Facial Port-Wine Stain Phenotypes Associated with Glaucoma Risk in Neonates

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• PURPOSE: To determine if the size and location of facial port-wine stains (PWS) can predict glaucoma risk in neonates.
• DESIGN: Retrospective cohort study.
• METHODS: Children with facial PWS who had undergone ophthalmologic examination within 4 weeks of their birth were included. Clinical information, including facial photographs, intraocular pressure, corneal diameter, optic disc cup-to-disc ratio, and Sturge-Weber syndrome (SWS) diagnoses were collected. Based on facial photographs, PWS distribution, eyelid involvement, and PWS scores according to degree of involvement in each embryonic facial vasculature distribution (segment [S]1, S2 and S3) were evaluated.
• RESULTS: Among the 34 patients, 7 (21%) had bilateral PWS lesions. Eighteen (53%) had diagnoses of glaucoma. The proportion of eyes showing PWS involving both S1 and S2 was the highest (n = 15, 37%), and the frequency of glaucoma diagnosis (n = 9, 60%) was also the greatest. In eyelid involvement analysis, among the 7 eyes with only lower-eyelid lesions, 5 (83%) had glaucoma. Among the 11 eyes with only upper-eyelid lesions, however, 2 (18%) had diagnoses of glaucoma. A logistic regression model showed that the significant factors associated with glaucoma risk were greater PWS scores in S2 (odds ratio [OR]: 3.604; 95% confidence interval: 1.078-12.050; $P = .037$) or lower-eyelid involvement (OR: 12.816; 95% CI: 1.698-96.744; $P = .013$).
• CONCLUSIONS: Among the newborns with facial PWS, 1) a greater extent of birthmarks involving the S2 area, and 2) lesions including the lower eyelid were associated with higher risk of glaucoma development within the neonatal period. (Am J Ophthalmol 2020;220: 183–190. © 2020 Elsevier Inc. All rights reserved.)

FACIAL PORT-WINE STAIN (PWS), ALSO KNOWN AS "nevus flammeus," is a congenital vascular birthmark present at birth and persisting into adulthood. It occurs in 3 per 1,000 live births, and affects males and females as well as all racial groups equally.[1,2] Facial PWS usually is an isolated finding; when associated with cerebral and ocular abnormalities, however, it forms part of the classical Sturge-Weber syndrome (SWS) triad.[3]

The most critical and frequent vision-threating ocular comorbidity associated with SWS is glaucoma.[4] The rate of glaucoma prevalence in patients with SWS is reported to be between 30% and 70%.[4,5] Although glaucoma can develop later, during adolescence or adulthood, early onset (infantile) glaucoma affects up to 60% of SWS-associated glaucoma patients.[6] Glaucoma in SWS patients is especially challenging to manage due to its early onset and the severe optic nerve damage frequently associated with it at the time of diagnosis.[7–9] Thus, in order to preserve visual function in children who have SWS-associated glaucoma, the earliest possible diagnosis and prompt intraocular pressure (IOP) management are vital.

In this context, a significant number of ophthalmologists recommend screening infants with PWS for glaucoma risk; still, several questions about which PWS phenotypes to screen for and when to screen for them remain unanswered. Previous studies attempting to determine the best predictors of glaucoma in patients with PWS have included a wide range of ages (from infancy to adulthood) in their patient cohorts and have shown inconsistent results.[10–13] Thus, the aims of the present study were 1) to examine a neonate to map facial PWS distribution (ie, its location and extent); and 2) to correlate the particular PWS phenotype with glaucoma risk within the neonatal period.

METHODS

THIS STUDY RETRIEVED DATA FOR ELIGIBLE PATIENTS (compiled between January 2004 and December 2019) from the clinical data warehouse of Seoul National

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University Hospital Patients Research Environment. Data included electronic medical records for neonatal patients (1-4 weeks old) who had visited the Childhood Glaucoma Clinic of Seoul National University Children's Hospital, which were retrospectively reviewed. The study was approved by the Institutional Review Board of Seoul National University Hospital and fully adhered to the Declaration of Helsinki tenets. Informed consent was waived due to the study's retrospective nature.

• **STUDY SUBJECTS:** Specific inclusion criteria for pediatric patients were as follows: 1) facial PWS; 2) initial ophthalmic examinations performed before 1 month of age; and 3) no additional congenital ocular anomalies (eg, aniridia, cataract, or vitreoretinal abnormalities).

The clinical data collected included age, sex, IOP, corneal diameter, presence of corneal abnormalities as evaluated by portable slit-lamp, and cup-to-disc ratio as assessed by dilated fundus examination with color fundus photographs. In cases of corneal opacity, the retinal examination was performed by ultrasonography. Additionally, neurological examinations, including brain magnetic resonance imaging (MRI), were performed for diagnosis of SWS within 6 months of birth; the final diagnosis was determined by a pediatric neurologist.

• **PLANIMETRIC ANALYSIS OF FACIAL PWS:** Facial photographs were taken of all of the subjects at the initial ophthalmic examination. Two independent ophthalmologists (A.H., J.K.), masked to the other clinical features, evaluated each photo according to the facial PWS classification system that uses the embryonic facial vasculature distribution,[12] as shown in Figure 1, and determined whether the distribution was unilateral or bilateral.

Subsequently, the photographic representations were scored based on the extent of PWS involvement by 2 raters (A.H., J.K.) independently. In each patient's photo, the distribution of each vasculature outer boundary was delineated using a commercial image processing tool (Photoshop CS3 version 10.0.1; Adobe, San Jose, California) by a single ophthalmologist (Y.K.K.). For each area, the fraction involving the PWS was calculated and scored from 0 to 4, where 0 = no involvement; 1 = 1%-25% involved; 2 = 26%-50% involvement; 3 = 51%-75% involvement; and 4 = 76%-100% involvement. The individual areas' scores were considered individually (segment [S]1 or S2 or S3) or, alternatively, were summed to yield total hemifacial scores (range: 0-12). For the final analysis, the 2 raters (A.H. and J.K.) average score was applied. Scalp involvement was not classified, simply because it was not shown adequately in most of the photographs.

• **IOP MEASUREMENTS AND DIAGNOSIS OF GLAUCOMA:** IOP was measured using a hand-held, anesthetic-free rebound tonometer (iCare PRO; Tiolat, Helsinki, Finland) using a new, disposable probe for each subject under conscious sedation (using chloral hydrate). Each IOP reading was obtained by touching the probe tip to the central cornea, with minimal manipulation of the eyelid. Each value was measured in the series mode: that is, 6 automatic measurements were taken for calculation of final IOP; the highest and the lowest readings were discarded, and the 4 remaining readings were averaged.[14]

During the neonatal period, the glaucoma diagnosis had been made based on the following criteria: 1) IOP >18 mm Hg[15]; 2) presence of glaucomatous optic disc change (eg, cup-to-disc ratio ≥0.4, asymmetric cup-to-disc ratio ≥0.2; 3) corneal diameter >10.5 mm; and 4) other corneal abnormalities (eg, Haab striae or corneal edema). Subjects meeting 2 or more of the above-noted criteria were diagnosed with glaucoma.

• **STATISTICAL ANALYSES:** The PWS score's interobserver reproducibility was evaluated by calculating the intraclass correlation coefficients with their confidence intervals (CIs). Logistic regression was used to investigate how the glaucoma risk diagnosis had been influenced by the facial PWS distribution and other factors (age, sex, or MRI abnormality). The logistic regression algorithm used the Firth penalized likelihood ratio method to calculate robust odds ratios (ORs) and 95% CIs, dealing with potential issues of small or imbalanced datasets.[16] The statistical analysis was performed with the R software version 3.6.0 (R Foundation, Vienna, Austria,). A 2-sided *P* value <.05 was considered to represent statistical significance.

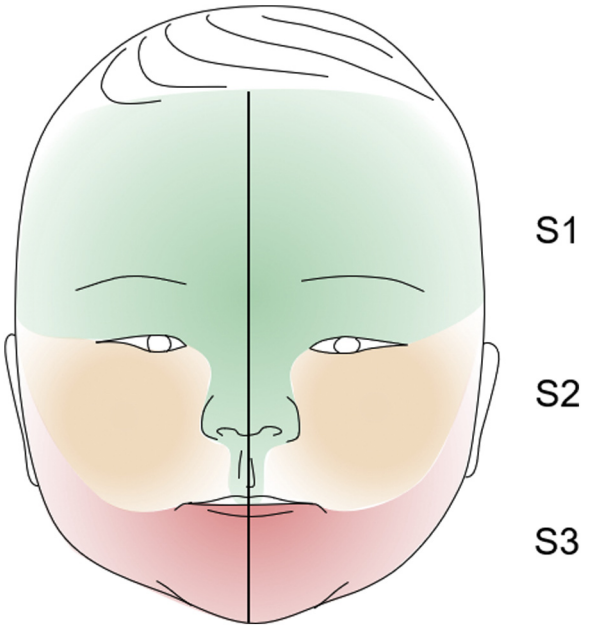

FIGURE 1. Facial port-wine stain distribution based on embryonic facial vasculature configuration. Note that the S1 area includes the upper eyelid, whereas the lower eyelid is included in the S2 area.

TABLE 1. Demographics and Clinical Characteristics of Study Patients at Neonatal Period (N = 34)

Characteristics	Values
Age at first visit (days)	16.0 ± 6.21 (4-28)
Males/females	15/19
Bilaterality of PWS	7 (21%)
Glaucoma	18 (53%)
Eyes with PWS involvement	18 (53%)
Eyes without PWS involvement	0 (0%)
IOP, mm Hg	
Eyes with PWS involvement	21.1 ± 10.7 (8.2-42.0)
Eyes without PWS involvement	10.4 ± 2.0 (8.0-17.2)
Corneal diameter, mm	
Eyes with PWS involvement	10.0 ± 0.6 (9.0-11.5)
Eyes without PWS involvement	9.5 ± 0.2 (9.2-10.3)
Cup-to-disc ratio[a]	
Eyes with PWS involvement	0.3 ± 0.1 (0.2-0.6)
Eyes without PWS involvement	0.2 ± 0.1 (0.2-0.4)
MRI abnormalities[b]	11 (32%)
Sturge-Weber syndrome	19 (56%)

IOP = intraocular pressure; MRI= magnetic resonance imaging; PWS = port-wine stains.

Values are mean ± standard deviation (range).

[a]15 eyes were unassessable due to corneal edema.

[b]Brain MRI was done within 6 months of birth.

RESULTS

A TOTAL OF 258 CHILDREN WITH FACIAL PWS (INCLUDING both new and follow-up patients) visited the authors' clinic between January 2004 and December 2019. Among the 258 patients, 41 fit the inclusion criteria of the study. Seven with missing data were excluded from the final analysis. Finally, 34 children (68 eyes) with facial PWS were included in the analysis.

• **DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF NEONATES WITH FACIAL PWS:** The demographics and clinical characteristics of the study population are provided in Table 1. The mean age at first visit was 16.0 ± 6.21 days (4-28 days). A total of 15 children (44%) were male and 19 (56%) were female. MRI indicated brain involvement in 11 patients (32%), and glaucoma was diagnosed in 18 (53%). In 10 patients, abnormality in MRI scan and glaucoma both were found. Therefore, the number of children diagnosed with SWS was 19 (56%), according to the definition of any facial PWS with either MRI abnormalities or glaucoma.

• **DISTRIBUTION OF FACIAL PWS AND INTRAOCULAR PRESSURE:** Among the 34 study subjects, 27 (80%) had unilateral PWS lesion, and 7 (20%) had bilateral lesions. The interobserver intraclass correlation coefficients for the PWS scores were 0.991 (95% CI: 0.988-0.993; $P < .001$), which indicated excellent interobserver reproducibility.[17] Table 2 shows the distributions of facial PWS and PWS score along with the number of eyes with glaucoma diagnosis and the IOP. In the present cohort, the proportion of eyes with facial PWS distribution in both S1 and S2 was the highest (n = 15; 37%), followed by PWS involving all 3 areas (n = 14; 34%). No subjects showed facial PWS involving only S2 or S3 or both S1 and S3 without S2.

In the S1+S2 group, the IOP (24.4 ± 11.4 mm Hg; range: 10.1-42.0 mm Hg) and frequency of glaucoma diagnosis (n = 9; 60%) were the highest. The S1+S2+S3 group showed the second highest mean IOP (21.6 ± 10.2 mm Hg; range: 8.0-39.8 mm Hg) and glaucoma diagnosis frequency (n = 7; 50%). Interestingly, none of the 4 eyes with the S1-only PWS distribution was diagnosed with glaucoma.

• **FACIAL PWS EYELID INVOLVEMENT AND INTRAOCULAR PRESSURE:** On closer examination of the data, it was found that none of the 9 eyes lacking PWS eyelid involvement were diagnosed with glaucoma. Thus, the facial PWS distribution was re-evaluated according to eyelid involvement. Among the 41 facial PWS lesions, 32 subjects (78%) had eyelid involvement. A total of 15 eyes had PWS that involved both the upper eyelid (UL) and lower eyelid (LL). Their mean IOP was 27.4 ± 9.6 mm Hg (range: 11.5-42.0 mm Hg), and 11 of them (73%) had diagnoses of glaucoma. Among the 11 eyes with only UL lesions, 2 (18%) were diagnosed as glaucoma with a mean IOP of 17.8 ± 9.0 mm Hg (range: 10.2-39.6 mm Hg). Among the 6 eyes with only LL lesions, 5 (83%) had glaucoma, and their mean IOP was 27.0 ± 9.7 mm Hg (range: 12.0-38.4 mm Hg). The associations among PWS eyelids and number of eyes with glaucoma diagnoses and IOP are presented in Table 3.

• **DETERMINATION OF FACTORS ASSOCIATED WITH GLAUCOMA:** Based on a univariate logistic regression model, the following factors were associated with glaucoma diagnosis: PWS score in the S2 area; total PWS score; UL involvement; LL involvement; and both UL and LL involvement. Among those 5 correlated factors, PWS score in the S2 area, UL involvement, and LL involvement were included in the multivariate model to deal with the problem of multicollinearity. The multivariate model showed that a PWS score in the S2 area (OR: 3.604; 95% CI: 1.078-12.050; $P = .037$) and LL involvement (OR: 12.816; 95% CI: 1.698-96.744; $P = .013$) were significant factors associated with risk of glaucoma. The detailed statistical results, including ORs and 95% CIs, are provided in Table 4.

• **REPRESENTATIVE CASES:** Figure 2 shows representative cases of neonates with facial PWS together with their ophthalmologic examination results (ie, facial photographs, anterior segment photographs, and colored fundus

TABLE 2. Distribution of Facial Port-Wine Stains and IOP in Study Eyes (n = 41)

PWS Distribution	n (%)	PWS Score	Glaucoma (n)	Frequency of Glaucoma (%)	IOP (mm Hg)
S1 only	4 (10)	3.0 ± 1.4 (1.0-4.0)	0	0	12.0 ± 4.3 (8.2-18.4)
S1, S2	15 (37)	5.5 ± 1.7 (3.5-8.0)	9	60	24.4 ± 11.4 (10.1-42.0)
S2, S3	8 (20)	4.0 ± 1.5 (2.0-7.5)	3	38	18.5 ± 10.3 (9.6-38.2)
S1, S2, S3	14 (34)	6.9 ± 2.9 (3.0-11.0)	7	50	21.6 ± 10.2 (8.0-39.8)

PWS = port-wine stains; IOP = intraocular pressure; n = number of eyes; S = segment.
Values are mean ± standard deviation (range).
PWS score was calculated and scored from 0 to 4, where 0 = no involvement; 1 = 1%-25% involved; 2 = 26%-50% involvement; 3 = 51%-75% involvement; and 4 = 76%-100% involvement in each segment. Then, the individual areas' scores were considered individually or were summed to yield total hemifacial scores (range: 0-12).

TABLE 3. Port-Wine Stain Eyelid Involvement and IOP in Study Eyes (n = 41)

PWS Distribution	n	PWS score	Glaucoma (n)	Frequency of Glaucoma (%)	IOP (mm Hg)
UL and LL	15	7.5 ± 2.3 (4.0-11.0)	11	73	27.4 ± 9.6 (11.5-42.0)
UL only	11	4.7 ± 1.8 (3.5-8.0)	2	18	17.8 ± 9.0 (10.2-39.6)
LL only	6	5.0 ± 1.4 (3.0-7.0)	5	83	27.0 ± 9.7 (12.0-38.4)
No eyelid involvement	9	3.2 ± 1.4 (1.0-6.5)	0	0	10.1 ± 2.5 (8.4-16.1)

PWS score was calculated and scored from 0 to 4, where 0 = no involvement; 1 = 1%-25% involved; 2 = 26%-50% involvement; 3 = 51%-75% involvement; and 4 = 76%-100% involvement in each segment. Then, the individual areas' scores were considered individually or were summed to yield total hemifacial scores (range: 0-12).
IOP = intraocular pressure; LL = lower eyelid; n = number of eyes; PWS = port-wine stain; UL = upper eyelid.
Values are mean ± standard deviation (range).

photographs). The first row (Figure 2) includes the results of 2 neonates with unilateral facial PWS involving mainly the S1 area. The patient's lesion on the left involved the S1 area only (PWS score: 4), and the patient's lesion on the right-side had a PWS involving both S1 and S2 areas (PWS score: 4+1). Glaucoma was not diagnosed in either patient.

The patient in the second row at left (Figure 2) showed unilateral PWS involving areas S1 and S2 (PWS score: 4+4). The patient's IOP was 39 mm Hg. With both corneal edema and increased cup-to-disc ratio, glaucoma was diagnosed for the right eye. On the right side of the second row (Figure 2), the results for patients with bilateral PWS are presented. The right hemiface shows a PWS involving areas S1 and S2 (PWS score: 1+4), and the left hemiface, S1, S2, and S3 (PWS score: 4+3+3). The patient was diagnoses of glaucoma in both eyes, based on corneal edema with increased IOP (37 mm Hg in the right and 23 mm Hg in left eye).

DISCUSSION

TO THE BEST OF THE AUTHORS' KNOWLEDGE, THIS IS THE first report of an analysis of facial PWS distribution and risk of early onset glaucoma in neonates. These results demonstrated a significant association of a greater S2 area involvement of PWS, specifically including the LL, with a higher risk of glaucoma.

The association between the risk of glaucoma development and the anatomic distribution of facial PWS has been reported. Enjolras and associates,[18] having analyzed 106 cases of facial PWS, demonstrated that only patients with lesions involving the V1 nerve (the ophthalmic branch of the trigeminal nerve), in which they included both the UL and LL, were at risk of associated ocular symptoms. Another study, including 350 children with facial PWS, showed that eyelid involvement was associated with a higher risk of glaucoma.[19] Interestingly, the authors also reported that glaucoma risk was not further increased in cases of additional, complete forehead involvement. The present results from neonatal patients were consistent with those previous findings: all newborns with glaucoma diagnoses had PWS involvement in the eyelids. On the contrary, however, none of the 9 eyes lacking PWS eyelid involvement were diagnosed with glaucoma.

Tallman and associates[10] analyzed the clinical data from 310 children with facial PWS with attention to eyelid involvement and separate assessment of the UL and LL.[10] In their series, all in whom glaucoma had been diagnosed showed PWS involvement of the eyelids; in 91% of cases both the UL and LL were involved, whereas only the LL

TABLE 4. Analysis of Significant Risk Factors for Glaucoma Diagnosis in Neonates with Facial port-wine Stains[a]

		Diagnosis of Glaucoma	
	Variable	Odds Ratio (95% CI)	*P*
Univariate analysis	Age	0.939 (0.842-1.047)	0.255
	Females	1.146 (0.332-3.952)	0.829
	Presence of MRI abnormality	0.625 (0.164-2.388)	0.492
	PWS score (hemifield)		
	S1	1.391 (0.901-2.148)	0.136
	S2	9.762 (2.377-40.091)	0.002
	S3	1.492 (0.807-2.756)	0.202
	Total	1.998 (1.308-3.054)	0.001
	Eyelid involvement		
	Upper eyelid	3.750 (0.940-14.963)	0.061
	Lower eyelid	10.000 (2.350-42.547)	0.002
	Upper and lower eyelids	6.187 (1.503-25.479)	0.012
Multivariate analysis	PSW score, S2	3.604 (1.078-12.050)	0.037
	Upper eyelid involvement	1.364 (0.167-11.123)	0.772
	Lower eyelid involvement	12.816 (1.698-96.744)	0.013

CI = confidence interval; MRI = magnetic resonance imaging; PWS = port-wine stains; S = segment.

[a]Table data show univariate and multivariate odds ratios and 95% confidence intervals of significant risk factors for glaucoma diagnosis in neonates with facial port-wine stains.

was involved in 9% of cases. A notable finding is that none of those with PWS in only the UL had ophthalmic complications. Similarly, in the present study, of the 6 eyes with PWS in the LL only, 5 (83%) developed glaucoma. However, in the 11 eyes with UL PWS only, only 2 eyes (18%) were diagnosed with glaucoma. Those 2 eyes had no LL involvement, but the PWS scores in S2 were all greater than 3. And indeed, as also based on the present logistic regression analysis results, PWS involvement of the S2 area, especially in the LL, are significant features associated with higher glaucoma risk in newborns.

An important goal of the present study was the establishment of a clinical sign that could alert the clinician to screen urgently for glaucoma in newborns with facial PWS. To date, the emphasis in the published studies in terms of ophthalmic complications has been on demonstrating how patterns of facial PWS are related to the likelihood of developing glaucoma in patients overall. Thus, the previous studies included patients of diverse ages (from newborns to teenagers).[10,18,19] It is known that glaucoma associated with PWS shows a bimodal peak in terms of age development: an early onset (infantile) form as well as a later-onset form during childhood and adolescence.[6] Although the pathogenesis of secondary glaucoma to PWS is not yet fully elucidated, it can be postulated that the main mechanisms of IOP increase in the 2 glaucoma subtypes may differ.[20–22] Therefore, the present study focused on analysis of neonates with facial PWS and the relationship with early onset risk of glaucoma. Glaucoma associated with PWS is a challenging disease due to its early development and its poor response to standard medical treatment.[23,24] Thus, early recognition of the risk of glaucoma based on the anatomic distribution of the PWS and prompt initiation of management are critical to preservation of visual function in children with facial PWS.

The reasons for the differential effects of UL and LL PWS involvement on the risk of glaucoma development are not yet clear. In cases of infantile SWS-related glaucoma, theories regarding the possible pathogenesis include anomalies in the anterior chamber angle structure,[20,25] as well as mechanical obstruction due to congenital malformation of the anterior chamber angle or premature aging of the trabecular meshwork-Schlemm's canal complex resulting in abnormal hemodynamics of the episclera and anterior chamber angle.[22,26] Also, PWS entails dilated, ectatic veins with elevated venous pressure.[27,28] Groundbreaking research by Shirley and associates[29] revealed the causative mutation underlying both SWS and most of the isolated cases of PWS,[29] which has been known to affect the endothelial cells lining the blood vessel walls.[30] The orbital venous system can be divided into 2 systems: the superior orbital venous system and the inferior orbital venous system.[31] In cases of PWS involvement in the UL only, an engorged superior ophthalmic vein and a cavernous sinus may be involved.[32,33] However, alternative venous blood drainage through the inferior ophthalmic vein and pterygoid plexus may delay the rise of IOP. LL involvement of PWS may include not only an engorged inferior ophthalmic vein and pterygoid plexus but also a cavernous sinus.[32] In such cases, there may not be sufficient alternative blood drainage capacity of the superior orbital venous system, which could lead to heightened IOP during the neonatal period (Figure 3). Certainly, further histoanatomic investigations should be conducted to reveal the

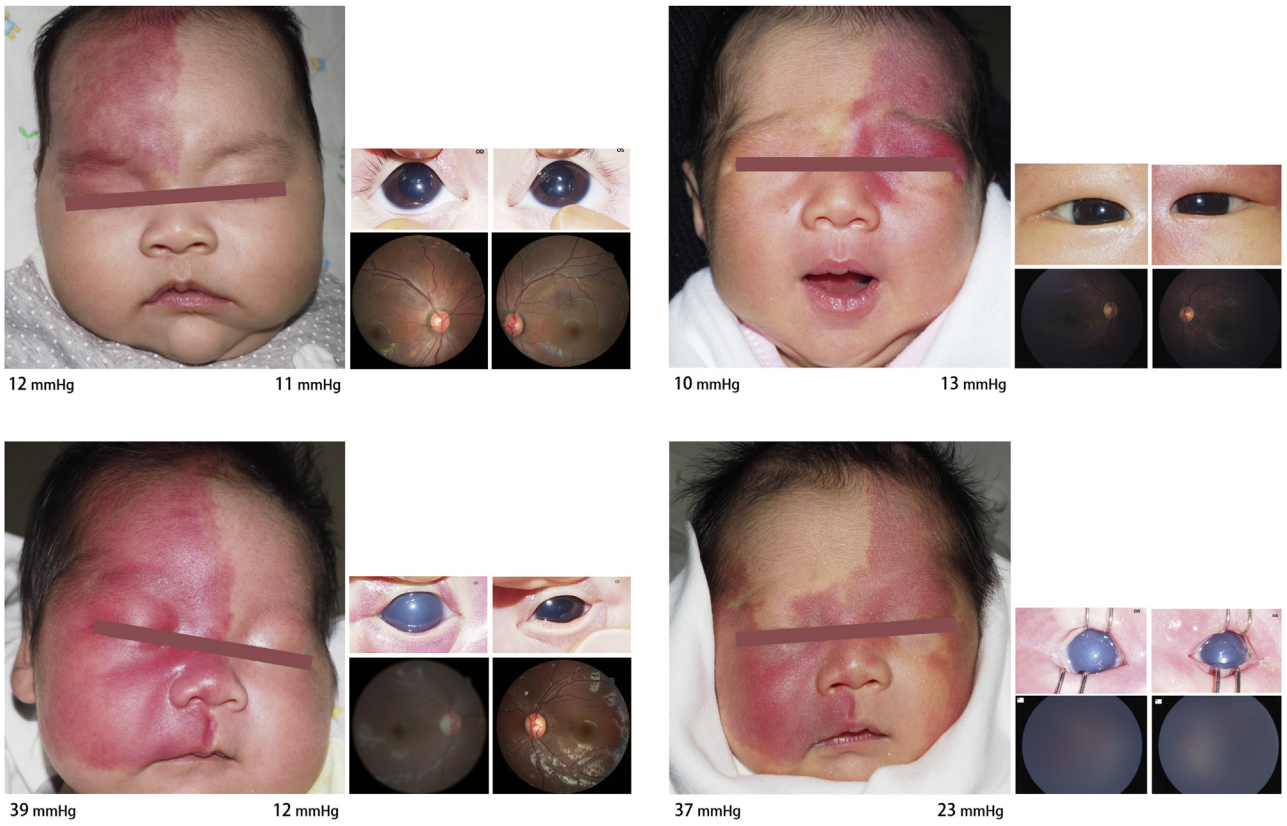

FIGURE 2. Representative cases of neonates with facial PWS. (Top left) Neonate with facial PWS involving only the S1 area (PWS score: 4) in the right hemiface. Anterior segment photography and colored fundus photography indicated normal results in both eyes. (Top right) PWS involving both the S1 and S2 regions in the left hemiface (PWS score: 4+1). The ophthalmologic examination results for both eyes were normal. (Bottom left) Patient with unilateral PWS involving the S1 and S2 regions (PWS score: 4+4) and IOP of 39 mm Hg. In addition to corneal edema and increased cup-to-disc ratio in the right eye, glaucoma was diagnosed. (Bottom right) Neonate with bilateral PWS in the right hemiface involving regions S1 and S2 (PWS score: 1+4) and left hemiface involving regions S1, S2, and S3 (PWS score: 4+3+3). Based on corneal edema and increased IOP (37 mm Hg in the right and 23 mm Hg in the left eye), glaucoma was diagnosed in both eyes. IOP = intraocular pressure; PWS = port-wine stain.

underlying pathophysiology of PWS eyelid involvement and glaucoma development.

When the results presented herein are interpreted, several points need to be kept in mind. First, one significant limitation is the facial position variability in the present patient photographs. The borders of the PWS area were visually approximated from the images by the rater. Although these estimations obviously reflect a degree of subjectivity, the subjectivity was partially resolved by the use of 2 independent raters of good inter-rater reliability whose scores were averaged. A future study should use standardized, multiple angle photographs taken of patients during visits to clinics. Second, the population of patients referred to the authors' hospital may represent a highly selected group. In addition, all subjects were Korean. Therefore, the relative proportion of patients showing facial PWS with eyelid involvement or with glaucoma in the present series may not be representative of the general population of children with PWS. Third, several factors regarding the measurement of IOP and the discrimination of glaucoma in the neonates must be considered. Generally, physiological IOP is lower in children than in adults and increases with age.[34,35] In the present study, IOP greater than 18 mm Hg was considered abnormally elevated, based on a previous study reporting an upper limit of ±2 SD of the mean IOP (17.65 mm Hg) in normal Korean newborns.[15] In the present cohort, most of the eyes (17 of 19; 90%) that were diagnosed with glaucoma met 3 or more of the relevant diagnostic criteria, which made the glaucoma discrimination relatively clear. However, as the IOP-diagnostic criteria for glaucoma can significantly affect results, this factor should be taken into account when interpreting this study's results. Fourth, a relatively small-sized cohort was cross-sectionally analyzed in order to investigate the relationship between anatomic distribution of facial PWS and risk of early onset glaucoma at birth. Children with facial PWS and normal IOP during the neonatal period are at risk of developing glaucoma later. A follow-up longitudinal study with a larger population certainly is warranted for investigation of the clinical factors associated

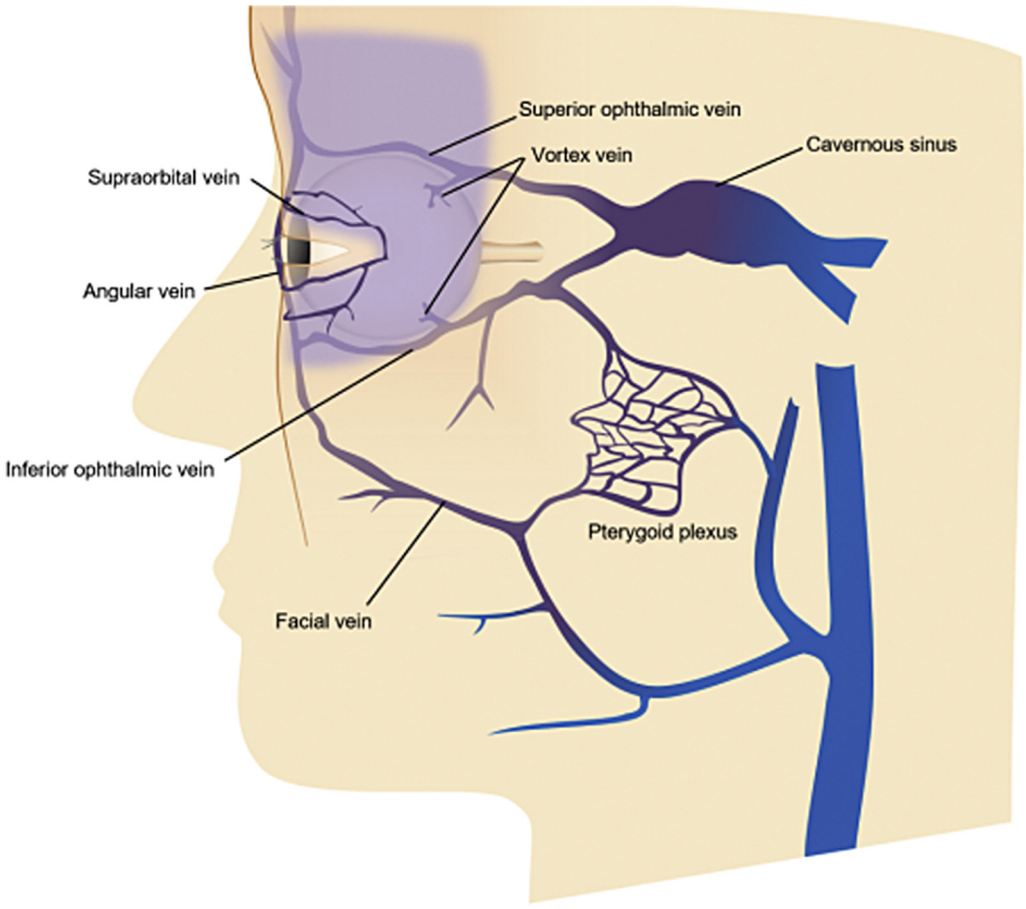

FIGURE 3. The orbital venous system shown separated into 2 systems: superior orbital venous system and the inferior orbital venous system. Cases of PWS involvement only in the upper eyelid are associated with engorged superior ophthalmic vein and cavernous sinus. However, a rise in IOP may be delayed by alternative venous blood drainage through the inferior ophthalmic vein and pterygoid plexus. PWS lower eyelid involvement includes not only engorged inferior ophthalmic vein and pterygoid plexus but also cavernous sinus. In this case, there may not be enough alternative blood drainage capacity of the superior orbital venous system, which may lead to increased IOP during the neonatal period. IOP = intraocular pressure; PWS = port-wine stain.

with ophthalmic complications arising in children with facial PWS. In fact, our analysis of the association of facial PWS distribution with glaucoma development after the neonatal period already is underway.

In conclusion, among the present cohort of newborns with facial PWS 1) greater extent of birthmarks involving the S2 area and 2) lesions including the LL were associated with higher risk of glaucoma within the neonatal period. The authors propose that newborns with a facial PWS affecting the S2 area, including the LL, should undergo an ophthalmological review as early as possible, ideally on the very first day of life, and with subsequent follow-up throughout life.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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