Original Article

Glaucoma in Patients with Eyes Close to Areas Affected by Port-wine Stain has Lateral and Gender Predilection

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Abstract

Background: The location of facial port-wine stain (PWS) may be helpful for predicting some associated anomalies; high glaucoma incidence is found in patients with eyes close to PWS-affected areas (V1, ophthalmic branch area of the trigeminal nerve). This study aimed to investigate the characteristics of glaucoma in V1-affected PWS.

Methods: A total of 569 patients with V1 area-affected PWS were reviewed in the study. The large series was based on the referral system between the Department of Plastic and Reconstructive Surgery and the Department of Ophthalmology. All patients were screened for glaucoma with assessments of intraocular pressure, cup-to-disc ratio, corneal diameter (only for infants), and axial length.

Results: Of the 569 patients, 110 (19.3%) patients had glaucoma. Among the patients, 18.1% (76/420) had early-onset glaucoma (under 4-year-old group). In the 4 to 18-year-old age group, 29.3% (29/99) of the patients had glaucoma. Compared with right lateral and bilateral PWS, left-sided PWS had a lower risk of glaucoma in this study (odds ratio = 0.432 [95% confidence interval, 0.264–0.706], $P = 0.01$). The under 4-year-old group showed a slight predominance of males (61.8%) in glaucoma.

Conclusions: High glaucoma incidence was observed in patients with eyes close to PWS. More attention should be paid to glaucoma screening for right lateral and bilateral PWS patients. The predominance of males in Sturge–Weber syndrome (SWS) early-onset glaucoma patients might be due to the limitation of the case number; however, it might also provide us a new clue of potential relationship between SWS and PCG.

Key words: Birthmark; Glaucoma; Port-wine Stain; Sturge–Weber Syndrome

Introduction

Port-wine stain (PWS) is a congenital birthmark that reflects embryonic vascular development abnormalities.[1] PWS can occur anywhere on the body. These lesions may present as large unilateral patches with a segmental distribution and midline demarcation or as small stains.[2] The reported incidence of PWS is approximately 0.3–0.6%.[3-6] Sturge–Weber syndrome (SWS), also called encephalotrigeminal angiomatosis, is a neurocutaneous disorder with angiomas that involve the leptomeninges and the skin of the face, typically in the ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve. The hallmark of SWS is a facial cutaneous venous dilation, also referred to as a nevus flammeus or PWS.[7] The locations of PWS may also be helpful for predicting some associated anomalies. A consensus has been reached that SWS occurs almost exclusively in patients whose PWS involves the distribution of the V1 (ophthalmic) branch of the trigeminal nerve, which is the region including the forehead, nose, upper eyelids, and lower eyelids that may also be innervated by the V2 branch.[8-11] Previous research has established that glaucoma affects the ipsilateral eyes of patients with PWS.[11,12] However, whether the onset of glaucoma has a lateral predilection is not clear. Furthermore, few studies have focused on the ocular manifestations in eyes close to PWS in patients. Thus, we designed a large-series cross-sectional study to investigate the characteristics of glaucoma in V1-affected PWS.

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Methods

Ethical approval

The study was approved by the institutional review board of Ninth People's Hospital Affiliated with the Shanghai Jiao Tong University School of Medicine.

Patients

Patients with eyes close to PWS (V1 branch area) who visited the Ophthalmology Department for glaucoma screening between 2011 and 2016 were enrolled in the study. Most of the PWS patients were children who were brought in by their parents to the Orthopedics Department or Laser Cosmetology Center for cosmetic needs. All diagnoses of PWS were made by the plastic surgeons of Shanghai Ninth People's Hospital. In addition, the patients whose superficial cutaneous vascular network ectasia involved the V1 division of the trigeminal nerve area were recommended to receive a screening at the Ophthalmology Department.

Screening procedures for low-compliance patients

Most of the PWS patients had poor compliance with eye examinations because of their young age. For sedation, chloral hydrate (10 ml: 1 mg) was administered orally to the patients after their legal guardians signed the consent form. An Icare® rebound tonometer (TA01, TIOLAT Oy, Finland) was used to measure intraocular pressure (IOP); compound tropicamide eye drops (SANTEN OY, Tampere, Finland) were applied to dilate the pupil; a direct ophthalmoscope was used to observe the vertical cup-to-disc ratio (C/D) and the posterior pole of both eyes; for the glaucoma suspect patients, especially the infant patients, a fundus photograph would be obtained by Retcam (Clarity Medical Systems, Pleasanton, CA, USA) for C/D observation, a flashlight was used to examine the cornea, a Type A ultrasound test was used to evaluate the axial length of the eye, and gonioscopy would be applied to glaucoma suspect patients.

If ipsilateral IOP >21 mmHg, C/D >0.3, obvious asymmetric IOP or C/D for both eyes, corneal edema, notably increased corneal diameter, Haab's striae, or apparent choroid thickening were detected, the PWS patients were required to be hospitalized for gonioscopy and ultrasound biomicroscopy under general anesthesia.

Diagnosis of glaucoma

The diagnosis of glaucoma was based on a general anesthesia examination for infants. Since IOP levels in newborns were lower than those in the adults, we did not use IOP as the single deciding index for the final diagnosis. However, IOP >21 mmHg (1 mmHg = 0.133 kPa) or obvious asymmetry between two eyes (>6 mmHg) was a warning index for close observation. In comparison, C/D >0.5 with obvious asymmetric C/D (>0.2) for both eyes, corneal diameter enlargement (D >11 mm in newborns or D >12 mm in 12-month-old children), and other corneal abnormalities, such as Haab's striae or corneal edema, were considered better indicators of glaucoma.

For adult patients, besides the IOP measurement and C/D observation mentioned above, visual field test and retinal nerve fiber layer assessment were also required for glaucoma diagnosis, but corneal conditions were not considered diagnostic signs.

Statistical analyses

All statistical analyses were performed by SPSS (Version 16.0, IBM Corporation, NY, USA). Data were summarized using mean and standard deviation or median and interquartile range (IQR). Categorical data were analyzed with Pearson's Chi-square test. The values in the PWS with glaucoma and PWS without glaucoma groups were compared using independent samples *t*-test or nonparametric test followed by Mann–Whitney *U*-test. A value of $P < 0.05$ was considered statistically significant.

Results

General characteristics of port-wine stain patients

The current study included 569 patients with eyes close to PWS [Table 1]. The median age was 15 months; 295 (51.8%) patients were male and 274 (48.2%) were female. PWS affected 278 (48.9%), 254 (44.6%), and 37 (6.5%) patients in the right, left, and both sides of the face, respectively. The median and IQR IOP and C/D were significantly different between ipsilateral eyes and contralateral eyes ($P < 0.001$), while the axial lengths did not differ between ipsilateral and contralateral eyes.

Table 1: Baseline demographic and clinical data of PWS patients

Baseline characteristics	Total (n = 569)	Statistic	P
Age (month), median (IQR)*	15 (4, 51)		
Gender, *n* (%)			
Male	295 (51.8)		
Female	274 (48.2)		
Affected sides, *n* (%)			
Right	278 (48.9)		
Left	254 (44.6)		
Both	37 (6.5)		
IOP (mmHg), median (IQR)		t = 8.165	<0.001†
Ipsilateral eyes	13 (9, 17)		
Contralateral eyes	11 (8, 15)		
C/D, median (IQR)		t = 7.016	<0.001†
Ipsilateral eyes	0.30 (0.30, 0.40)		
Contralateral eyes	0.30 (0.25, 0.30)		
Axial lengths (mm), mean ± SD		U = 51713	0.323‡
Ipsilateral eyes	21.52 ± 2.17		
Contralateral eyes	21.27 ± 2.10		
Total glaucoma in PWS patients, *n* (%)	110 (19.3)		

*IQR shown as 25%, 75%; †Mann-Whitney *U*-test; ‡Independent-samples *t*-test. IQR: Interquartile range; IOP: Intraocular pressure; C/D: Cup-to-disc ratio; PWS: Port-wine stain; SD: Standard deviation.

Table 2: Incidences of glaucoma in different age groups

Age groups (years)	PWS Patients (n = 569)			Glaucoma in PWS Patients (n = 110)			Statistic	P*
	Male, n (%)	Female, n (%)	Total, n	Male, n (%)	Female, n (%)	Total, n		
Under 4	214 (51.0)	206 (49.0)	420	47 (61.8)	29 (38.2)	76	$\chi^2 = 4.403$	0.036†
4–18	58 (58.6)	41 (41.4)	99	15 (51.7)	14 (48.3)	29	$\chi^2 = 0.796$	0.372†
>18	23 (46.0)	27 (54.0)	50	3 (60.0)	2 (40.0)	5	–	0.651‡

*P value was obtained by comparing the PWS with glaucoma patients' gender constituent ratio to the PWS patients without glaucoma affected; †Chi-square test; ‡Fisher's exact test. PWS: Port-wine stain.

Incidence of glaucoma in patients with eyes close to port-wine stain

According to the glaucoma diagnosis criteria, 110 (19.3%) patients were diagnosed with glaucoma. In our study, we divided our patients into three groups by age [Table 2]. There were 420, 99, and 50 patients in the under 4, 4 to 18, and >18-year-old groups, respectively. In addition, glaucoma incidence varied among the different age groups, with 18.1% (76/420) in the under 4-year-old group, 29.3% (29/99) in the 4 to 18-year-old group, 10.0% (5/50) in the >18-year-old group. There were significant gender differences between glaucoma-affected PWS patients and PWS without glaucoma patients in the under 4-year-old age group (P = 0.036). A slight predominance of males was common (61.8%) in glaucoma patients with eyes close to PWS under 4 years of age (odds ratio [OR] = 1.718, 95% confidence interval [CI] 1.033–2.857, P = 0.037).

Characteristics of glaucoma in port-wine stain patients

The median age of glaucoma patients was 15 months; 65 (59.1%) patients were male and 45 (40.9%) were female [Table 3]. Regarding the gender ratio, there was no significant difference between the glaucoma group and PWS without glaucoma group (P = 0.09). However, the distribution location of PWS in the glaucoma group was significantly different from that in the PWS without glaucoma group (P = 0.011). Notably, in all unilateral PWS patients in the glaucoma group, the glaucomatous eyes were on the ipsilateral side. In our study, bilateral PWS (at least one side was affected close to an eye) was a risk factor for glaucoma (OR = 3.686, 95% CI 1.649–8.242, P = 0.037), while for left-sided PWS, even if the V1 distributed area was affected, the risk of glaucoma was low (OR = 0.432, 95% CI 0.264–0.706, P = 0.01). Nevertheless, bilateral PWS patients did not always exhibit bilateral glaucoma; five of seven patients had unilateral glaucoma despite PWS-affected bilateral V1 areas, and the remaining two patients had unilateral glaucoma because only one side of the eyes around the area was affected by the PWS. The IOP, C/D, axial length, and corneal diameter (under 4 years old) were significantly different between glaucomatous and unaffected eyes ($P < 0.05$).

Discussion

SWS is a rare, sporadically occurring, congenital neurocutaneous disorder characterized by capillary venous malformations,[13] and the estimated incidence is between 1:20,000 and 1:50,000.[14] Among all SWS-related ocular complications, the most common is glaucoma, which affects 30–70% of SWS patients.[15-17] The cutaneous hallmark of SWS is facial PWS, which could represent an intuitive method to screen SWS from PWS.

Studies[10,11] have reported that 12.2–26.0% of patients with partial or full V1 involvement have glaucoma. In our study, a total of 19.3% patients with eyes around the PWS-affected area had glaucoma regardless of the age stratification. This result agrees with previous studies. However, the reality might be more complex. According to the presentation of glaucoma in SWS patients, the following bimodal phenomenon has been shown: 60% developed glaucoma in infancy when the eyes were susceptible to increased IOP and became buphthalmic and 40% developed glaucoma in late childhood or early adulthood.[15,18] The pathogenesis of bimodal onset glaucoma is different. The etiology of early-onset glaucoma is known to involve anterior chamber angle anomalies.[18,19] Juvenile- or adulthood-onset glaucoma has been attributed to elevated episcleral venous pressure.[20] Our results strongly support this theory. In the under 4-year-old group, corneal diameter, which indicates the enlargement of eyes, was significantly larger in glaucomatous eyes than that in unaffected eyes. However, not all the angle abnormalities could be observed, according to our study, residual of mesoderm in anterior chamber angle could be found in only 46 out of 110 patients by gonioscopy. Even so, early trabeculotomy has been reported to control the IOP in intermediate term.[21] In addition, 18.1% of the V1-involved PWS patients under 4 years old developed glaucoma, which represents the incidence of early-onset glaucoma in SWS. This finding provides a reasonable explanation for the increased incidence of glaucoma (29.29%) in the 4 to 18-year-old group based on the previously mentioned theory. Among the glaucoma patients in this age group, bimodal onset times might occur; according to the incidence of early-onset glaucoma mentioned above, the incidence of late-onset glaucoma might be approximately 11% in this age group. However, more evidence is needed from further studies to demonstrate the two mechanisms of glaucoma in this age group. Although the incidence of glaucoma in the above 18-years-old group was low, we noticed that the number of cases in these groups was much smaller than those in the low age groups. Furthermore, 50% of the glaucoma patients in these two groups had eye complaints before diagnosis, which suggests that some potential glaucoma

Table 3: Clinical features of glaucoma in port-wine stain patients

Characteristics	Total (n = 110)	Statistic	P
Age (year), median (IQR)*	0.7 (0.6, 6.2)		
Gender (proportions), n (%)		$\chi^2 = 2.867$	0.09†,§
Male	65 (59.1)		
Female	45 (40.9)		
PWS-affected sides (proportions), n (%)		$\chi^2 = 8.985$	0.011†,§
Right	61 (55.5)		
Left	37 (33.6)		
Both	12 (10.9)		
Glaucoma-affected sides (proportions), n (%)			
Right	64 (58.2)		
Left	41 (37.3)		
Both	5 (4.5)		
IOP (mmHg), median (IQR)		$U = 2460$	<0.001‖
Glaucomatous eyes	22 (15, 32)		
Unaffected eyes	14 (10, 18)		
C/D, median (IQR)		$U = 363.5$	<0.001‖
Glaucomatous eyes	0.7 (0.6, 0.8)		
Unaffected eyes	0.3 (0.3, 0.4)		
Axial lengths (mm), mean ± SD		$t = 2.321$	0.023¶
Glaucomatous eyes	21.57 ± 2.09		
Unaffected eyes	20.50 ± 1.89		
Cornea diameter (mm)‡, median (IQR)		$U = 205$	<0.001‖
Glaucomatous eyes	12.5 (12.0, 13.0)		
Unaffected eyes	11.0 (11.0, 11.5)		

*IQR shown as 25%, 75%; †P value was obtained by comparing the gender or lateral constituent ratio to the PWS patients without glaucoma affected; ‡Corneal diameters were measured for the patients aged under 4 years under general anesthesia; §Chi-square test; ‖Mann-Whitney U-test; ¶Independent-samples t-test. PWS: Port-wine stain; IQR: Interquartile range; IOP: Intraocular pressure; C/D: Cup-to-disc ratio; SD: Standard deviation.

patients who had eye complaints might visit other clinics for their ocular examination. Thus, we believe that the incidence of glaucoma in these two groups was underestimated.

The anterior chamber angle and outflow defects in early-onset glaucoma are similar to those in primary congenital glaucoma (PCG), which represents another eye anterior anatomical defect and the most common form of glaucoma in infants.[22] Tanwar *et al*.[23] have found mutations in a PCG-related gene, CYP1B1, in SWS patients with early-onset glaucoma. Mandal and Chakrabarti determined that p. R390H homozygous mutations in CYP1B1 are also associated with severe ocular phenotypes in SWS patients. In our study, the under 4-year-old group showed a slight predominance of males (61.8%) in glaucoma, but the 4 to 18-year-old age group did not show this specific gender distribution. However, the same gender distribution has also been found in congenital glaucoma (male proportion was approximately 65%).[24] Unlike PCG, SWS has been demonstrated to be a somatic mutation disease,[25] but the similarities in the pathogenesis, gender distribution, and CYP1B1 mutations suggest a close relationship between PCG and early-onset glaucoma in SWS.

Previous research has commonly focused on using the PWS distribution regularity for SWS prediction. In our study, we focused on the following common major risk factor: an eye close to (V1 area) a PWS-affected area. Other risk factors, such as bilaterality, involvement of the whole V1–V3 distribution region, and PWS affecting the entire V1 distribution, have also been reported.[10,11,26] In our study, bilateral PWS with at least one eye close to a PWS-affected area was identified as a risk factor for glaucoma, which is consistent with previous reports. However, left-sided PWS is a not a risk factor of glaucoma in (V1 area) PWS-affected area in this study, which has not been previously reported. Previous study showed that the tissues from affected areas were genetically mosaic in SWS patients.[27] Shirley *et al*. speculated that somatic mutation in SWS might occur earlier in development, in progenitor cells that were precursors to a larger variety of cell types and tissues, leading to the syndromic phenotype.[25] Likewise, we assume that left-sided PWS may represent a late origin of the somatic mutation; thus, fewer progenitor cells are affected, preventing abnormalities in a larger variety of tissues.

Most patients were referrals from the Orthopedic Department or Laser Cosmetology Center; however, among these patients, some guardians also reported an "eye abnormality" in their children. The eye complaint rate before visiting the Ophthalmology Department for patients under 18 years old with glaucoma was only 20.19%. The low proportion of eye complaints in these patients might be due to a lack of self-awareness in the young patients, who only presented obvious clinical signs, such as significantly increased corneal diameter, corneal edema, or strabismus that could be found by their guardians. Glaucoma is a progressive optic neuropathy, and irreversible visual loss in this disease occurs due to glaucomatous neuronal death.[28] A referral system and eye health education are urgently needed for the related clinics and for PWS patients and their guardians. Early diagnosis and treatment of glaucoma are necessary to provide optic nerve protection. However, it is worth mentioning that the referral system may also contribute to selection bias of the study. A prospective study for PWS and SWS needs to be designed in the future.

Patients with eyes close to PWS-affected areas have a higher incidence of glaucoma during infancy and childhood. More attention should be paid to glaucoma screening for right lateral and bilateral PWS patients. The predominance of males in SWS early-onset glaucoma patients might be due to the limitation of the case number; however, it might also provide us a new clue of potential relationship between SWS and PCG. Further studies needed to reveal the similarities and differences of the anterior chamber angle defects between the two diseases. A referral system and eye health education are urgently needed for the related clinics and for PWS patients and their guardians.

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Conflicts of interest

There are no conflicts of interest.

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