Forehead location and large segmental pattern of facial port-wine stains predict risk of Sturge-Weber syndrome

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Background: Children with forehead port-wine stains (PWSs) are at risk of Sturge-Weber syndrome (SWS). However, most will not develop neurologic manifestations.

Objective: To identify children at greatest risk of SWS.

Method: In this retrospective cohort study of children with a forehead PWS, PWSs were classified as "large segmental" (half or more of a contiguous area of the hemiforehead or median pattern) or "trace/small segmental" (less than half of the hemiforehead). The outcome measure was a diagnosis of SWS.

Results: Ninety-six children had a forehead PWS. Fifty-one had a large segmental PWS, and 45 had a trace/small segmental PWS. All 21 children with SWS had large segmental forehead PWSs. Large segmental forehead PWSs had a higher specificity (0.71 vs 0.27, $P < .0001$) and a higher positive predictive value (0.41 vs 0.22, $P < .0001$) for SWS than any forehead involvement by a PWS.

Limitations: Retrospective study at a referral center.

Conclusion: Children with large segmental forehead PWSs are at highest risk of SWS. (J Am Acad Dermatol 2020;83:1110-7.)

Key words: leptomeningeal angiomatosis; port-wine stain; prediction; segmental; Sturge-Weber syndrome.

Facial port-wine stains (PWSs) are congenital capillary malformations that occur in approximately 0.02% to 0.06% of newborns.[1,2] Sturge-Weber syndrome (SWS) is a neurocutaneous syndrome defined by the presence of a facial PWS as well as leptomeningeal capillary or capillary-venous malformations ("leptomeningeal angiomatosis"). Approximately half of patients with SWS will also have glaucoma, although this is not required for diagnosis. Epilepsy, progressive encephalopathy, and hemiparesis are also commonly associated with SWS.[3,4]

Sporadic and SWS-associated facial PWS are both associated with somatic mutations in the *GNAQ* gene.[5] Facial PWSs associated with increased risk of SWS have historically been thought to follow the divisions of the trigeminal nerve, but the constellation of abnormalities associated with SWS is more likely secondary to abnormal vasculature associated with embryonic placodes rather than trigeminal

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nerve divisions.[6] Specifically, the development of the embryologic frontonasal prominence and optic vesicles via neural crest cell migration from the prosencephalon and anterior mesencephalon is believed to be significant in the pathogenesis of SWS, because the forehead, cerebral cortex, and eye all develop from these structures.[6] As such, a facial PWS associated with a somatic *GNAQ* mutation in the context of SWS may be expected to have a distribution that more closely resembles a developmental unit or facial metamere.[7]

Eye or brain involvement will develop in approximately 10% of infants with a facial PWS.[8] Waelchli et al[6] found that forehead involvement by a PWS appears to have complete sensitivity for SWS. Among patients with forehead involvement, larger size of the PWS (including a hemifacial PWS) and bilateral forehead involvement are risk factors for SWS.[8-10] The pattern of facial PWS has also been suggested to be a predictor of SWS (Fig 1).[11] The "hemifacial" (pattern 5) and "median" (pattern 6) patterns have been significantly associated with SWS, whereas the "frontotemporal" (pattern 2) and "combined linear and cheek" (pattern 4) patterns may also impart risk.[11]

The goal of this study was to combine PWS location and pattern data to create a more specific screening tool to identify patients with a facial PWS at highest risk for SWS. We hypothesized that highest risk of SWS is conferred by the presence of a facial PWS involving the forehead that has a large, segmental distribution involving more than half of the hemiforehead or having a median pattern, as described by Dutkiewicz et al[11] and Zallman et al.[12] We further hypothesized that children without large segmental involvement of the forehead are at low risk of SWS and may warrant less aggressive SWS screening.

CAPSULE SUMMARY

- Children with forehead port-wine stains are at risk of Sturge-Weber syndrome, but most will not develop neurologic manifestations.
- Large segmental forehead involvement by a port-wine stain is more specific for Sturge-Weber syndrome than forehead involvement in general. Children without such involvement may require less aggressive evaluation for neurologic disease.

MATERIALS AND METHODS

Seattle Children's Hospital Institutional Review Board approval, including a waiver of consent, was obtained before all study activities. Patients were eligible for this study if they had a facial PWS and were cared for at our institution between January 1, 2009, and December 31, 2018. Because neurologic involvement in SWS usually occurs within the first year of life,[3,13] patients were required to have documented follow-up until at least age 1 year.

Owing to the variety of potential diagnostic descriptions and codes for facial PWS, a query of Seattle Children's Hospital electronic medical records included patients with a coded diagnosis of (1) hamartoses not elsewhere classified (International Classification of Diseases [ICD] Ninth Revision code 759.6), (2) congenital malformation of the peripheral vascular system, unspecified (ICD-10th Revision code Q27.9), (3) congenital non-neoplastic nevus (ICD-10th Revision code Q82.5, which includes nonspecific diagnoses including "birthmark"), or (4) other phakomatoses not elsewhere classified (ICD-10th Revision code Q85.8). This search identified 1104 patients whose medical records were subsequently reviewed by 1 of the authors (M.D.B., X.B., C.A.L.) to identify patients with a facial PWS.

Medical records, cutaneous photography, and neuroimaging of patients with a facial PWS were reviewed. Data collected included distribution of the facial PWS and method of PWS description (photographic and verbal or verbal only). Verbal description was considered sufficient for study inclusion if specific anatomic language was used to describe the distribution of the facial PWS (ie, "in the distribution of the ophthalmic nerve"); patients lacking such descriptions and clinical photography were excluded. Developmental status, onset of seizure activity, and diagnosis of epilepsy were recorded. Available magnetic resonance imaging (MRI) neuroimaging was reviewed by a pediatric neuroradiologist (F.P.) to confirm the presence of leptomeningeal angiomatosis. Clinical findings supportive of SWS were defined as focal onset epilepsy or hemiparesis in a child with a facial PWS.

Facial PWSs were initially classified based on involvement of the forehead, defined by Waelchli et al[6] as any involvement of the face (excluding the scalp) superior to a line connecting the outer canthus of the eye and the top of the ear, including the upper eyelid (Fig 2). Facial PWSs with forehead involvement were further divided into 2 categories:

Abbreviations used:

ICD:	International Classification of Diseases
MRI:	magnetic resonance imaging
PHACE:	posterior fossa malformation, hemangioma, arterial anomalies, cardiac defect, eye abnormalities
PWS:	port-wine stain
SWS:	Sturge-Weber syndrome

1. Half or more of a contiguous area of the hemiforehead or a median pattern, as previously described,[11,12] consistent with a "large segmental" distribution (Fig 2), or
2. Less than half of the hemifacial forehead and not a median pattern, consistent with "trace" (ie, nonsegmental) or "small segmental" distribution, defined as patterns that appear geographic or as specific anatomic segments but do not involve sufficient surface area to be termed large segmental.

The median pattern PWS was included in the first category due to its classification as high risk in prior studies[11,12] and its geographic similarity to frontonasal segmental (S4) hemangiomas of PHACE (posterior fossa malformation, hemangioma, arterial anomalies, cardiac defect, eye abnormalities) syndrome, another neurocutaneous syndrome associated with vascular anomalies.[14]

Facial PWSs were classified by a pediatric dermatologist and a pediatric neurologist (M.D.B., C.A.L.). A senior dermatologist (R.S.) not involved in the initial record review then independently classified each PWS. The sensitivity and specificity of forehead involvement in general and of trace or small

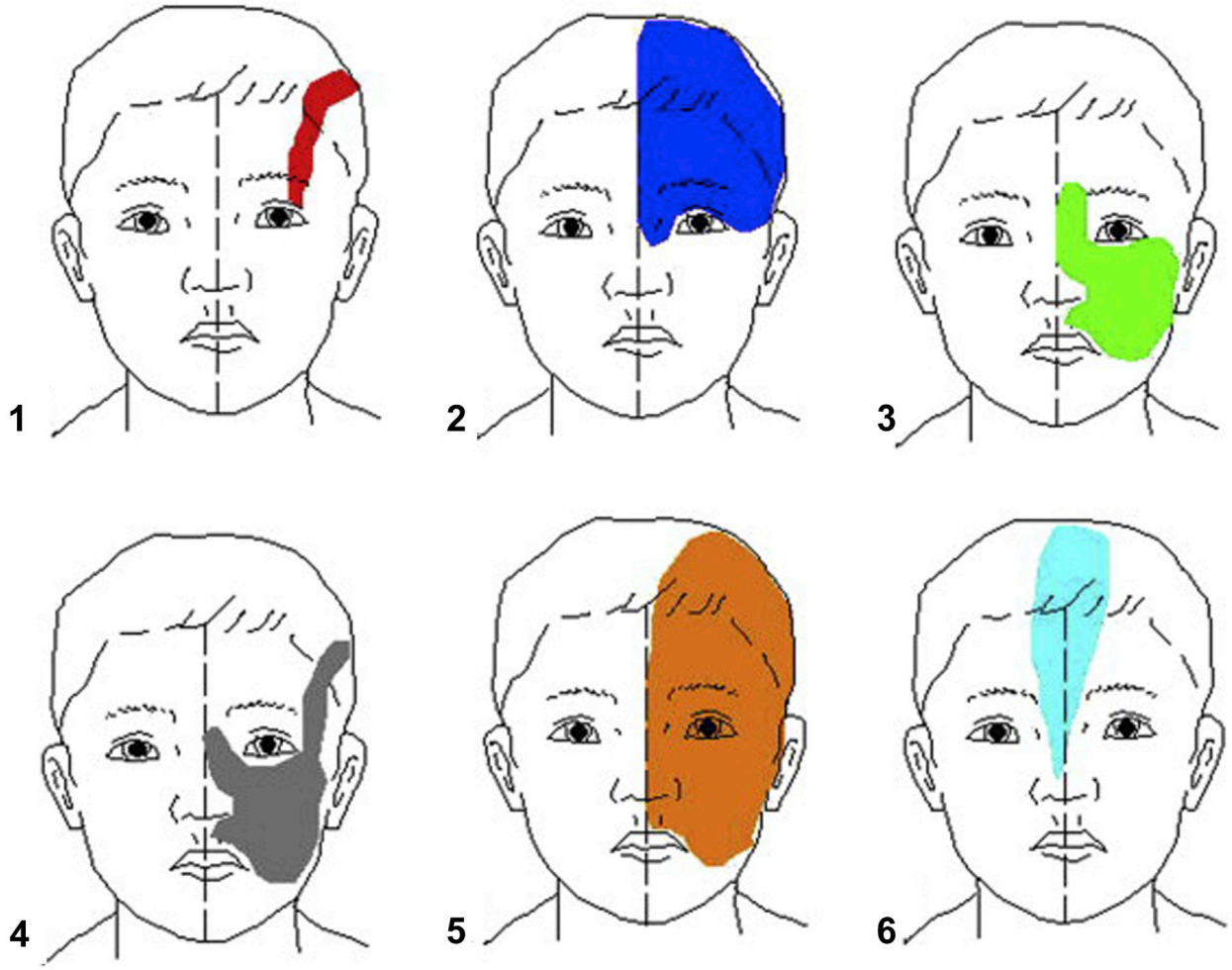

Fig 1. Patterns of facial port-wine stains as described by Dutkiewicz et al[11]: (**1**) linear, (**2**) frontotemporal, (**3**) isolated cheek and canthus, (**4**) combined linear and cheek, (**5**) hemifacial, and (**6**) median. Reprinted from the *Journal of the American Academy of Dermatology*, 72(3), Dutkiewicz AS et al, "A prospective study of risk for Sturge-Weber syndrome in children with upper facial port-wine stain," Pages 473-480, 2015, with permission from Elsevier.

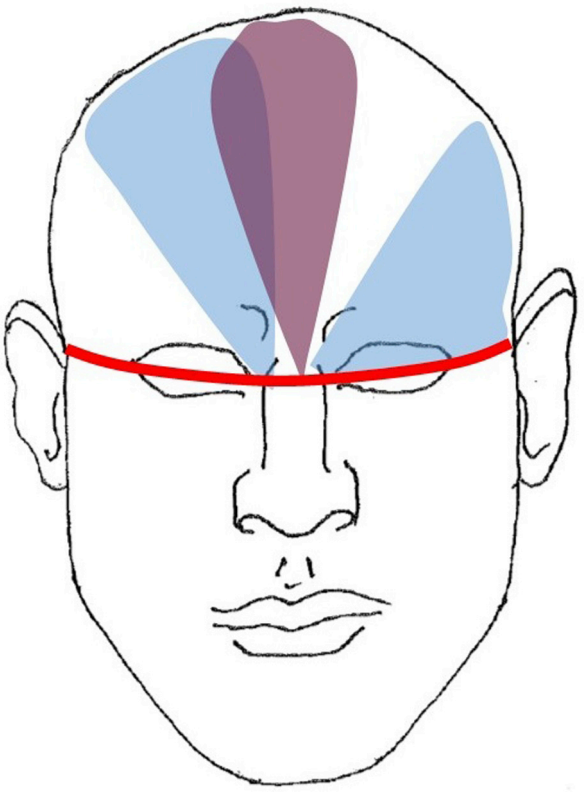

Fig 2. Forehead involvement by port-wine stains. This study defined forehead involvement as involvement by a port-wine stain of the face superior to a line connecting the outer canthus of the eye and the top of the ear, including the upper eyelid (*red line*), according to Waelchli et al.[6] Large segmental forehead involvement was defined as involvement of half or more of a contiguous area of the hemiforehead (*light blue*) or median (*purple*) patterns. Trace or small segmental forehead involvement was defined as involvement of less than half of the hemiforehead in the absence of median forehead patterning.

segmental vs large segmental forehead involvement for predicting neurologic involvement (seizures or leptomeningeal angiomatosis on head MRI) were then determined.

Data were analyzed using the epiR package[15] and DTComPair package[16] in R 3.5.0 statistical software (The R Foundation for Statistical Computing, Vienna Austria). Confidence intervals were calculated using methods in Collett.[17] Differences in sensitivity and specificity were analyzed using methods proposed by Moskowitz and Pepe.[18]

RESULTS

Study population

We identified 165 patients with a facial PWS; of these, 29 patients (18%) without PWS photography were excluded due to insufficient verbal description of the extent of the PWS. The PWS in the remaining 136 patients was documented by both clinical photography and verbal description in 124 patients or by verbal description alone describing the specific facial segments involved in 12. We excluded 12 patients (7%) due to insufficient follow-up (last follow-up at less than age 1 year); of these, 1 patient had large segmental forehead involvement, 8 had trace or small segmental forehead involvement, and 3 had no forehead involvement. Our final study cohort consisted of 124 children with a facial PWS. Of these, only 10 had not been evaluated in person by a pediatric dermatologist, and 3 of these had photographs available for review.

Classification of facial PWSs

The forehead was involved in 96 patients (51 males); of these, 51 had large segmental forehead involvement (8 bilateral, 1 with median pattern) and 45 had trace or small segmental forehead involvement. There was no forehead involvement in 28 patients (12 males).

SWS was confirmed in 21 children (7 males) by the presence of leptomeningeal angiomatosis on neuroimaging (19 with head MRI and 2 initially with head computed tomography but later confirmed on MRI) performed at a median of 4 months (range, 1 day-6 years) (Table I; Fig 3, *A*). All but 3 diagnostic neuroimaging studies were available for review by the study neuroradiologist, although these studies had been reviewed as part of clinical care. Two of the 3 patients whose initial imaging was not available had subsequent confirmatory neuroimaging available for review. Of the 21 patients with leptomeningeal angiomatosis on neuroimaging, 19 also had epilepsy. All of these children had large segmental involvement of the forehead, 5 with bilateral large segmental involvement.

Of the remaining 103 children without SWS, 30 (17 males) had large segmental involvement of the forehead (29 with >50% of a contiguous area of hemiforehead involved and 1 with a median pattern) but no neurologic symptoms of SWS (focal seizures, stroke-like episodes, hemiparesis) at a mean age of 5.3 years (median, 4.1 years; range 1.1-16.1 years) (Fig 3, *B*). MRI neuroimaging was performed in 14 at a median age of 6 months (range, 1 day-12 years). None showed leptomeningeal angiomatosis. Three of these children had bilateral hemiforehead involvement, although 2 of these 3 also had extensive involvement of the rest of their body by capillary malformations.

Among the 51 children with large segmental forehead involvement, SWS was present in 37% (16 of 43) of the children with unilateral involvement

Table I. Characteristics of patients with Sturge-Weber syndrome

Patient	Sex	Dutkiewicz pattern	Age at diagnostic head MRI	Age at epilepsy onset
1	M	2	4 mo* (repeat MRI diagnostic at 6 y)	4 mo
2	F	5	2 mo	6 mo
3	M	5	4 mo	4 mo
4	F	5	2.5 y* (CT diagnostic at 2 mo)	4 mo
5	F	Not classifiable	3 mo	2 mo
6	F	5	6 y	40 d
7	M	5	24 mo	21 mo
8	M	5	2 y	2 y
9	M	5	2 d	2 d
10	F	5	1 mo	1 mo
11	F	Not classifiable	5 y	5 y
12	M	5	4 mo*	4 mo
13	F	5	1 mo	1 mo
14	F	2	11 mo	11 mo
15	F	5	3 d	2 mo
16	F	5	1 d	<4 mo
17	M	Not classifiable	5 mo	5 mo
18	F	Not classifiable	10 mo	None at 25 mo
19	F	2	1 mo	None at 8.9 y
20	F	Not classifiable	11 mo (CT diagnostic at 7 mo)	1 y
21	F	Not classifiable	1 d	3 d

CT, Computed tomography; *F*, female; *M*, male; *MRI*, magnetic resonance imaging.
*By neuroimaging report only. These 3 imaging studies were not available for central review.

and in 63% (5 of 8) of the children with bilateral involvement.

Forty-five children (27 males) had trace or small segmental involvement of the forehead by a PWS (Fig 3, *C*). None had neurologic symptoms of SWS at a mean of 5.9 years (median, 4.1 years; range, 1.1-17.5 years). MRI neuroimaging was performed in 12 patients at a median of 3 years (range, 1 day-14 years), none of which showed leptomeningeal angiomatosis.

The remaining 28 children had a PWS that did not involve the forehead. None of these children have been diagnosed with SWS.

During review by the senior dermatologist (R.S.), there was initial disagreement regarding forehead involvement in 1 patient who had subtle staining of the lateral forehead; this patient was ultimately classified as having trace or small segmental forehead involvement. There was otherwise complete concordance among reviewers in the classification of forehead PWSs in the remaining 95 patients.

The use of distinct segmental patterns, as described by Dutkiewicz et al[11] to identify patients at greatest risk for SWS, was also explored (Fig 1). Of 21 patients with SWS, 15 had patterns that the Dutkiewicz classification proposes to impart an increased risk for SWS: 12 patients (57%) had pattern 5 (hemifacial involvement of forehead and maxilla), 3 (14%) had pattern 2 (frontotemporal involvement), and 6 (29%) could not be classified into one of the Dutkiewicz patterns. In contrast, among the 75 children with forehead involvement who did not have SWS, 28 were classified as having at-risk patterns, consisting of 7 with "combined linear and cheek" pattern, 15 with "hemifacial" pattern, 5 with "frontotemporal" pattern, 1 with "median" pattern, and 36 could not be classified.

The 21 patients who developed SWS were among the 51 patients who had a forehead PWS in a large segmental pattern according to our classification. Large segmental forehead involvement was more specific (0.71 vs 0.27, $P < .0001$), with a higher positive predictive value (0.41 vs 0.22, $P < .0001$) than forehead involvement in general, whereas both methods had a sensitivity of 1.0 in our cohort (Table II).

DISCUSSION

Our study confirms that forehead involvement by a PWS identifies all children at risk for SWS. However, we also found that children with SWS were more specifically identified by the presence of a forehead PWS in a large segmental pattern. Current guidelines for management of facial PWSs recommend that any child with forehead involvement be considered at risk for SWS.[19-21] Early diagnosis of

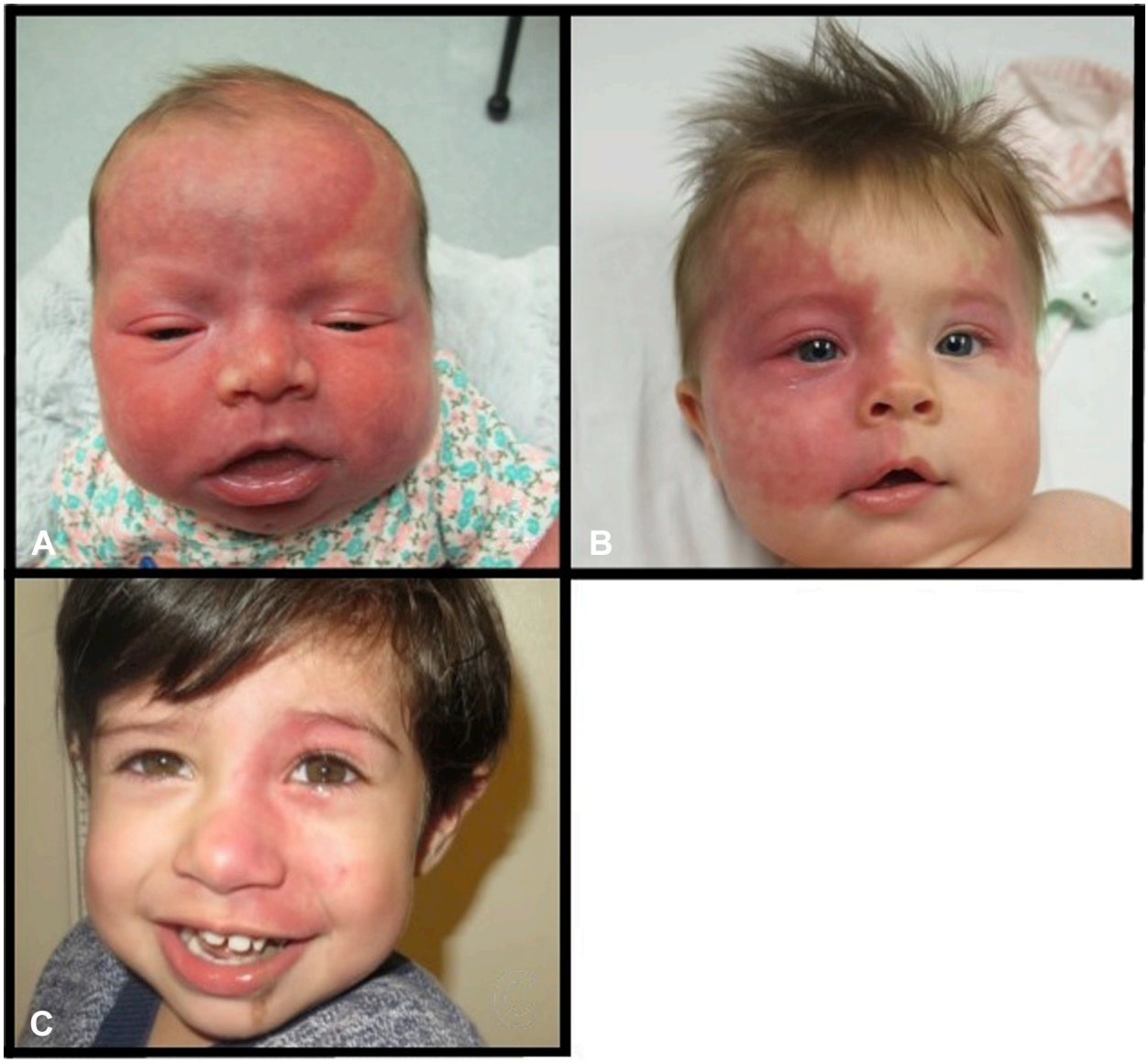

Fig 3. Classification of facial port-wine stains. **A**, A patient with large segmental forehead involvement and Sturge-Weber syndrome. **B**, A patient with large segmental forehead involvement but without Sturge-Weber syndrome. **C**, A patient with small segmental forehead involvement of the left medial canthus and upper eyelid.

Table II. Statistical comparison of Waelchli and current methodology for evaluating risk of Sturge-Weber syndrome based on facial port-wine stain

Method	Patients (n/N)	Sensitivity (95% CI)	Patients (n/N)	Specificity (95% CI)	Patients (n/N)	PPV (95% CI)	Patients (n/N)	NPV (95% CI)
Waelchli	21/21	1 (0.84-1.00)	28/103	0.27 (0.19-0.37)	21/96	0.22 (0.14-0.31)	28/28	1 (0.88-1.00)
Current methodology	21/21	1 (0.84-1.00)	73/103	0.71 (0.61-0.79)	21/51	0.41 (0.28-0.56)	73/73	1 (0.95-1.00)

CI, Confidence interval; *NPV*, negative predictive value; *PPV*, positive predictive value.

SWS, including MRI screening of asymptomatic patients with a high-risk facial PWS, has been recommended to potentially minimize neurologic morbidity and to assess whether interventions, including presymptomatic treatment, can modify the course of the disease.[6,11,13,19]

Because SWS will not develop in most children with a facial PWS, the ability to visually identify those children at greatest risk in an easily applied method may affect the nature or frequency of screening studies. Our method is a pragmatic, easily implemented screening tool that allows counseling and evaluation to focus on those children who may benefit from early diagnosis and intervention while limiting unnecessary testing. In our study, a large segmental pattern was defined as ≥50% of a contiguous area of hemiforehead or a median pattern. However, only 1 patient in our study had a PWS in a median pattern, and the patient did not have SWS. Our results are therefore not sufficiently powered to assess whether a PWS in a median pattern imparts an increased risk of SWS. Nevertheless, because the median pattern has been reported in association with SWS[11] and has phenotypic similarity to frontonasal segmental hemangiomas seen in PHACE syndrome, we recommend that patients with a median forehead PWS be considered at increased risk of SWS. Importantly, median PWSs must be carefully differentiated from nevus simplex involving the forehead and glabella. Nevi simplex are congenital capillary malformations that can be distinguished from PWS by their mostly blanchable nature, poorly demarcated borders, and their propensity to fade with time.[22]

The greater specificity of a larger PWS in a segmental distribution may reflect the development of the forehead, cerebral cortex, and eye from the embryologic forebrain. SWS may be a congenital vascular overgrowth syndrome akin to PHACE syndrome, which is hypothesized to be a congenital vasculopathy.[14,23] In PHACE syndrome, segmental infantile hemangiomas involving the frontotemporal (S1) and frontonasal (S4) segments, both of which include the forehead, are correlated with an increased risk of cerebrovascular, brain, and ocular anomalies.[14,24]

For diagnostic purposes, segmental hemangiomas that are consistent with a "definite" diagnosis of PHACE are defined as involving a discrete anatomic field of the head/neck/upper chest and measuring at least 5 cm in diameter.[25,26] Similarly, among children diagnosed with SWS, a larger facial PWS appears to correlate with more severe neurologic involvement.[9,27] Importantly, smaller hemangiomas with a segmental distribution have also been reported in PHACE syndrome, although we did not find an equivalent association between trace or small segmental PWS and SWS in our cohort. SWS and PHACE can both also occur in the absence of associated facial vascular anomalies.[28-31]

Our study has important limitations. Our population was composed of children referred to a tertiary academic medical center and may not be representative of all children with facial PWSs. Because this was a retrospective study, some children were excluded due to inadequate PWS description (18%) or inadequate follow-up to assess neurodevelopmental outcomes (7%). Some children may also have been missed if their PWS was inappropriately coded. The classification of PWS in 10% (12 of 124) of our patients was based on a verbal description without cutaneous photography, although only those patients for whom specific facial anatomic language was used to describe their PWS were included. It is also possible that patients without signs or symptoms of SWS could develop SWS later in life, including in adulthood.

CONCLUSION

The goal of this study was to combine location and patterning of facial PWS to create a more specific screening tool for patients with forehead PWSs at risk for SWS. In our cohort, large segmental forehead involvement identified all patients with SWS and did so with higher specificity than any forehead involvement. Moreover, SWS did not develop in any child with trace or small segmental involvement of the forehead (approximately half of the cohort with forehead PWS). This offers a pragmatic method to identify children who are at greatest risk for SWS and may benefit from early diagnosis and intervention. Future prospective studies with rigorous dermatologic description and standardized outcome data are needed to confirm the validity of our risk stratification system, including in a nonreferral population.

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REFERENCES

1. Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4,641 newborns. *Pediatr Dermatol*. 1983;1(1):58-68.
2. Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics*. 1976;58(2):218-222.
3. Sujansky E, Conradi S. Sturge-Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children. *J Child Neurol*. 1995;10(1):49-58.
4. Pascual-Castroviejo I, Pascual-Pascual SI, Velazquez-Fragua R, Viaño J. Sturge-Weber syndrome: study of 55 patients. *Can J Neurol Sci*. 2008;35(3):301-307.
5. Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ*. *N Engl J Med*. 2013;368(21):1971-1979.
6. Waelchli R, Aylett SE, Robinson K, Chong WK, Martinez AE, Kinsler VA. New vascular classification of port-wine stains: improving prediction of Sturge-Weber risk. *Br J Dermatol*. 2014;171(4):861-867.

7. Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes, and their relationship to race, ethnicity, and sex. *Arch Dermatol*. 2002; 138(12):1567-1576.
8. Tallman B, Tan OT, Morelli JG, et al. Location of port-wine stains and the likelihood of ophthalmic and/or central nervous system complications. *Pediatrics*. 1991;87(3):323-327.
9. Dymerska M, Kirkorian AY, Offermann EA, Lin DD, Comi AM, Cohen BA. Size of facial port-wine birthmark may predict neurologic outcome in Sturge-Weber syndrome. *J Pediatr*. 2017;188:205-209.e1.
10. Day AM, McCulloch CE, Hammill AM, et al. Physical and family history variables associated with neurological and cognitive development in Sturge-Weber syndrome. *Pediatr Neurol*. 2019; 96:30-36.
11. Dutkiewicz AS, Ezzedine K, Mazereeuw-Hautier J, et al. A prospective study of risk for Sturge-Weber syndrome in children with upper facial port-wine stain. *J Am Acad Dermatol*. 2015;72(3):473-480.
12. Zallmann M, Mackay MT, Leventer RJ, Ditchfield M, Bekhor PS, Su JC. Retrospective review of screening for Sturge-Weber syndrome with brain magnetic resonance imaging and electroencephalography in infants with high-risk port-wine stains. *Pediatr Dermatol*. 2018;35(5):575-581.
13. Comi AM. Sturge-Weber syndrome. *Handb Clin Neurol*. 2015; 132:157-168.
14. Puttgen KB, Lin DD. Neurocutaneous vascular syndromes. *Childs Nerv Syst*. 2010;26(10):1407-1415.
15. Stevenson M, Nunes T, Marshall CHJ, et al. epiR: Tools for the Analysis of Epidemiological Data. R version 1.0-14. 2019. Available at: https://CRAN.R-project.org/package=epiR. Accessed January 6, 2020.
16. Stock C, Hielsche T. DTComPair: Comparison of Binary Diagnostic Tests in a Paired Study Design. R version 1.0.3. 2015. Available at: http://CRAN.R-project.org/package=DTComPair. Accessed January 6, 2020.
17. Collett D. Modelling Binary Data (Chapman & Hall/CRC Texts in Statistical Science). Boca Raton, FL: Chapman & Hall/CRC; 1999.
18. Moskowitz CS, Pepe MS. Comparing the predictive values of diagnostic tests: sample size and analysis for paired study designs. *Clin Trials*. 2006;3(3):272-279.
19. De la Torre AJ, Luat AF, Juhász C, et al. A multidisciplinary consensus for clinical care and research needs for Sturge-Weber syndrome. *Pediatr Neurol*. 2018;84:11-20.
20. Zallmann M, Leventer RJ, Mackay MT, Ditchfield M, Bekhor PS, Su JC. Screening for Sturge-Weber syndrome: a state-of-the-art review. *Pediatr Dermatol*. 2018;35(1):30-42.
21. Comi A. Current therapeutic options in Sturge-Weber Syndrome. *Semin Pediatr Neurol*. 2015;22(4):295-301.
22. Juern AM, Glick ZR, Drolet BA, Frieden IJ. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. *J Am Acad Dermatol*. 2010;63(5):805-814.
23. Darrow DH, Greene AK, Mancini AJ, Nopper AJ, Section On Dermatology, Section On Otolaryngology-Head & Neck Surgery, and Section On Plastic Surgery. Diagnosis and management of infantile hemangioma. *Pediatrics*. 2015;136(4):e1060-e1104.
24. Metry DW, Haggstrom AN, Drolet BA, et al. A prospective study of PHACE syndrome in infantile hemangiomas: demographic features, clinical findings, and complications. *Am J Med Genet A*. 2006;140(9):975-986.
25. Darrow DH, Greene AK, Mancini AJ, Nopper AJ, Section On Dermatology, Section On Otolaryngology-Head & Neck Surgery, and Section On Plastic Surgery. Diagnosis and management of infantile hemangioma: executive summary. *Pediatrics*. 2015;136(4):786-791.
26. Garzon MC, Epstein LG, Heyer GL, et al. PHACE syndrome: consensus-derived diagnosis and care recommendations. *J Pediatr*. 2016;178:24-33.e2.
27. Haggstrom AN, Garzon MC, Baselga E, et al. Risk for PHACE syndrome in infants with large facial hemangiomas. *Pediatrics*. 2010;126(2):e418-e426.
28. Roach ES. Neurocutaneous syndromes. *Pediatr Clin North Am*. 1992;39(4):591-620.
29. Sekioka A, Fukumoto K, Horikoshi Y, Nii M, Urushihara N. PHACE syndrome with unnoticeable skin lesion and rare anomaly of coronary artery. *Pediatr Int*. 2019;61(5):524-526.
30. Chan YC, Eichenfield LF, Malchiodi J, Friedlander SF. Small facial haemangioma and supraumbilical raphe—a forme fruste of PHACES syndrome? *Br J Dermatol*. 2005;153(5):1053-1057.
31. Torer B, Gulcan H, Kilicdag H, Derbent M. PHACES syndrome with small, late-onset hemangiomas. *Eur J Pediatr*. 2007; 166(12):1293-1295.