused on dermatomal distribution and found strong correlations between V1 dermatome involvement and SWS, Dutkiewicz and colleagues recently sought to redefine the PWS map. They propose six patterns of PWS distributions based on a prospective analysis of 66 patients with PWS (Figure 3). This study, utilizing prospective data collection and innovative facial mapping documentation identified two of the following patterns (Figure 3, numbers 5 and 6) to have a statistically significant association with SWS. Of the 11 patients who developed neurological proof of SWS or were suspected to have neurological manifestations of SWS, the association between PWS distribution and SWS reached significance in patterns 5 (OR 7.70, p=0.003) and 6 (OR 17.08, p-0.008). Pattern 2 had three patients out of seven who fit this definition of SWS; however, this trend did not reach significance (OR 2.99, p=0.19).[1]

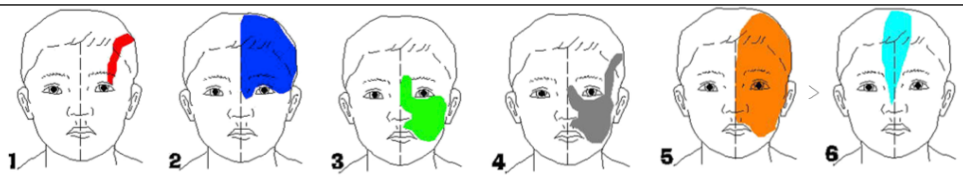
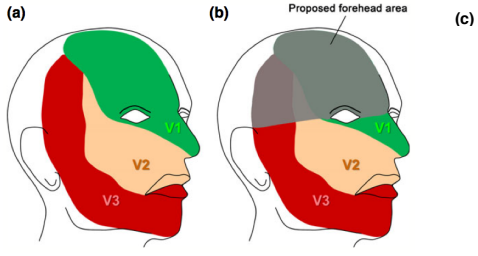


Figure 3: Patterns of facial PWS identified by Dutkiewicz and colleagues[1]

When comparing patterns 5 and 6, and noting pattern 2, the common ground lies over the V1 dermatome. Patterns 1, 3 and 4 – without associated SWS – exclude the V1 dermatome. Considering these factors, one must consider the true utility of adopting this more complex model of PWS distribution as a clinically applicable management guideline. Since presence or absence of V1 involvement has a similar association to SWS when compared to patterns 5 and 6, it serves as a more utilitarian model for clinical practice.

In a larger patient population with a much higher presence of syndromic disease, Waelchli and colleagues approached the same question with more physiological framework. In a cohort of 192 patients with facial PWS, they utilized multivariate logistic regression to predict adverse outcome measures from clinical phenotype. The forehead area, defined as "the area from the midline to an imaginary line between the outer canthus of the eye and the top of the ear including the upper eyelids" (Figure 4b), to have the strongest association with an abnormal MRI.[2] For patients with any involvement of this area, they report a significantly increased associations with seizures (OR 15.8, p=0.008), neurodevelopmental delay (OR 24.7, p=0.002), and glaucoma (OR 14.4, p=0.011). These findings led them to recommend urgent ophthalmological assessment and a brain MRI with gadolinium contrast for any child with PWS affecting any part of the forehead area described above.



(c)

	Forehead involved	Forehead not involved	Fisher's exact P-value
Seizures	36/111	0/33	< 0·001
Abnormal neurodevelopment	42/93	0/30	< 0·001
Glaucoma	45/92	0/15	< 0·001
Abnormal magnetic resonance imaging scan	69/94	0/4	0·002

Figure 4: (a) Distribution of the three branches of the trigeminal nerve. (b) Distribution of the "forehead" (c) Table relating clinical outcomes and forehead classification[2]

This study aimed to compare these PWS mapping systems and their relative association with SWS. All areas studied had a strong association with SWS except for Dutkiewicz area 6. Therefore, further analysis with a significantly larger population of patients with facial PWS is required to assess both the sensitivity and specificity of these screening tools. For the time being, any patient with a PWS that covers any part of the V1 dermatome or the upper eyelid – well-known geographic areas – should be immediately referred for ophthalmologic evaluation and brain imaging to screen for the presence of associated syndrome disease.

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