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The risk of glaucoma associated with phacomatosis cesioflammea and phacomatosis cesioflammeo-marmorata

Background: The ocular features of phacomatosis pigmentovascularis (PPV) have rarely been reported, and glaucoma is the leading cause of blindness in patients with this condition. To protect vision in these patients, it is important to identify glaucoma as early as possible. *Objectives:* To systematically report the systemic and ocular manifestations of phacomatosis cesioflammea and phacomatosis cesioflammeo-marmorata, and to investigate a glaucoma risk scoring system. *Materials & Methods:* In this prospective study, patients with PPV from 2014 to 2021 were included. Clinical information was collected, and associations with glaucoma were evaluated. The suitability of the scoring system was assessed. A systematic literature review and analysis of reported cases of PPV was performed. *Results*: A total of 28 participants with PPV were included. Their ocular findings were similar, ranging from episcleral hyperpigmentation (78.5%), glaucoma (75%), choroid haemangioma (38%), and retinal vascular abnormalities (48%), to hyperpigmentation of the cornea, iris, lens and fundus. Glaucoma was associated with multiple factors, especially a thick choroid (odds ratio: 2.61; $p = 0.008$) and a diffuse mass-type of episcleral hyperpigmentation (odds ratio: 41.3; $p = 0.027$). The risk scoring system was characterized by high sensitivity (84%) and specificity (80%; AUC = 0.91) in predicting glaucoma. *Conclusion:* In addition to involving the systemic system, phacomatosis cesioflammea and phacomatosis cesioflammeo-marmorata also represent a specific spectrum of ophthalmic vascular malformations and hyperpigmentation. Early and periodic detailed ocular examination are recommended. The novel scoring system will help to tailor follow-up for visual protection.

Key words: glaucoma, nevus of Ota, ocular manifestation, phacomatosis pigmentovascularis, port-wine stains, pigmentation

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Phacomatosis pigmentovascularis (PPV) is a rare, congenital, multisystemic disorder characterized by the coexistence of extensive cutaneous vascular malformations and pigmented naevus [1]. Approximately 300 cases of PPV have been reported worldwide. Note that approximately 50% of patients with PPV also demonstrate extracutaneous involvement with variable manifestations [2], predominantly ocular or brain abnormalities [3]. However, only a few studies in the dermatologic literature mentioned ocular examination [2, 4, 5], and no case–control study has addressed glaucoma risk factors in PPV due to its rarity.

Glaucoma is the major cause of blindness (31%) in patients with phacomatosis cesioflammea, cesiomarmorata, and cesioflameo-marmorata [3]. Challenging management of the related glaucoma has been reported previously [6, 7]. Multiple mechanisms may be involved in the etiopathogenesis of glaucoma in PPV [8] but currently remain ambiguous. Recognition of the risk factors and the earliest possible detection of glaucoma are critical in preserving visual function. However, the ocular features and the glaucoma risk factors in PPV are not well understood.

For cosmetic purposes, most patients with PPV consult dermatologists first. It is incumbent on these practitioners to be fully aware of the ocular complications of PPV, and possibly to query patients with a risk of eye disease early for referral to an ophthalmologist. The pattern of birthmarks has been recognized as a predictor of glaucoma but includes diverse conditions (port wine stains [PWS], Sturge-Weber syndrome (SWS), nevus of Ota, and PPV) [9, 10]. Compared with those diseases, PPV is rarer and appears to be influenced by more factors. In this study, we aimed to present the detailed ocular manifestations in 28 patients with PPV and investigate a risk scoring system for the associated glaucoma. We also performed a systematic literature review to explore the ocular features of different types of PPV.

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Methods

This research comprises a case–control study for which approval was obtained from the Ethical Committee of Zhongshan Ophthalmic Center (NO. 2020KYPJ106) and the tenets of the Declaration of Helsinki were adhered to. All subjects and their parents received explanations of the purposes, procedures, risks, and benefits of this study. Informed consent was obtained.

All subjects who were both diagnosed with PPV and were referred to Zhongshan Ophthalmic Center from January 2014 were included. Routine follow-up for new-onset glaucoma screening and detection of the progression of glaucoma was planned for each subject after their first visit. PPV was defined as the coexisting presentation of cutaneous vascular malformations and pigmented naevus. All subjects were requested to undergo physical examination, comprehensive ocular examination, routine laboratory studies, abdominal ultrasound and brain magnetic resonance imaging (MRI). Any patient who refused was excluded from the study. PPV was classified into six types according to the updated Happle classification [11]. The distribution pattern of pigmentary naevus at the level of the trunk and limbs was classified into four types ("cape", "bathing trunk", "fingerless glove" and "toeless stocking" distribution), and at the level of the head was classified into another three types (frontonasal, mid-face and mandibular) [12]. Eyes with glaucoma were considered as cases, and those without glaucoma were considered as controls.

Analysis of facial capillary naevus and pigmented naevus was performed for patients without a history of cutaneous laser therapy at the first visit. Facial capillary naevus was documented by photography and classified according to the facial PWS classification system (S1, S2, and S3) [9, 13], which is based on embryonic facial vasculature distribution, rather than the trigeminal nerve. The colour parameters of facial capillary naevus were expressed using the L*, a*, and b* colour system of the Commission Internationale de l'Eclairage (CIELAB). Colour was assessed in a single-blind manner by Dr. YF Yang using Adobe Photoshop, and values were converted by optical equations described in a previous study [14]. The values of ΔE, Δa^*, and Δb^* were defined as the differences between naevus and normal-like skin on the face.

Ocular examination included slit-lamp biomicroscopy, intraocular pressure (IOP) evaluation, gonioscopy, fundus photography, visual field testing, B-scan ultrasonography, and fundus angiography. Notably, gonioscopy and angiography were conducted on cooperative patients or children under anaesthesia. Visual field testing was conducted on cooperative patients older than 12 years old. The diagnosis of glaucoma was made by the same ophthalmologist (Pro. Yu MB) according to the Childhood Glaucoma Research Network (CGRN) diagnostic criteria for children [15] and the criteria of the United Kingdom Glaucoma Treatment Study (UKGTS) for adolescents and adults [16].

Limbal involvement (clock hour) and the width of the episcleral pigmentation were collected. The width was defined as the distance from the area with limbus-involved pigmentation to the most distal boundary of the pigmented area. We classified episcleral hyperpigmentation into two types: (1) scattered-plaque type (SP type) (affected area <two connected quadrants); and (2) diffuse-mass type (DM type) (affected area >2 connected quadrants).

Literature review

A systematic literature search was performed in PubMed, Web of Science, Embase and Scopus (1982-2021) to include all reported patients diagnosed with "phacomatosis/phakomatosis pigmentovascularis". We critically assessed the appearance of each patient and reclassified them. Cases mentioned only in the abstract were not included. Cases with naevus roseus were excluded due to the general confusion and misdiagnosis of phacomatosis spilorosea and phacomatosis melanorosea [11]. The birthmarks, type of PPV and the ocular manifestations of the patients were extracted from each article.

Statistical analysis

Descriptive data are presented as mean ± SD or median (interquartile range [IQR]). Data that were non-normally distributed in the two groups were compared using a non-parametric test followed by the Kruskal-Wallis test and $\chi 2$ test. The correlations among variables were analysed with Spearman's correlation analysis. Backward variable selection was used to construct a multivariate logistic regression model. Each significant feature in the univariate logistic regression model was scored with 1 point, and each significant feature in the multivariate model was scored with 2 points. The total risk score was investigated through receiver operating characteristic (ROC) curve analysis. Two-sided tests were considered statistically significant with a p value <0.05. All statistical analyses were performed with SPSS software (SPSS, Inc., Chicago, IBM).

Results

Subject characteristics

A total of 28 subjects with PPV were included from January 2014 to January 2021. Except for four patients with glaucoma who were followed via telephone, all patients were followed in our outpatient department. Through May 2021, the average follow-up period was 37 months (range: 1.5-89 months). The mean age at the first visit was 2.73 years (range: 0.03-26.4 years). Fifteen subjects (54%) were male.

Systemic involvement

Cerebral MRI of 25 patients was available, demonstrating abnormalities in nine (36%), including: varicose veins, loss of the posterior communicating artery, contrast-enhanced leptomeningeal vascular anomalies, choroid plexus cysts and cerebral atrophy. Other systemic involvement included bilateral symmetrical triangular alopecia (2/28), lower limb asymmetry (2/28), seizures (6/28) and anaemia (2/28).

Table 1. Clinical characteristics of patients with phacomatosis cesioflammea or phacomatosis cesioflammeo-marmorata.

Characteristic	Values
Type of PPV † (no. patients, %)	
Cesioflammea	25 (89)
Cesioflammeo-marmorata	3 (11)
Naevus anaemicus † (no. patients,%)	15 (54)
Distribution pattern of pigmented naevi † (no. patients, %)	
Cape distribution	17 (61)
Bathing trunk distribution	19 (68)
Fingerless glove distribution	9 (32)
Toeless stocking distribution	7 (25)
MRI abnormalities †† (no. patients, %)	9 (36)
Glaucoma † (no. patients, %)	21 (75)
Bilateral glaucoma	10 (36)
No. eyes with glaucoma	31
Distribution of ipsilateral facial capillary naevus (no. eyes, %)	
S1, S2	6 (66.7)
S1, S2, S3	23 (74.2)
S1, S3	2 (100)
S1/S2/S3 only	0
Eyelid involvement of capillary naevus (no. eyes, %)	
Without	1 (7)
Upper eyelid	2 (50)
Lower eyelid	4 (67)
Both upper and lower eyelids	24 (75)
Distribution of ipsilateral nevus of Ota (no. eyes, %)	
Without	18 (56)
Frontonasal	8 (53)
Mid face	7 (58)
Frontonasal & mid face	4 (66)
Eyelid involvement of nevus of Ota (no. eyes, %)	
Without	23 (58)
Upper eyelid	3 (38)
Lower eyelid	2 (67)
Both upper and lower eyelids	3 (60)
Episcleral hyperpigmentation (no. eyes, %)	
Scattered plaque type	6 (55)
Diffuse mass type	20 (74)
Iris heterochromia (no. eyes, %)	30 (64)
Reduction of iris crypt (no. eyes, %)	26 (67)
Iris mammillation (no. eyes, %)	8 (73)
Choroidal haemangioma ††† (no. eyes, %)††	20 (100)
Abnormal FFA ‡ (no. eyes, %)	11 (92)
Abnormal ICGA § (no. eyes, %)	3 (100)

MRI: magnetic resonance imaging; FFA: fundus fluorescein angiography; ICGA: indocyanine green angiography.† A total of 28 participants were included.†† MRI examination was only available in 25 cases and unavailable temporarily in three children who did not have glaucoma.††† Ultrasonograph was performed for 29 and 23 eyes with and without glaucoma, respectively.‡ FFA was performed for 11 (21 eyes) and 4 patients (8 eyes) with and without glaucoma, respectively.§ ICGA was performed in 8 (15 eyes) and 1 patient (2 eyes) with and without glaucoma, respectively.

Cutaneous findings

The cutaneous characteristics of our subjects are listed in *table 1*. Phacomatosis cesioflammea (89%) was the most common type (*figure 1A-C*). All patients had bilateral extensive naevus. Facial capillary naevus varied in terms of how dark it was (*figure 2A, B*) and was present in 27 patients, 19 of whom (70%) had bilateral lesions. The mosaic type of capillary naevus showed a flag-like pattern.

Sixteen patients (57%) had lip hypertrophy, mostly with capillary naevus involving S3. Oral mucosal vascular malformation and plaque pigmentation were observed in 78% and 46% of patients, respectively. Genital mucosa was normal.

Ocular involvement

Ocular features are shown in *table 1*, all of which were ipsilateral to the facial capillary naevus. Vascular malformation (*figure 2C-H*) presented on the sclera, retina and choroid in 64%, 41% and 38% of eyes, respectively. Choroidal thickness gradually increased by approximately 0.2 mm without choroidal/retinal detachment over eight years of follow-up. Retinal vascular malformations were stable during follow-up, and most of them involved peripheral vascular leakage and tortuous capillaries, followed by increased vascular branching. Peripheral nonperfusion or venous shunts were present in one eye. The colour scores (ΔE, Δa^*) of the facial capillary naevus were positively correlated with choroidal

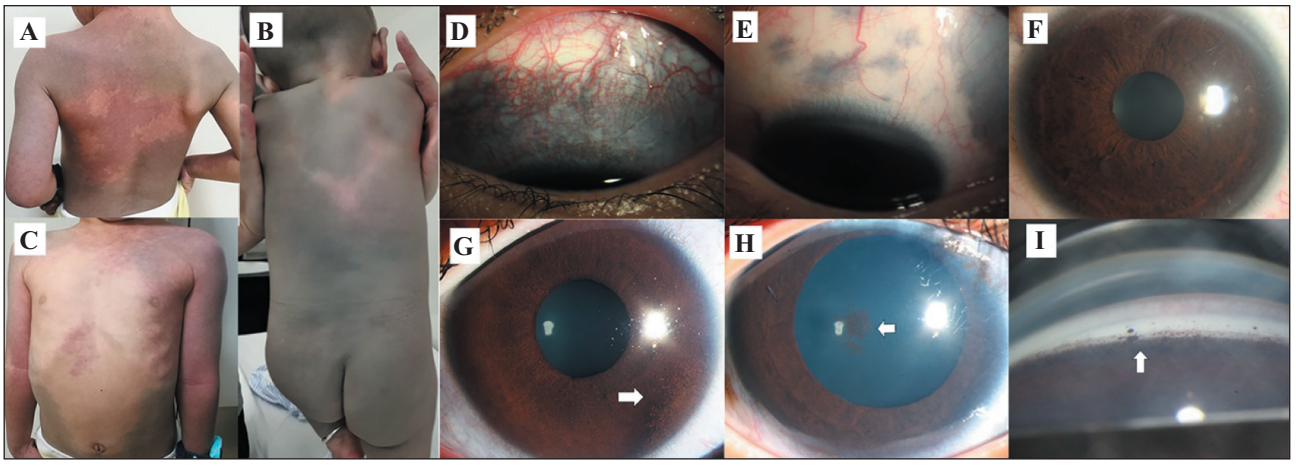

Figure 1. Segmental dermal melanocytosis and ocular hyperpigmentation in patients with phacomatosis pigmentovascularis. **A-C**) Extensive grey macules in a "cape" distribution and "bathing trunk" distribution, overlapping with naevus flammeus. **D**) Episcleral hyperpigmentation presents as diffuse mass-type in a patient with glaucoma and (**E**) scattered plaque-type in a patient without glaucoma. **F**) Diffuse iris heterochromia with iris mammillation. **G**) Obvious hyperpigmentation is detected on the pericornea (white arrow) with a reduced number of iris crypts. **H**) Punctate hyperpigmentation on the lens (white arrow) and iris heterochromia are shown in a patient treated with 1% tropicamide for mydriasis. **I**) Gonioscopy reveals increased pigmentation of the anterior chamber angle.

thickness ($p < 0.001$). Hyperpigmentation mostly presented on the sclera, anterior chamber angle, and iris, and for a few patients, the cornea and lens (*figure 1D-I*). Bilateral episcleral hyperpigmentation was common. Of note, one patient had Peters-like anomaly.

Surprisingly, laser spot-like pigmentation was observed on the fundus of a patient after two sessions of photodynamic therapy (PDT) for the treatment of facial PWS (Annexe A*supplementary figure 1*). However, the impact on visual function could not be assessed due to non-cooperation of the patient.

Glaucoma risk factor analysis associated with phacomatosis cesioflammea and phacomatosis cesioflammeo-marmorata

Twenty-one patients had glaucoma in 31 eyes at presentation, and 52% of them were younger than 1.5 years old. There was no new-onset glaucoma during follow-up. The median age at diagnosis of glaucoma (1.29 years) was slightly greater than the age at the last follow-up visit among patients without glaucoma (1.24 years) ($p > 0.1$). The median follow-up period was longer for patients with glaucomatous eyes (61.17 months, relative to controls: 5.73 months) ($p = 0.01$).

At the patient level, glaucoma was not associated with naevus anaemicus ($p = 0.076$) or total pigmentary naevi involving body segments ($p = 0.274$). At the eye level, glaucoma was not associated with nevus of Ota, but associated with PWS, iris heterochromia (OR = 14.118; $p = 0.016$) and choroid haemangioma (CH) ($p < 0.01$). Univariate logistic regression (*table 2*) revealed glaucoma associated with darker facial PWS, PWS with S1S2 involvement, PWS with both upper and lower eyelid involvement, a thick choroid, DM-type episcleral hyperpigmentation, iris heterochromia and a reduction in iris crypts. In the multivariate model, a thick choroid and DM-type episcleral hyperpigmentation were associated with glaucoma.

The risk scoring system demonstrated good accuracy in predicting glaucoma associated with the two types of PPV with a cut-off of 6.5 (area under the ROC curve: 0.91 [AUC], 95% CI: 0.85-0.99) (Annexe A*supplementary figure 2*) and high sensitivity (84%) and specificity (80%).

Ocular involvement in reported cases

We included 238 patients from 95 articles presenting with certain types of PPV and having undergone ocular examination, including 39 patients without facial PWS. The details of the reported ocular features are summarized in *table 3*. Consistent with our results, ocular involvement mostly occurred in patients with phacomatosis cesioflammea. Episcleral hyperpigmentation was the most common manifestation, followed by glaucoma. Most glaucoma (74%) occurred before the age of three. The incidence of glaucoma was 32% in patients with phacomatosis cesioflammea, and 55% and 27% in patients with phacomatosis cesiomarmorata and phacomatosis cesioflammeo-marmorata, respectively. However, glaucoma was not significantly correlated with type of naevus cesius–associated PPVs ($p = 0.805$) or naevus anaemicus ($p = 0.517$). CH and retinal vascular abnormalities were rarely reported.

A summary of the data based on the literature search and the present study is presented in Annexe A*supplementary tables 1, 2*.

Discussion

A particular spectrum of ophthalmic features associated with phacomatosis cesiomarmorata and phacomatosis cesioflammeo-marmorata was presented in our study. Our results demonstrate a significantly higher risk of glaucoma in patients presenting with CH, DM-type episcleral hyperpigmentation, and dark facial PWS, especially involving

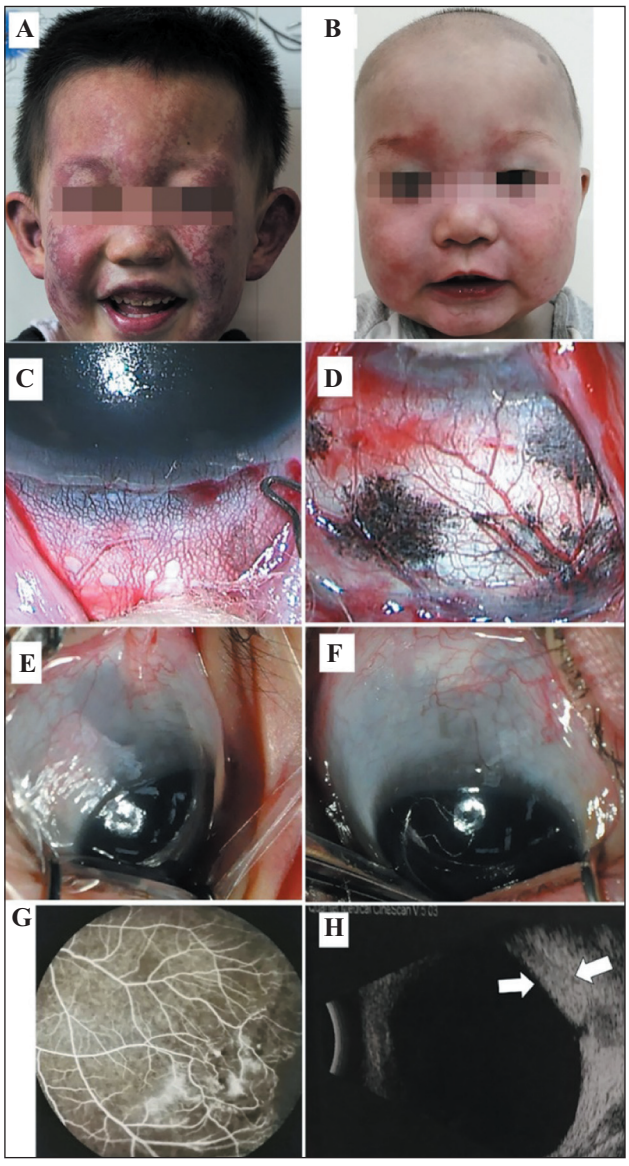

Figure 2. Capillary naevus and ocular vascular malformation in patients with phacomatosis pigmentovascularis. Facial naevus flammeus is darker in a patient with glaucoma (**A**) than a patient without glaucoma (**B**). **C**, **D**) Dilated episcleral vessels with increased density present a reticulate appearance with episcleral melanosis. **E**, **F**) Dark and total perilimbal episcleral hyperpigmentation are shown in the eyes. **G**) Fundus fluorescein angiography shows peripheral retinal vascular leakage, venous shunts and tortuous capillaries. **H**) Choroidal haemangioma (white arrow) demonstrated by B-scan ultrasonography.

S1S2. Most glaucoma occurs in early childhood. Early evaluation of the risk of glaucoma based on our risk scoring system may help to detect high-risk patients and tailor individual lifelong follow-up.

To further understand the relationship between ophthalmic complications and the different types of PPV, we critically reviewed and assessed the published cases of PPV. Of note, in most published cases, eyes were not assessed systematically and follow-up was short, thus the incidence of ocular disorders might have been underestimated. Consistent with a previous study [3], ocular complications were most common in patients with phacomatosis cesioflammea. However, we could not demonstrate a significant correlation between glaucoma and type of naevus cesius–associated PPV. In a large study of PPV, systemic involvement was not associated with the extent of naevus, presence of naevus anaemicus, site of PWS or type of mosaicism [17]. Our risk scoring system showed that ocular features were risk factors for glaucoma. Therefore, for glaucoma, these risk factors, rather the type of PPV, are recommended for surveillance. We suggest that frequent ophthalmic examination is unnecessary for patients whose risk scores are less than 6. Other patients will need follow-up visits every three months initially, although eventually, this can be reduced to every six months.

CH and retinal vascular abnormalities were common in our patients with glaucoma, but were rarely reported previously due to a lack of systematic assessment of the fundus. Consistent with our results, studies demonstrated that CH only occurred in patients with glaucoma [4, 18–20]. Mandal *et al*. [6] recently reported that an overlooked diagnosis of retinal vascular abnormalities could potentially lead to retinal detachment after trabeculectomy for treating glaucoma. Therefore, fundus examination in patients with PPV, even children, warrants attention.

Our results also suggest that the distribution of facial PWS is a predictive factor of glaucoma. In the literature review, numerous studies described PWS according to the distribution of the trigeminal nerve, however, this view is outdated and should be abandoned [21]. A recent study suggested that PWS follows the distribution of the embryonic facial vasculature [13], and PWS involving the eyelids and forehead [19] or S2 is a risk factor for glaucoma [9]. Based on this new classification, our results are consistent with the finding that S1S2 involvement is related to glaucoma in patients with PPV.

In the present study, the hue of the facial capillary naevus was positively related to the severity of CH. Regarding pathogenesis, *GNAQ* mutations have been confirmed in Sturge-Weber syndrome and PWS [22], episcleral haemangioma [23] and CH [24], and progressive dilation of the superficial cutaneous vascular plexus has been reported to cause PWS [25]. Therefore, dark facial capillary naevus possibly reflects severe congestion and a thicker choroid as well as greater episcleral venous pressure (EVP), leading to high intraocular pressure (IOP), as the pathogenesis of late-onset glaucoma. Though most glaucoma occurs in early childhood in patients with PPV, those with facial capillary naevus that gradually darkens should be monitored closely regarding IOP. Of note, assessment of naevus would be impacted after laser treatment.

Nevus of Ota has previously been shown not to be correlated with glaucoma [19]. However, as episcleral hyperpigmentation has a higher prevalence in patients with PPV [17], it warrants more attention. Similar to our results, Teekhasaenee *et al*. [26] proposed that the coexistence of naevus flammeus and oculodermal melanocytosis was associated with congenital glaucoma in patients with PPV. Aqueous outflow obstruction, secondary to excessive melanocytes of the trabecular meshwork, leads to high IOP [8]. Based on this theory, the extent of elevated IOP possibly depends on the number of melanocytes in the context of facial PWS. However, the exact extent of episcleral pigmentation has

Table 2. Analysis of risk factors of glaucoma.

Univariate analysis			Multivariate analysis‡	
Value	**Odds ratio (95% CI)**	***p* value**	**Odds ratio (95% CI)**	***p* value**
Age	0.822 (0.596-1.133)	0.232		
Facial PWS distribution				
S1,S2§	18.455 (3.594-94.766)	0.006	29.658 (0.493-178.545)	0.105
PWS involvement of eyelid				
Both UL and LL§	7.286 (2.218-23.938)	0.001		0.798
Colour value of facial capillary naevus				
△E†§	1.108 (1.040-1.180)	0.001		
△a*§	1.236 (1.088-1.405)	0.001		0.249
△b*	0.972 (0.835-1.131)	0.712		
Episcleral pigmentation				
Limbal involvement§	1.260 (1.072-1.480)	0.005		0.776
Width of involvement >2mm	1.607 (1.233-2.093)	<0.001	41.296(1.542-110.566)	0.428
Diffuse Mass type§	4.68 (1.49-14.64)	0.008		0.027
Iris				
Iris heterochromia§	14.118 (1.624-122.701)	0.016		0.449
Reduction of iris crypts§	4.800 (1.39-16.55)	0.013		0.976
Choroidal thickness§,				
Per 0.1mm	1.875 (1.329-2.645)	<0.001	2.612 (1.280-5.331)	0.008

†*The data of △E was influenced by △a* and was excluded from the multivariate model.*‡*Based on the univariate logistic regression model, the factors associated with glaucoma were used for the multivariate logistic regression with a backward strategy.*§*Difference is significant at p < 0.05.*

rarely been reported [27]. Instead of "diffuse oculodermal melanocytosis", a vague term, we suggest a more specific classification for increased attention to the DM-type.

PDT with haemoporfin has been demonstrated to be effective for PWS [28, 29] with minimal adverse events. However, we observed retinal damage after PDT, however,

Table 3. Ocular manifestations in different types of phacomaotsis pigmentovascularis.

Type of PPV	Ocular anomaly in reported cases (number of cases)	Ocular anomaly in this study (number of cases)
Phacomatosis cesioflammea (206 reported cases and 25 cases in the present study)	Episcleral hyperpigmentation (97) Glaucoma (66) Choroidal melanoma [27, 30–32] (15) Choroidal melanocytosis (6) Iris heterochromia [18, 27, 30, 32–34] (9) Choroidal haemangioma [18, 19, 35, 36] (3) Iris mamillation [18, 37, 38] (6) Goniodysgenesis/gonio-synechia [39-41] (2) Retinal vascular abnormality [2, 42] (4) Iris hamartomas [43, 44] (1) Megalocornea [37, 45] (3) Buphthalmos [46, 47] (2) Trabecular hyperpigmentation [41] (1) Astigmatism (1)	Episcleral hyperpigmentation (16) Glaucoma (17) Iris heterochromia (20) Choroidal haemangioma (12) Iris mamillation (4) Pigmented cornea (1) Fundus hyperpigmentation (7) Lenticular hyperpigmentation (3) Retinal vascular abnormality (4) Corneal leukoplakia (1) Gonio-synechia(1)
Phacomatosis cesiomarmorata (18 reported cases)	Episcleral hyperpigmentation (10) Glaucoma (7) Small cornea [48] (2) Trabecular hyperpigmentation [41] (1)	-
Phacomatosis cesioflammeo-marmorata (11 reported cases and 3 cases in the present study)	Episcleral hyperpigmentation (4) Glaucoma (3) Retinal vascular abnormality [2, 42] (1) Buphthalmos [49] (1)	Episcleral hyperpigmentation (4) Glaucoma (3) Iris heterochromia (3) Retinal vascular abnormality (3) Iris mamillation (2) Choroidal haemangioma (2) Pigmented cornea (1)
Phacomatosis melano-cesioflammea (3 reported cases)	Episcleral hyperpigmentation (2)	-

more observational studies are needed. Fundus examination before and after PDT is recommended, especially for patients with glaucoma.
Several factors limit the interpretation of our study. The follow-up period was relatively short, and patients without glaucoma could have developed glaucoma later in life. Our specialised tertiary referral centre may have introduced bias regarding the high frequency of glaucoma in this study. Moreover, patients were not equally distributed with regards to the different types of PPV between the present cases and published cases. Lastly, an investigation into the genes affecting PPV was lacking. However, a cohort of rare diseases, including PPV, has already been established, and the related genetic studies are underway.

Conclusions

This research comprises the largest study comprehensively investigating different ocular features of PPV. In patients with naevus cesius–associated PPVs, the ophthalmic manifestations are similar. Detailed ocular evaluation, including fundus examination, and lifelong follow-up, are recommended. Our novel risk scoring system may help in providing information on individualized risk in patients and scheduling periodic ocular examinations.

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Conflicts of interest: none.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ejd.2022.4317.
Figure S1 Laser spot-like pigmentation (arrow) developing around the optic nerve after photodynamic therapy for facial naevus flammeus.
Figure S2 ROC curve for the risk scoring system to investigate the ability to predict glaucoma.
Table S1 Characteristics of patients with phacomatosis pigmentovascularis.
Table S2 Studies linking glaucoma to phacomatosis pigmentovascularis.

References

1. Ota M, Kawamura T, Ito N. Phacomatosis pigmentovascularis (Ota). *Jpn J Dermatol* 1947; 52: 1-3.

2. Thanos A, Shwayder T, Papakostas TD, *et al*. Retinal vascular abnormalities in phakomatosis pigmentovascularis. *Ophthalmology Retina* 2019; 3: 1098-104.

3. Kumar A, Zastrow DB, Kravets EJ, *et al*. Extracutaneous manifestations in phacomatosis cesioflammea and cesiomarmorata: case series and literature review. *Am J Med Genet A* 2019; 179: 966-77.

4. van der Merwe EB, Bhika RE, Meyer D. Glaucoma in phacomatosis pigmentovascularis in a young African adolescent boy: a case report. *J Glaucoma* 2019; 28: e124-5.

5. Chiu HH, Chen GS, Wu CS, Ke CL, Cheng ST. Phakomatosis cesioflammea with late-onset glaucoma and acquired nevus spilus-like lesion – 15 years of follow-up. *Int J Dermatol* 2009; 48: 416-8.

6. Mandal A, Kodavati K, Gothwal V. Outcomes of management of glaucoma in phacomatosis pigmentovascularis over the last three decades: a single-center experience. *Ophthalmol Glaucoma* 2021; 5: 101-9.

7. Yang Y, Guo X, Xu J, Ye Y, Liu X, Yu M. Phakomatosis pigmentovascularis associated with Sturge-Weber syndrome, Ota nevus and congenital glaucoma. *Medicine* 2015; 94: e1025.

8. Abdolrahimzadeh S, Pugi DM, de Paula A, Scuderi G. Ocular manifestations in phakomatosis pigmentovascularis: current concepts on pathogenesis, diagnosis, and management. *Surv Ophthalmol* 2021; 66: 482-92.

9. Ha A, Kim JS, Baek SU, *et al*. Facial port-wine stain phenotypes associated with glaucoma risk in neonates. *Am J Ophthalmol* 2020; 220: 183-90.

10. Wu Y, Yu RJ, Chen D, *et al*. Glaucoma in patients with eyes close to areas affected by port-wine stain has Lateral and gender predilection. *Chin Med J (Engl)* 2017; 130: 2922-6.

11. Torchia D. Phacomatosis spilorosea versus phacomatosis melanorosea: a critical reappraisal of the worldwide literature with updated classification of phacomatosis pigmentovascularis. *Acta Dermatovenerol Alp Pannonica Adriat* 2021; 30: 27-30.

12. Kinsler VA, Larue L. The patterns of birthmarks suggest a novel population of melanocyte precursors arising around the time of gastrulation. *Pigment Cell Melanoma Res* 2018; 31: 95-109.

13. 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: 861-7.

14. Vander Haeghen Y, Naeyaert JM, Lemahieu I, Philips W. An imaging system with calibrated color image acquisition for use in dermatology. *IEEE Trans Med Imaging* 2000; 19: 722-30.

15. Weinreb RN, Grajewski AL, Papadopoulos M, Grigg J, Freedman S. *Childhood glaucoma*. Amsterdam: Kugler Publications, 2013.

16. Garway-Heath DF, Lascaratos G, Bunce C, Crabb DP, Russell RA, Shah A. The United Kingdom glaucoma treatment study a multicenter, randomized, placebo-controlled clinical trial: design and methodology. *Ophthalmology* 2013; 120: 68-76.

17. Shin H, Kim YG, Kim YE, Park H. Clinical characteristics and treatment of 52 cases of phakomatosis pigmentovascularis. *J Dermatol* 2019; 46: 843-8.

18. Plateroti AM, Plateroti R, Mollo R, Librando A, Contestabile MT, Fenicia V. Sturge-weber syndrome associated with monolateral ocular melanocytosis, iris mammillations, and diffuse choroidal haemangioma. *Case Rep Ophthalmol* 2017; 8: 375-84.

19. Rujimethapass N, Manuskiatti W, Wanitphakdeedecha R, Petchyim S. Ocular manifestations of facial port-wine stain, nevus of Ota and phakomatosis pigmentovascularis in Asians. *J Am Acad Dermatol* 2021; 85: 1194-200.

20. Wu Y, Huang L, Liu Y, Xu L, Guo W. Choroidal alterations of Sturge-Weber syndrome secondary glaucoma and non-glaucoma port-wine stain patients distinguished by enhanced depth imaging optical coherence tomography. *BMC Ophthalmol* 2020; 20: 477.

21. 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: 473-80.

22. 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: 1971-9.

23. Wu Y, Peng C, Huang L, *et al*. Somatic GNAQ R183Q mutation is located within the sclera and episclera in patients with Sturge-Weber syndrome. *Br J Ophthalmol* 2021; 106: 1006-11.

24. Francis JH, Milman T, Grossniklaus H, *et al*. GNAQ mutations in diffuse and solitary choroidal hemangiomas. *Ophthalmology* 2019; 126: 759-63.

25. Smoller BR, Rosen S. Port-wine stains. A disease of altered neural modulation of blood vessels? *Arch Dermatol* 1986; 122: 177-9.

26. Teekhasaenee C, Ritch R. Glaucoma in phakomatosis pigmentovascularis. *Ophthalmology* 1997; 104: 150-7.

27. Shields CL, Di Nicola M, Pellegrini M, Shields JA. Choroidal melanoma in phakomatosis pigmentovascularis with Klippel-Trenaunay syndrome. *Retina* 2018; 38: 2220-7.

28. Gao K, Huang Z, Yuan K, Zhang B, Hu Z. Side-by-side comparison of photodynamic therapy and pulsed-dye laser treatment of port-wine stain birthmarks. *Br J Ophthalmol* 2013; 168: 1040-6.

29. Wu Q, Tu P, Zhou G, *et al*. A dose-finding study for hemoporfin in photodynamic therapy for port-wine stain: a multicenter randomized double-blind phase IIb trial. *Photodermatol Photoimmunol Photomed* 2018; 34: 314-21.

30. Tran HV, Zografos L. Primary choroidal melanoma in phakomatosis pigmentovascularis IIa. *Ophthalmology* 2005; 112: 1232-5.

31. Zhou H, Han JD, Mao RX, Chen MK. Choroidal melanoma in phacomatosis pigmentovascularis cesioflammea. *Indian J Dermatol Venereol Leprol* 2016; 82: 339-42.

32. Fry MV, Williams BK Jr., Kim HJ, Nicola MD. Choroidal melanoma in phakomatosis pigmentovascularis with overlapping Sturge-Weber syndrome and Klippel-Trenaunay syndrome. *Retin Cases Brief Rep* 2021 Apr 16. doi: 10.1097/ICB.0000000000001154. Online ahead of print.

33. Saricaoglu MS, Guven D, Karakurt A, Sengun A, Ziraman I. An unusual case of Sturge-Weber syndrome in association with phakomatosis pigmentovascularis and Klippel-Trenaunay-Weber syndrome. *Retina* 2002; 22: 368-71.

34. Shields CL, Kligman BE, Suriano M, *et al*. Phacomatosis pigmentovascularis of cesioflammea type in 7 patients: combination of ocular pigmentation (melanocytosis or melanosis) and nevus flammeus with risk for melanoma. *Arch Ophthalmol* 2011; 129: 746-50.

35. Finklea L, Mohr M, Warthan M, Darrow D, Williams J. Two reports of phacomatosis pigmentovascularis type IIb, one in association with Sturge-Weber syndrome and Klippel-Trenaunay syndrome. *Pediatric Dermatol* 2010; 27: 303-5.

36. Patil B, Sinha G, Nayak B, Sharma R, Kumari S, Dada T. Bilateral Sturge-Weber and phakomatosis pigmentovascularis with glaucoma, an overlap syndrome. *Case Rep Ophthalmol Med* 2015; 2015: 106932.

37. Vidaurri-de la Cruz H, Tamayo-Sánchez L, Durán-McKinster C, Orozco-Covarrubias Mde L, Ruiz-Maldonado R. Phakomatosis pigmentovascularis II A and II B: clinical findings in 24 patients. *J Dermatol* 2003; 30: 381-8.

38. Krema H, Simpson R, McGowan H. Choroidal melanoma in phacomatosis pigmentovascularis cesioflammea. *Can J Ophthalmol* 2013; 48: e41-42.

39. Kono T, Erçöçen A, Chan H, *et al*. Treatment of phacomatosis pigmentovascularis: a combined multiple laser approach. *Dermatol Surg* 2003; 29: 642-6.

40. Singal A, Mittal H, Aggarwal A, Das S, Manchanda S. Phacomatosis pigmentovascularis type 2b (phacomatosis cesioflammea) with double superior vena cava, abdominal varicosities, and natal tooth: Novel associations. *Pediatr Dermatol* 2018; 35: e151-4.

41. Singh K, Dangda S, Mutreja A, Bhattacharyya M, Jaisingh K. Bilateral phacomatosis pigmentovascularis in a young male with developmental glaucoma and varicose veins. *J Curr Glaucoma Pract* 2018; 12: 94-8.

42. Gupta A, Dubey S, Agarwal M. A case of Sturge-Weber syndrome in association with phacomatosis pigmentovascularis and developmental glaucoma. *J AAPOS* 2007; 11: 398-9.

43. Van Gysel D, Oranje A, Stroink H, Simonsz H. Phakomatosis pigmentovascularis. *Pediatr Dermatol* 1996; 13: 33-5.

44. Madke B, Kar S, Gangane N, Singh N. Phacomatosis cesioflammea in association with von Recklinghausen disease (neurofibromatosis type I). *Cutis* 2017; 99: e35-7.

45. Senthilkumar VA, Krishnadas R, Puthuran GV, Ravichandar A. Early onset glaucoma manifesting as buphthalmos in an infant with phakomatosis pigmentovascularis type IIa. *Ophthalmol Glaucoma* 2020; 3: 481-3.

46. de Luna ML, Barquin MA, Casas JG, Sidelsky S. Phacomatosis pigmentovascularis with a selective IgA deficiency. *Pediatr Dermatol* 1995; 12: 159-63.

47. Ben Saif GA, AlShehab SA, Almutawa A. Unusual combination of pigmentary lesions. *Int J Dermatol* 2010; 49: 1059-62.

48. Torrelo A, Zambrano A, Happle R. Cutis marmorata telangiectatica congenita and extensive mongolian spots: type 5 phacomatosis pigmentovascularis. *Br J Dermatol* 2003; 148: 342-5.

49. Chehad AS. New case of phacomatosis cesio-flammeo-marmorata: the time is right to review the classification for phacomatosis pigmentovascularis. *Int J Dermatol* 2019; 58: e237-40.