Size of Facial Port-Wine Birthmark May Predict Neurologic Outcome in Sturge-Weber Syndrome

Malgorzata Dymerska, BA[1], Anna Y. Kirkorian, MD[2,3], Elizabeth A. Offermann, BA[4], Doris D. Lin, MD, PhD[5], Anne M. Comi, MD[4,6,7,*], and Bernard A. Cohen, MD[2,*]

Objective To determine whether the size of the birthmark in patients with Sturge-Weber syndrome (SWS) who have brain involvement can help predict neurologic disability.

Study design Fifty-one patients with SWS with facial birthmarks and brain involvement documented on magnetic resonance imaging were included in this retrospective chart review. A neuroradiologist, blinded to all clinical information, assigned a previously validated SWS neuroimaging score. A pediatric neurologist prospectively assigned previously validated neurologic severity scores, based on seizures, hemiparesis, visual field cut, and cognitive impairments. Three raters, blinded to clinical scores, independently graded the size of facial birthmark in each patient based on photographs. Their scores were averaged. Birthmark scores were compared with the imaging and neurologic severity results using nonparametric correlation analysis.

Results Size of facial port-wine birthmark correlates with magnetic resonance imaging scores on the left and right sides (ρ = 0.57 and 0.66 [$P < .001$], respectively). Size is also positively associated with the neurologic severity rating for patients age 6 years and above (1-sided Fisher exact, $P = .032$).

Conclusions The size of facial port-wine birthmark in SWS brain involvement can be developed as a tool to predict neurologic severity of the disease. *(J Pediatr 2017;188:205-9).*

Sturge-Weber syndrome (SWS) is generally defined by the constellation of a facial capillary malformation referred to as a port-wine birthmark (PWB), malformation of the vasculature of the eye, and/or vascular malformation in the brain (leptomeningeal angioma). The incidence of SWS is estimated at 1 in 20 000 to 50 000 live births, affecting male and female infants equally.[1] Individuals with SWS may have impairment of neurologic function including seizures or stroke-like episodes, cognitive impairment, visual field defects, and hemiparesis, all with a variable degree of severity. One challenge to developing optimal treatment strategies and providing prognoses to families of infants with SWS is the tremendous variability in neurologic outcomes from individuals with normal intelligence to those with severe epilepsy, neurologic deficits, and severe intellectual disability.

Not all facial PWB are associated with SWS. Traditionally, PWB occurring in the ophthalmic, or V1, division of the trigeminal nerve, especially with upper eyelid involvement, carried the highest risk of association with SWS. A more recent study has noted that the risk for SWS appears not to be determined by the dermatome but rather by embryonic vascular placodes, specifically one delineated by a line from the lateral canthus drawn to the top of the helix.[2] This territory reflects the etiology of SWS, which is caused by an activating somatic mutation in GNAQ affecting the pluripotent progenitor cells that give rise to the brain, eye, and skin in this location.[3] Various studies suggest that individuals born with a facial PWB on the forehead or upper eyelids have a 20%-50% chance of SWS brain involvement depending on the extent of PWB.[4-6] However, current knowledge of the relationship between the size of PWB and the severity of neurologic dysfunction in those with SWS brain involvement is limited. We hypothesized that larger PWB would be associated with worse neurologic outcome. Our study aims to characterize that relationship to provide insight into future neurologic outcomes at the time of diagnosis with SWS brain involvement early in life.

Methods

Subjects for this study are patients from the Hunter Nelson Sturge-Weber Center at Kennedy Krieger Institute participating in a multidisciplinary study protocol

MRI	Magnetic resonance imaging
PWB	Port-wine birthmark
SWS	Sturge-Weber syndrome

From the [1]Johns Hopkins University School of Medicine; [2]Division of Pediatric Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD; [3]Division of Dermatology, Children's National Health System, Washington, DC; [4]Division of Neurology, Kennedy Krieger Institute; [5]Department of Radiology; [6]Department of Neurology; and [7]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD

*Contributed equally.

Supported by the National Institute of Neurological Disorders and Stroke (NINDS) (National Institutes of Health [NIH] U54NS065705) (PI: Lawton; Sturge-Weber syndrome project to A.C.) and from Celebrate Cure Foundation (to A.C.). The Brain Vascular Malformation Consortium (U54NS065705) is a part of the NIH Rare Disease Clinical Research Network, supported through the collaboration between the NIH Office of Rare Diseases Research at the National Center for Advancing Translational Science and the NINDS. The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.05.053

approved by the institutional review board. The inclusion criteria were diagnosis of SWS, with presence of a facial PWB, and SWS brain involvement on brain magnetic resonance imaging (MRI). For this retrospective study, neurologic scores were assigned prospectively at the time of each subject's visit. However, the skin scores and MRI scores were assigned retrospectively to images previously obtained.

Conventional magnetic resonance sequences including T1, T2, fluid-attenuated inversion recovery, and postgadolinium contrast T1 and fluid-attenuated inversion recovery images were evaluated. The MRI of each patient was rated by a single rater, a neuroradiologist blinded to the size of PWB and the degree of clinical severity of each patient. In the case of patients who had multiple MRI images available, the MRI rated was the one obtained at the time closest to the time the neurologic score was obtained. The scoring system was modified from a previously published system.[7] Scores from 1 to 4 were assigned to each of the 4 brain regions (frontal, temporal, parietal, and occipital) for each hemisphere individually, where 1 signified no asymmetry, 2 mild asymmetry (angiomatosis only), 3 moderate asymmetry (angiomatosis and mild atrophy), and 4 severe asymmetry (angiomatosis and severe atrophy). The total score was then determined for each hemisphere, ranging from 4 to 16.

The neurologic severity of the syndrome in each patient was evaluated by a single rater, a pediatric neurologist, who assigned ratings prospectively after carefully evaluating neurologic function of the patients during their regular care or study visits utilizing a previously published system.[8] The degree of visual field cut, hemiparesis, seizure frequency, and cognitive function (differently for each age group: infant/preschooler, child, and adult) was rated as shown in the **Table** (available at www.jpeds.com). The individual scores were then summed, with the total score ranging from 0 to 15. In the case of patients for whom multiple scores were available from neurology visits at different time points, the score from the visit closest to the time of the MRI was used.

Photographs showing patients' faces were obtained from their families. We asked families to provide photographs showing both sides of the face, as well as a full-frontal photograph. For the majority of our subjects, we were able to obtain all of these; however, we were able to obtain only full frontal photographs for some of the patients (n = 10). The photographs reflected the original size of their facial PWB in the case of patients who underwent laser treatments, with the majority of patients' photographs dating from infancy. Three independent raters scored each patient's photo using both the traditional facial PWB classification system using the trigeminal nerve distribution (3 raters), shown in **Figure 1**, A, as well as the recently published embryonic facial vasculature distribution (3 raters),[2] shown in **Figure 1**, B. The photographs were scored using the 2 different systems on 2 separate occasions, with the raters blinded to the other scores, and to the results of the MRI and neurologic scores. For each territory (trigeminal dermatome or embryonic placode), the fraction of the area involving the PWB was visually approximated and scored from 0 to 4, assigning 0 to areas with no involvement, 1 to 1%-25% of a particular surface area involved, 2 to 26%-50% involvement, 3 to 51%-75% involvement, and 4 to 76%-100% involvement. The individual areas' scores were either considered individually (V1 and placode 1) or summed to yield total facial (ranging from 0 to 24) and hemifacial (ranging from 0 to 12) scores. Scalp involvement was not evaluated, as the majority of photographs did not provide the opportunity to do so.

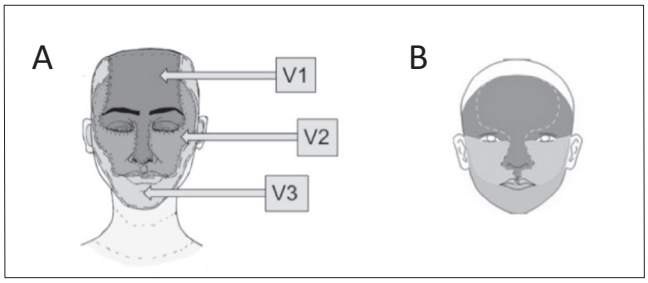

Figure 1. Port-wine birthmark distribution: **A,** utilizing trigeminal nerve distribution; and **B,** utilizing the embryonic facial vasculature distribution; top to bottom: placode 1, placode 2, and placode 3.[2]

Statistical Analyses

Stata/IC 14.0 (STATA College Station, Texas) and IBM SPSS Statistics 23.0 (SPSS, Armonk, New York) were used for statistical analysis. The skin scores from the 3 raters were averaged, and inter-rater reliability was evaluated using Cohen kappa. The correlation between MRI scores and skin scores was calculated via Spearman correlation. Linear regression was applied to determine the correlation between skin scores (independent variable) and neurologic scores. The association between better or worse neurologic scores and skin scores was tested using Fisher exact test; because neurologic status tends to stabilize after 4-5 years of age, only patients age 6 years and older at the time of their neurologic evaluation were included in that analysis (n = 21). Skin scores were classified into 2 categories: (1) <12 and (2) ≥12. Clinical severity scores were classified into (1) <4 and (2) ≥4, a cut-score previously shown to discriminate impaired and unimpaired individuals with regard to both intellectual and adaptive functioning.[9]

We used hierarchical multiple regression to determine the effect of using size of PWB as a predictor of neurologic outcome in addition to the degree of brain involvement obtained from evaluation of the MRI. The first model used MRI score as the independent variable and neurologic severity score as the dependent variable. The second model used both MRI score and total skin score as independent variables and neurologic severity score as the dependent variable. These were computed only for patients whose neurologic function was evaluated at age 6 years and beyond. The difference in the R-squared value in the 2 models was then calculated.

Results

Photographs of patients were collected in July 2014, at which time the Center's research database of study patients in-