Periocular Port Wine Stain: The Great Ormond Street Hospital Experience

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Purpose: To identify the sensitivity and specificity of risk factors for the development of glaucoma in patients with port wine stain (PWS).

Design: A retrospective case-control study involving a large cohort of patients with PWS.

Participants: A total of 216 patients (total of 252 eyes) with unilateral or bilateral PWS seen in the eye department in Great Ormond Street Hospital, London, United Kingdom.

Methods: We studied the anatomic distribution of PWS and the incidence of choroidal hemangioma, episcleral hemangioma, iris heterochromia, and Sturge–Weber syndrome (SWS). We analyzed the sensitivity and specificity of these features as risk factors for glaucoma.

Main Outcome Measures: Development of glaucoma.

Results: Mean age at presentation was 2.9 years (3 weeks to 18.8 years). Mean follow-up was 3.2 years (0–15 years). A total of 180 patients (83.3%) had unilateral lesion, and 36 patients (16.7%) had bilateral lesion. Thirty-one patients (14.3%) had isolated V1 lesion, 35 patients had V2 lesion only (16.2%), and 93 patients (43%) had both V1 and V2 involved. On the last visit, 46 eyes (18.3%) in 39 patients had glaucoma; their mean age was 3.25 years. Glaucoma was more common if PWS was bilateral ($P=0.0001$), both upper and lower lids were involved ($P < 0.0001$), and episcleral hemangioma ($P < 0.0001$), iris heterochromia ($P=0.004$), or choroidal hemangioma ($P < 0.0001$) was present. Twenty-four patients had SWS; this was significantly associated with upper lid PWS ($P=0.001$) and bilateral PWS ($P=0.0003$). Glaucoma was more common in patients with SWS compared with those without (66.7% vs. 18%, $P=0.01$). Combined upper and lower lid PWS, episcleral hemangioma, SWS, and iris heterochromia are sensitive prognosticators for the development of glaucoma.

Conclusions: Iris heterochromia is associated with the development of early glaucoma in patients with PWS. Patients at high risk of glaucoma should be seen more often in clinic. Patients who do not have combined lid involvement or episcleral hemangioma have a lower risk and can therefore be seen less often in clinic.

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Port wine stain (PWS) is a relatively common congenital vascular lesion, seen in the area of cutaneous distribution of trigeminal nerve.[1–3] A PWS is a well-defined macular lesion, initially pink in color with a smooth surface that, unlike hemangiomas, partially blanches with pressure. With time, the lesions become dark red to purple, and the overlying skin becomes hypertrophied and nodular.[4] A PWS is a vascular capillary malformation composed of ectatic vessels in the papillary dermis.[5,6]

A PWS is frequently isolated, but different associations can occur, including orbital vascular anomalies, glaucoma, and leptomeningeal angiomatosis.[7] Some of these associations are syndromic, such as Klippel–Trenaunay–Weber syndrome (ipsilateral varicosities and bony hypertrophy),[8] cutis marmorata telangiectasia congenita, and Sturge–Weber syndrome (SWS), which is a congenital sporadic condition with neuro-ocular and cutaneous vascular manifestations.[9]

It is well recognized that periocular PWS predisposes to risk of glaucoma.[10] Furthermore, glaucoma management in the context of PWS or SWS is especially difficult whether medically or surgically as shown by a number of published articles.[11–14] By taking this into consideration it becomes evident that the management burden of these patients is high, because many visits would be required if we were to diagnose glaucoma and start treatment in a timely fashion. It would then be directly beneficial to identify some prognosticators for development of glaucoma that will allow us to categorize patients into low-risk and high-risk groups, and thus plan their follow-up accordingly. This study reviewed 216 patients with periocular PWS seen in one center to evaluate the clinical features that may help plan patients' review rates.

Patients and Methods

This is a retrospective case-control study evaluating a large cohort of patients with PWS from Great Ormond Street Hospital for Children. We identified these patients from our hospital's dermatology department database, where patients receive laser ablation of the vascular lesion.[9,15,16]

These patients are managed by a multidisciplinary team that includes the ophthalmology and neurology departments. By fol-

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lowing findings of previous reports, only patients with PWS in the area of the ophthalmic (V1) or maxillary (V2) branches of the trigeminal nerve are referred for ophthalmic examination. Patients with isolated mandibular (V3) lesion would not normally be referred to the ophthalmology team.

Between 1981 and 2005, 530 patients with PWS were seen in Great Ormond Street Hospital. A total of 367 patients had facial lesions, and 216 of them (58%) were referred for ophthalmic assessment. The remaining 151 patients were not seen in our department; among them are patients with facial involvement but no periocular involvement, patients with V3 lesion alone, and a small number of patients seen by an ophthalmologist elsewhere. All patients have been reviewed by the dermatology department.

We collected our data on a standard proforma and compiled it into a database using FileMaker 5 software from FileMaker Inc. (Santa Clara, CA). The data collected included date of birth; sex; age at presentation; symptoms at presentation; distribution of the PWS and involvement of lids; extra-facial involvement; visual acuity; detailed examination of the eye with special attention to the presence of episcleral vessels, iris heterochromia, and choroidal hemangioma; and the presence of epilepsy or intracranial hemangioma.

We also recorded diagnosis of glaucoma, treatment given, surgery performed, final visual outcome, and intraocular pressure. We used categoric data analysis using chi-square and Fisher exact tests with $P < 0.05$ from open source and logistic regression, receiver operating characteristic curve, and area under the curve analysis using MedCalc software from MedCalc. We looked for sensitivity and specificity of different clinical signs and their validity as prognosticators for the development of glaucoma. This study was approved by the ethics committee at Great Ormond Street Hospital and the Institute of Child Health, London, United Kingdom.

Results

A total of 216 notes were reviewed on 124 female (57.4%) and 92 male (42.6%) patients. The mean age at presentation was 2.9 years (3 weeks to 18.8 years), and the mean follow-up period was 3.2 years (0–15 years). A total of 180 patients (83.3%) had unilateral lesions, and 36 patients (16.7%) had bilateral lesions, making the total number of eyes involved 252.

Thirty-one patients (14.3%) had isolated V1 lesion, 35 patients (16.2%) had V2 lesion only, and 93 patients (43%) had both V1 and V2 lesions; the remaining 57 patients (26%) had PWS involving areas beyond V1 and V2. Extra-facial PWS was more common in bilateral compared with unilateral cases (66.7% vs. 23.9%) $P=0.0001$.

Glaucoma

Diagnosis of glaucoma was made on the basis of a sustained intraocular pressure elevation of >21 mmHg, with the presence of one of the following: increased cup/disc ratio, myopic shift, increased corneal diameter, corneal haziness, or visual field defect when tested.

A total of 26 eyes (10.3%) in 22 patients were diagnosed with glaucoma on presentation; their mean age was 3.25 years (range 0.01–10.8 years). Twenty eyes in 17 patients (7.8%) developed glaucoma during follow-up; their mean age was 1.6 years (range, 0.25–6.94 years). On the last visit, 46 eyes (18.25%) in 39 patients had glaucoma.

Glaucoma was more commonly associated with bilateral PWS. On their last visit, 22 patients of 180 (12.2%) with unilateral PWS had glaucoma, compared with 17 of 36 patients (47.2%) with bilateral PWS ($P=0.0001$). Glaucoma was also more commonly associated with PWS involving both upper and lower lids; 43 eyes of 46 with glaucoma (93.5%) had both lids involved, compared with 109 eyes of 206 (53%) in the non-glaucoma group ($P < 0.0001$).

Episcleral hemangioma, iris heterochromia, and choroidal hemangioma were all statistically significantly associated with the development of glaucoma. The incidence of glaucoma associated with episcleral hemangiomas was 45% (41 eyes of 91 with episcleral hemangioma, $P < 0.0001$). Glaucoma was also more common in patients with iris heterochromia ($P=0.004$), with 7 of 14 eyes (50%) diagnosed by the last follow-up. The same applies to choroidal hemangioma; 24 eyes of 60 (40%) with choroidal hemangioma were diagnosed with glaucoma ($P < 0.0001$).

Among patients who developed glaucoma during their follow-up, 5 had bilateral PWS (13% of 36 patients) and 12 were unilateral (6.7% of 180 patients). Similar to the glaucoma-on-presentation group, combined upper and lower lid involvement seems to be a strong indicator for developing glaucoma later ($P=0.01$, Table 1).

We divided patients with glaucoma by age to 3 groups: (1) age <18 months on presentation; (2) age 1.5 to 4 years; and (3) age >4 years on presentation. We looked at the association of glaucoma with the above clinical factors (Table 2), and it seems that factors such as combined V1+V2 and episcleral hemangioma are statistically significantly associated with glaucoma in any age group. Factors such as choroidal hemangioma and iris heterochromia are only significantly associated with the early onset of glaucoma (i.e., before 1.5 years at presentation).

Treatment of glaucoma required surgical intervention in 22 of 46 eyes. This included one or more of the following: goniotomy, trabeculotomy, trabeculectomy, and cyclodestruction. Glaucoma in 24 eyes (52%) was controlled with medical treatment alone. In patients who developed glaucoma later, the disease was easier to control by medications only and was less severe, therefore requir-

Table 1. Comparison Between Different Clinical Features of Port Wine Stain and Their Association with Glaucoma in Patients Aged <18 Months, 1.5–4 Years, and >4 Years at Presentation

Age at Presentation	Glaucoma 0–1.5 yrs N=29	P	Glaucoma 1.5–4 yrs N=8	P	Glaucoma >4 yrs N=9	P	No Glaucoma N=206
V1+V2	28	0.0002	8	0.015	9	0.009	121
Choroidal hemangioma	18	<0.0001	3	0.15	3	0.19	35
Episcleral hemangioma	25	<0.0001	6	0.012	8	0.0006	61
Iris heterochromia	7	0.0004	0	0.76	0	0.73	7

V1+V2 = ophthalmic and maxillary branches of the trigeminal cranial nerve.
P value is calculated using chi-square or Fisher exact analysis.

Table 2. Logistic Regression Analysis of Independence of Prognosticators for Port Wine Stain–Related Glaucoma, with Odds Ratio and Confidence Intervals

Sample size	252
Cases without glaucoma	206 (81.75%)
Cases with glaucoma	46 (18.25%)
Chi-square	90.65
df	6
Significance level	$P < 0.0001$

Coefficients, Standard Errors, Odds Ratios, and Confidence Intervals

Variable	*Coefficient*	*SE*	P	*OR*	*95% CI*
V1+V2	2.44	1.39	0.08	11.57	0.75–179.28
UL+LL	0.34	0.97	0.73	1.40	0.21–9.53
SWS	2.05	0.49	<0.0001	7.80	2.99–20.35
Iris heterochromia	0.33	0.68	0.63	1.39	0.36–5.31
Episcleral hemangioma	1.97	0.54	0.0002	7.21	2.51–20.68
Choroidal hemangioma	0.23	0.50	0.65	1.25	0.47–3.36
Constant	−5.54				

ROC curve analysis

AUC	0.885
SE	0.0331
95% CI	0.839–0.922

AUC = area under the ROC curve; CI = confidence interval; *df* = degrees of freedom; ROC = receiver operating characteristic; SE = standard error; SWS = Sturge–Weber syndrome; UL+LL = upper lid and lower lid; V1+V2 = ophthalmic and maxillary nerves.

ing less surgery. In the group with a late presentation of glaucoma, 6 eyes of 20 (30%) required surgery compared with 18 of 27 (67%) in the group with glaucoma on presentation.

Other Ocular Findings

Episcleral hemangioma was found in 91 eyes (36.1%), of which 33 also had both V1 and V2 PWS (35%). Iris heterochromia was found in 14 eyes (5.6%). None of our patients developed rubeosis. Choroidal hemangioma was found in 60 eyes (23.8%), 15 of which were solitary well-circumscribed hemangiomas, and the rest were the diffuse deep red hemangioma traditionally identified as tomato catsup.

Neurologic Findings and Sturge–Weber Syndrome

Diagnosis of SWS was made by the consultant neurologist on the basis of clinical examination and signs of neurologic involvement, such as convulsions, developmental delay, or hemiplegia. Neuroimaging was also sought to detect intracranial vascular abnormalities or angiomas. In this series, a total of 24 cases had a definite diagnosis of SWS. All patients with SWS had an upper lid PWS, and that association was statistically significant ($P=0.001$). Nineteen patients (79%) had bilateral PWS, and that association also was significant ($P=0.0003$).

Glaucoma was more common in patients with SWS and was found in 16 of 24 patients (66.7%, $P=0.01$). Five of these patients (31.2%) had bilateral glaucoma with bilateral PWS, and the remaining 11 (68.8%) were unilateral, including 4 who had bilateral PWS.

Proteus syndrome was diagnosed in 1 patient, cutis marmorata telangiectasia congenita was diagnosed in 1 patient, and phenylketone urea was diagnosed in 1 patient.

Statistical Analysis

We performed a logistic regression analysis of the factors identified previously, and this revealed that episcleral hemangioma and SWS are the only factors independently associated with development of glaucoma in patients with PWS.

We further looked at sensitivity and specificity of these clinical signs as prognosticators for the development of glaucoma. Table 3 lists these findings and shows that V1+V2 PWS and episcleral hemangioma have high sensitivity and high negative predictive value (NPV). Iris heterochromia and SWS have high specificity and high positive predictive value (PPV). Combining some of these factors will increase their PPV as in V1+V2 and episcleral hemangioma, or episcleral hemangioma and iris heterochromia. We also performed receiver operating characteristic curve and area under curve analyses for the above factors (Fig 1, available at http://aaojournal.org).

Discussion

Although the exact cause is yet to be determined, PWS is caused by progressive ectasia of the cutaneous superficial vascular plexus.[17,18] One theory suggests this is caused by an abnormal neural regulation of blood flow secondary to deficiency of autonomic nerves around blood vessels. This leads to significant shift in skin blood flow regulation, which leads to progressive vascular ectasia.[18,19]

Table 3. Study of Specificity and Sensitivity of Glaucoma Prognosticators

Predictive Factors for Glaucoma	True Positive	False Positive	False Negative	True Negative	Total	Sensitivity	Specificity	PPV	NPV
V1+V2	45	121	1	85	252	97.8%	41%	26.9%	98.8%
UL+LL	43	3	109	97	252	93.4%	47%	28.2%	97%
SWS	16	8	23	169	216	41%	95.4%	66.7%	88%
Iris heterochromia	7	7	39	199	252	15.5%	96.6%	50%	84%
Choroidal hemangioma	24	36	20	172	252	54.5%	65.5%	40%	90%
Episcleral hemangioma	41	50	5	156	252	89.1%	75.7%	45%	96.8%
UL+LL+EsH	36	38	10	168	252	78.2%	81.5%	48.6%	94.4%
EsH+IH	7	6	39	200	252	15%	97%	53.8%	93.6%

EsH = episcleral hemangioma; IH = iris heterochromia; LL = lower lid; NPV = negative predictive value; PPV = positive predictive value; SWS = Sturge–Weber syndrome; UL = upper lid; V1+V2 = ophthalmic and maxillary branches of the trigeminal cranial nerve.
Glaucoma in 46 eyes of 39 patients, series of 252 eyes in 216 patients.

Another theory published in a recent study[20] suggests that vascular ectasia in PWS is secondary to localized venous dysplasia affecting some of the emissary veins in the cranial circulation periphery, which leads to retrograde increased venous pressure affecting nearby areas via existing channels and to engorgement of the superficial venous plexus that manifests as PWS and its associations. This theory accounts for the fact that PWS may not follow trigeminal distribution. It may also explain the difficulty in managing PWS-related glaucoma.[10,13,14,21–24] The hypothesis that laser obliteration of facial PWS would increase the retrobulbar venous pressure and therefore worsen glaucoma control in these patients[20] cannot be supported or denied by our retrospective study. However, the incidence of glaucoma is limited in this series even though all patients underwent laser ablation treatment. Similar findings have been reported recently.[25]

Glaucoma in PWS is often reported as being ipsilateral, unilateral, and congenital. Its incidence in the literature is approximately 30%, with ~60% of these cases occurring in early childhood and resulting in buphthalmos, whereas the remaining 40% do not develop glaucoma until late childhood or early adulthood and therefore do not have buphthalmos.[13] Patients who do not develop glaucoma in childhood are reported to have a higher risk of glaucoma in adulthood.[26] Bilateral glaucoma, however, has also been reported, usually with bilateral PWS.

From a histopathologic point of view, the available literature suggests that glaucoma in PWS and SWS is similar to that in the general population when an immature trabecular structure is found in affected babies, but in older children, premature degenerative changes affect the trabeculum and Schlemm's canal.[13,22]

Because glaucoma can occur late in the context of PWS, even though it may be of less severity than early glaucoma, regular follow-ups and evaluations are necessary. Our aim has been to look at predictive factors of onset of glaucoma. It follows that if there is no glaucoma at presentation, the longer the follow-up is, the greater the chance of glaucoma onset. Although we acknowledge this, our findings provide a useful guide to help predict onset of glaucoma.

By using specificity and sensitivity alone, absence of upper and lower lid PWS and episcleral hemangioma have the highest NPV, that is, if these factors are not present, the chance of later glaucoma onset is significantly reduced. The presence of SWS or iris heterochromia has the highest PPV, suggesting that the presence of either increases the possibility of glaucoma development.

If logistic regression is applied, then only the presence of 2 independent factors becomes significant: SWS and episcleral hemangioma.

We would suggest that patients who do not have combined upper and lower lid PWS or episcleral hemangioma, do not need to be seen frequently in clinic. They may be seen annually or be referred to the local optometrist for annual review. Infants aged <6 months who do not have combined upper and lower lid PWS may be seen every 6 months or more often if one of the above is present. Patients with more than 1 of these factors—upper and lower lid PWS, iris heterochromia, episcleral hemangioma—should be seen 3 months initially with follow up reduced after 1 year to 4 monthly, reducing eventually to 6 monthly.

Iris heterochromia association with PWS is not widely recognized, but was found in 10.6% of patients in this series. These patients seem to have a higher propensity for glaucoma (53.8%) at an earlier age.

Sturge–Weber syndrome in this study was more common (11%) compared with previous literature,[27] probably because we have a tertiary referral epilepsy service in our hospital. Although SWS diagnosis was more commonly associated with upper lid PWS (46%), this association was not statistically significant ($P=0.24$), nor was the association with unilateral PWS ($P=0.36$, chi-square). Patients with SWS need 4 months follow up reducing at most to 6 monthly.

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Footnotes and Financial Disclosures

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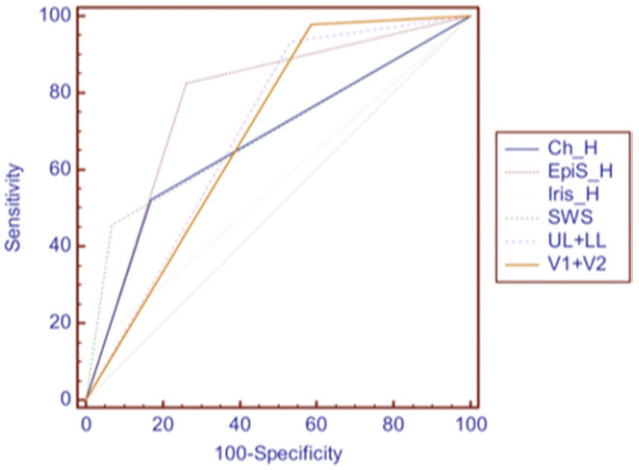

Figure 1. Comparison of receiver operating characteristic curves for PWS-related glaucoma indicators. Ch_H = choroidal hemangioma; EpiS_H = episcleral hemangioma; Iris_H = iris heterochromia; PWS = port wine stain; SWS = Sturge–Weber syndrome; UL+LL = upper lid and lower lid; V1+V2 = ophthalmic and maxillary nerve distribution.