Outcomes of Retinal Pigment Epithelial Detachment in Vogt-Koyanagi-Harada Disease

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Research Article

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Abstract

Introduction

The aim of this study was to report the clinical profile and outcomes of retinal pigment epithelial detachment (PED) in Vogt-Koyanagi-Harada (VKH) disease, and to evaluate the correlation between PED and the subsequent development of central serous chorioretinopathy (CSC) throughout the whole corticosteroid treatment course.

materials and methods

A total of 470 eyes with VKH were reviewed, and 12 eyes with VKH and PED were recruited. Patients were divided into two groups according to the CSC onset or not throughout the whole course (CSC group and non-CSC group). Best-corrected visual acuity (BCVA) improvement, and PED angle (PEDA, the angle between the two lines of the vertex of the lifted retinal pigment epithelium to the two edge points of the Bruch membrane) were compared between the two groups.

Results

The prevalence of PED and CSC in VKH was 2.55% (12/470) and 1.06% (5/470), respectively. BCVA improvement in the non-CSC group was greater than that in the CSC group, but without a statistical difference (P=0.25). PEDA was significantly smaller in the CSC group than in the non-CSC group (P=0.03).

Discussion

PEDA is an ideal parameter to reflect hydrostatic pressure and stretches for RPE. As PED predisposes to the development of CSC in selected VKH eyes, PEDA may be a valuable predictive factor for the development of CSC in VKH patients.

Introduction

Vogt-Koyanagi-Harada (VKH) disease is an immune-mediated multisystem disorder characterized by bilateral ocular inflammation, neurological (meningeal), auditory, and dermatological symptoms [1]. The hallmarks of posterior ocular manifestations at the acute stage are bilateral multiple exudative retinal detachments (ERD), optic disc swelling, and thickening of the posterior choroid [1]. Multimodal imaging examinations, including fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT), provide aid for diagnosis and change evaluations [2]. The mainstream therapeutic regimen is a rapid and aggressive high-dose systemic corticosteroid to suppress acute intraocular inflammation, followed by gradual tapering [1-3]. The early and aggressive systemic corticosteroids are the cornerstone of initial treatment for VKH [1], the oral corticosteroid should be tapered off slowly and maintained for at least 6 months for avoiding the high recurrence rate and poor prognosis [4].

Pigment epithelial detachment (PED) is the anatomical separation between the basement membrane of the retinal pigment epithelium (RPE) and the inner collagenous layer of the Bruch membrane [5]. Isolated serous PED is frequently associated with choroidal hyperpermeability on ICGA and is regarded as an intermediate stage between pachychoroid and classic CSC [6]. Nonetheless, serous PED is an unusual finding in acute VKH characterized by choroidal thickening [7]. Although VKH and CSC diseases are different in nature, they occasionally require differentiation because they share some common clinical features, including bullous serous retinal detachment on OCT and multifocal leakage on FFA. Sometimes CSCs can also develop in VKH patients [8]. Early diagnosis of CSC in VKH patients is important because the therapeutic strategies for these two diseases are contradictory, and adjustment of treatment is imperative once CSC occurs.

Few studies have investigated the clinical value of PED in VKH and its relationship with subsequent CSC development. Therefore, we conducted the first longitudinal analysis to describe the outcomes of PED in VKH cases and searched for a simple predictive factor for different clinical prognoses based on the PED contour. We found that PED with high choroidal hydrostatic pressure predisposes to the later development of CSC in VKH cases during corticosteroid therapy. Hence, we hypothesized that the contour of PED between the lifted edge of the RPE and Bruch membrane could be a predictor for subsequent development of CSC in VKH cases with corticosteroid treatment.

Materials And Methods

Institutional review board approval (No.2020KY (L)-37) was obtained from Tianjin Medical University Eye Hospital (TMUEH) for the retrospective review of clinical records for all VKH patients at the Uveitis & Ocular Immune Department from August 1, 2011, to August 31, 2020. This research adhered to the tenets of the Declaration of Helsinki. According to the 2001 diagnostic criteria [9], all VKH patients were identified from the medical records and were included if OCT presented well-demarcated, abrupt elevations of the RPE with a homogeneously hyporeflective sub-RPE space and diagnosed with PED by two different ophthalmologists. The retrieved data included demographics, the best-corrected visual acuity (BCVA) at baseline and every follow-up visit, details of the ocular and systemic examination, imaging details of OCT scans, FFA and ICGA, therapeutic regimen, treatment response and complications, long-term anatomical outcomes, and clinical outcomes.

We conceived PED angle (PEDA) based on the contour of PED as a useful parameter for predicting the prognosis of PED, under the enlightenment of the macular hole angle [10]. The PEDA was defined as the angle between the two lines of the vertex of the lifted RPE to the two edge points of the Bruch membrane (Fig. 1). PEDA was measured using Digimizer software (Version 5.4.4). For standardization purposes, the average of three measurements was used for analysis. To determine the clinical value of the PEDA, a cut-off value for CSC occurrence was used for grouping. Therefore, eyes were classified into two groups: CSC and non-CSC groups. The PEDA and clinical outcomes for each group were evaluated and recorded. The CSC diagnosis criteria in our VKH

patients included: there was no active inflammation in both anterior chamber (AC) and vitreous cavity when ERD occurred; FFA disclosed the intense leakage at the RPE level with an “ink-blot” or “smokestack” pattern, which was colocalized with the neurosensory retinal detachment on OCT; the VKH patient responded well to the corticosteroid treatment before CSC development, and the neurosensory retinal detachment resulted from CSC could subside with the cessation of corticosteroid therapy and the adoption of other alternative treatments.

Statistical analyses were performed using the SPSS Statistics software. BCVA measurements were transferred to the logarithm of the minimum resolution angle (LogMAR) for statistical analysis. Descriptive statistics included mean and standard deviation for normally distributed continuous variables, median and range for non-normally distributed variables. Owing to the small sample sizes in our study, all statistical analyses were conducted using the nonparametric Wilcoxon (paired samples) or Mann-Whitney (independent samples) signed rank sum tests. Statistical significance was set at $P < 0.05$.

Results

A total of 470 eyes (235 patients) with VKH were identified, 44 patients were diagnosed with complete VKH disease, 144 with incomplete VKH, and 77 with probable VKH. The population consisted of 128 female (54.5%) and 107 male (45.5%) patients aged a mean of 46.7 ± 15.6 years (range: 7-85). The most frequent extraocular finding was meningismus. The characteristic fundus manifestations were multiple ERDs at the posterior pole and optic edema. Auxiliary examinations were used to provide aid for diagnosis and evaluate relevant changes in eyes. FFA revealed multifocal areas of pinpoint leakage, pooling, and optic disc staining. ICGA disclosed multiple hypofluorescent dark dots. OCT presented serous retinal detachment with choroidal thickening, and the typical manifestations of RPE were undulating RPE line and RPE bumps. Based on empirical findings, first choice of treatment was systemic high dose corticosteroids. For those patients who were intolerant or resistant to corticosteroids, immunosuppressive agents and/or biological agents were employed to suppress the ocular inflammation.

A total of 12 eyes (10 patients) developed serous PED (12/470, 2.55%). PED occurred in 10 eyes (8 patients) at the onset of VKH, and two eyes (2 patients) developed superimposed PED during the treatment follow-up. The demographic and clinical data of the 12 eyes (10 patients) are summarized in Tables 1 and 2.

In the 10 eyes with PED occurring at the onset of the disease, PED gradually resolved in 6 eyes, and developed into CSC in the remaining 4 eyes, among which, CSC occurred after the pre-existing ERD and both anterior chamber and vitreous cavity inflammation resolved in two eyes (case 5 and case 9); interestingly, PED, VKH, and CSC were considered to occur simultaneously in another two eyes (bilateral eyes of case 10). PED occurred in two eyes during the course of systemic corticosteroid therapy, which gradually resolved in one eye and developed into CSC in the other. Overall, fundus photography, OCT, and FFA images indicated that 5 eyes of 4 VKH patients experienced superimposed CSC (5/470, 1.06%), in which neurosensory retinal detachment colocalized with PED on OCT. OCT also revealed microrips of RPE in the bilateral eyes of case 10.

We divided the 12 eyes into two groups according to whether CSC developed or not: the CSC group and the non-CSC group. The average time taken between PED and CSC occurrence was 2.2 ± 2.5 months (range 0-6 months). Upon CSC diagnosis, corticosteroid was rapidly tapered off, and alternative therapies were applied, including immunosuppressants and biologics (azathioprine [AZA], cyclosporin A [CsA], mycophenolate mofetil [MMF], adalimumab [ADA]), continuous-wave laser photocoagulation for outside foveal leakage, and subthreshold micropulse laser photocoagulation (577 nm) for foveal leakage. After the treatment was adjusted, all PED and subretinal fluid resolved completely, except for the PED in case 5.

BCVA with a statistical difference was observed between the initial visit and the last follow-up in the 12 eyes (P=0.02) (Table 1). There was no difference in BCVA at baseline between the two groups (P = 0.68), but BCVA improvement until the last visit in the non-CSC group was greater than that in the CSC group, although the difference was not statistically significant due to the small sample size (P = 0.25) (Table 3). The PEDA values ranged from 59.992 to 133.868 in the 12 eyes, which in the CSC group was significantly smaller than that in the non-CSC group (77.69 ± 11.06 VS 106.87 ± 22.62, P = 0.03) (Table 3).

Representative three eyes of CSC group with clear choroidal morphology on OCT recordings were displayed here.

Case 5

A 40-year-old man presented with progressive vision loss in both eyes accompanied by a headache for five days. His BCVA was 20/50 in the right eye and 20/200 in the left eye. Fundus photography revealed multiple bubble-like elevations at the posterior pole in both eyes (Fig. 2A). FFA revealed optic disc hyperfluorescence and multiple pinpoint leakage at the level of RPE, with subsequent pooling of dye in the subretinal space of both eyes. ICGA showed bilateral hypofluorescent areas corresponding to overlying ERD, multiple hypofluorescent dark dots and disseminated spotted choroidal hyperfluorescence, and blurred choroidal vessels. OCT presented multilobular ERD and hyperreflective dots, colocalized PED, and undulating RPE in the left eye (Fig. 2C). A diagnosis of acute VKH disease was made based on extraocular and ocular manifestations. The multiple ERD gradually subsided, and ocular inflammation was controlled under systemic prednisone treatment with a starting dose of 1 mg/kg/day followed by gradual tapering. Three weeks after presentation, BCVA improved to 20/20 in the right eye and 20/25 in the left eye. Only a slit-like neurosensory retinal detachment on OCT remained in the left eye, without any changes in PED; meanwhile, the thinned inner choroidal layer and dilated large choroidal vessel under the PED was noticeable (Fig. 2D). However, both the AC and vitreous cavity were quiet at the two-month follow-up, dome-shaped neurosensory retinal detachment reoccurred in the macular region (Fig. 2E), FFA showed multiple punctate leakages in the left eye, which increased in size and intensity as the angiogram progressed (Fig. 2F), and barely visible hyperfluorescent spots in the right eye, OCT revealed neurosensory retinal detachment of the macular region and colocalized PED, the thinned inner choroidal layer and dilated large choroidal vessel under the PED (Fig. 2G). A diagnosis of steroid-induced multiple CSC was made. Oral prednisone was rapidly tapered to a low dose, and mycophenolate mofetil was added. Continuous-wave laser photocoagulation was performed for outside fovea leakage, and subthreshold micropulse laser photocoagulation was used for foveal leakage. One month after the adjusted therapy, bilateral BCVA was

20/20, and complete resolution of subretinal fluid was observed on OCT of the left eye; however, the PED, thinned inner choroidal layer and dilated large choroidal vessel persisted until the end of follow-up (Fig. 2H).

Case 10

A 47-year-old woman presented with bilateral acute vision loss for 1 day, accompanied by metamorphopsia and headache. She delayed prior systemic or ocular history. On examination, BCVA was 20/32 in the right eye and 20/40 in the left eye. The anterior segment examination showed bilateral shallow anterior chambers. Ultrasound biomicroscopy revealed bilateral ciliary body detachment. Fundus examination revealed multiple ERDs at the posterior pole in both eyes (Fig. 3A-B). The wide-field FFA demonstrated bilateral optic disc hyperfluorescence and multilobular dye pooling in the late period (Fig. 3C-D). On OCT, serous subretinal fluid accumulation with subretinal septa, hyperreflective dots, and multiple PEDs were evident in both eyes. Simultaneously, the attenuation of inner choroidal vessels below the RPE and dilation of the outer large choroidal vessels were prominent (Fig. 3E-F). Based on the above clinical examinations, a provisional diagnosis of acute VKH was made and treated with 500 mg/day of methylprednisolone intravenously for 3 days, followed by oral prednisolone. However, the ERD and PED showed no improvement, and there was no benefit upon adding adalimumab and mycophenolate mofetil. The patient's BCVA continuously deteriorated to hand movement and 20/160 in 3 weeks. FFA combined with ICGA was performed, and FFA revealed multifocal leakage at the macula followed by pooling into the subretinal space in the form of a 'ink-blot', which became more prominent on late-phase, but late optic disc staining and multilobular dye pooling disappeared, and the location of 'ink-blot' coincided with intense hyper-fluorescence of her first FFA. ICGA showed apparent dilatation of large choroidal venous (Fig. 3K-L). Furthermore, we carefully checked the OCT performed with the line scan pattern of 256 images at her first visit and found microrips of the RPE at the margin of the PED (Fig. 3G-J). These findings strongly suggest that VKH and CSC might have simultaneously attacked this patient. Subsequently, oral prednisone taper was accelerated and withdrawn in 15 days, adalimumab and mycophenolate mofetil were maintained, cyclosporine was added, and the subthreshold micropulse laser was used to seal the RPE microrips. ERD and PED in both eyes subsided gradually in one month. On the last examination, eight months after the stroke, BCVA improved to 20/63 in both eyes. OCT indicated complete remission of neurosensory retinal detachment and PED in both eyes, but the thinned inner choroidal layer and dilated large choroidal vessel still existed in bilateral eyes (Fig. 3M-N).

Discussion

To the best of our knowledge, the association between PED, CSC, and VKH has not been reported. Our study, for the first time, revealed that the occurrence of PED might be associated with CSC development in VKH. Notably, our results indicated that PEDA might be a significant predictive factor for CSC development in VKH cases.

VKH disease and CSC are considered to be completely two different diseases with different pathophysiologies. However, CSCs may clinically mimic VKH or develop in VKH cases, and these two diseases need to be differentiated in some cases. Multimodal imaging examinations are useful in discriminating CSCs from VKH. On OCT, fluctuations of ILM, subretinal septa, subretinal membranous structures and hyperreflective dots, bulge of RPE, folds of RPE, and resultant high RPE undulation index are characteristics of VKH. However, isolated serous PED always points to CSC because of its high prevalence in CSC, and it is regarded as an intermediate stage between pachychoroid and classic CSC [11-15]. Meanwhile, mechanical disruption at the RPE level is the most plausible factor responsible for generating the focal leakage points in CSC [16]. The choroid thickens in both CSC and VKH, although the thickness is thicker in CSC than in VKH [11,13]. The choroidal thickening of CSC is considered to be resulted from a thinned inner choroidal layer and enlarged underlying hyporeflective choroidal lumina, and the thickness of the total choroid is significantly correlated with the diameter of the largest lumen [17-19]. The thick choroid of acute VKH is diffuse and homogenous, the inflammatory cell infiltration and the proteinaceous fluid exudates produced in this stage accumulate in the choroid stroma and may obscure the choroidal vessels margin [19]. The typical FFA manifestations of VKH are numerous punctate hyperfluorescent dots at the RPE level in the early stage, followed by staining and pooling of the dye in the subretinal space, optic disc hyperfluorescence and leakage in the late stage [3]. Nonetheless, in classic CSC, unifocal leakage at RPE level with "ink-blot" or "smokestack" pattern is typical, but in eyes with steroid-induced CSC, the intense leakage from multiple regions is often seen [15,20]. Typical ICGA signs of VKH include early hyperfluorescent stromal vessels, which indicates severe choroidal stromal inflammatory vasculopathy, and late hypofluorescent dark dots, which are thought to correspond to choroidal granulomas, and fuzzy or lost vascular patterns of large stromal vessels due to choroidal inflammation [1-3,21]. Whereas, the hallmark of choroidal hyperpermeability in CSC is geographic areas of hyperfluorescence with blurred contours, and other alterations of the choroidal vasculature include delayed initial filling of arteries and choriocapillaris enlarged choroidal veins in the early phase, and hyperfluorescent punctate spots during mid- and late phase corresponded to the leakage points on FFA [15].

CSCs can develop following the administration of corticosteroids via diverse routes [22]. Corticosteroids could elicit or aggravate CSC by inducing choroidal enlargement, and the underlying mechanism is the inappropriate mineralcorticoid receptor activation through upregulation of endothelial vasodilatory potassium channel KCa2.3 (calcium-dependent channel) [23]. However, the pilot study demonstrated that steroid-induced CSC might be an idiosyncratic response in selected vulnerable individuals rather than a dose-dependent effect [24]. CSC induced by corticosteroids has been reported to occur in a wide variety of ocular inflammatory conditions but with a relatively low incidence. Majumder et al. revealed that the prevalence of CSC in uveitis was approximately 0.12% in a large retrospective study involving 22,721 patients in India [25]. We found that the specific incidence rate of CSC in VKH was 1.06% in our cohort of 235 patients. This rate is much higher than that revealed in the Indian uveitis population, which included patients with all types of uveitis.

The pathogenesis of CSC remains poorly understood; however, increased permeability of the choriocapillaris is believed to be the primary underlying pathophysiology [26]. The most widely accepted theory is that the abundant fluid arising from the hyperpermeable choriocapillaris and increased hydrostatic pressure resulted from dilated large choroidal vessels pushes the RPE forward, resulting in the development of PED and defects in the RPE

monolayer, subsequently allowing fluid to leak under the neuroretina [26]. Increased permeability of the choriocapillaris under inflammatory conditions is a typical pathological change in VKH [1]. When choroidal inflammation causes increased vascular permeability, as well as long-standing inflammation breaks down the blood ocular barrier, accumulation of fluid with abundant protein between RPE and Bruch membrane or under the neurosensory retina subsequently occurs, these are believed to be the theoretical bases of PED and ERD in VKH [25,27,7]. Briefly, the major cause of leakage in CSC is high hydrostatic pressure, while in VKH it is the inflammation. In general, the high hydrostatic pressure resulted from dilated large choroidal vascular and hyperpermeability of choriocapillaris constitute the pathophysiology of PED in CSC, while the pathophysiology of PED in VKH is composed of hyperpermeability of choroidal vessels resulted from choroidal inflammation and the relatively low hydrostatic pressure across the swelling choroidal vascular bed. The fluid within the PED applies pressure to the RPE and stretches it, the PED enlarges as the pressure increases, which will add angulation and mechanical stress to the base of the PED and may weaken or rupture the RPE layer [28]. PED was observed in 0-10% of eyes with acute VKH disease, according to several cross-sectional OCT-based studies [14,11-13,29]. Conversely, PED with or without associated ERD has been reported to occur in 44.2–100% of eyes with CSC [11,13,12,15]. The prevalence of PED in acute VKH patients in our study was 2.55% (12/470). Although isolated case reports have shown regression of PED in VKH patients with the treatment of oral prednisone and immunosuppressants [7], there are two different outcomes of PED in our cohort: PEDs in 7 eyes (7/12, 58.3%) resolved with corticosteroid therapy, while in the other 5 eyes (5/12, 41.7%), PEDs persisted and colocalized CSC developed during the follow-up; both CSC and PED resolved after the adjusted treatment strategies in four eyes; CSC regressed, but PED persisted in the remaining one eye (case 5). Therefore, it is reasonable to infer that PEDs with relatively high hydrostatic pressure in VKH patients, who are the selected vulnerable individuals, may develop into classic CSC following systemic corticosteroid administration. The common pathomechanism of PED, caused by the increased permeability of the choriocapillaris in CSC and VKH, might lead to a higher rate of classic CSC in VKH patients than in other uveitis patients.

Interestingly, VKH and CSC seemed to occur simultaneously in case 10 before corticosteroid application since multimodal images revealed characteristic changes in both VKH and CSC at her first visit, just one day after the disease onset. Compared with the first FFA, both multiple subretinal staining and optic disc hyperfluorescence disappeared on the second FFA, which indicates that the high-dose systemic corticosteroid has effectively suppressed the acute intraocular inflammation. Meanwhile, the location of ‘ink-blot’ indicating the leakage point of CSC on the second FFA coincided with the intense hyper-fluorescence of the first FFA, and all the characteristics of CSC displayed on the first OCT, including attenuation of inner choroidal vessels below the RPE and dilation of the outer large choroidal vessels, and microrips of the RPE at the margin of the PED. Overall, the inflammation of VKH and high hydrostatic pressure of CSC together led to the multiple leakage in the first FFA, the second FFA indicated that the leakage caused by VKH inflammation was significantly improved with three weeks of systemic high-dose corticosteroid treatment, but the leakage caused by the high hydrostatic pressure of CSC did not change significantly, or even worsened. This case suggests that idiopathic high hydrostatic pressure in the choroid, instead of the administration of systemic corticosteroids, might be the major cause of classic CSC development in this patient. According to this case, we can speculate that in other VKH patients who developed CSC after the application of systemic corticosteroid, the initial PED may result from a combination of two distinct mechanisms, VKH and intermediate stage between pachychoroid and classic CSC, as suggested by Arif et al.[6], while the systemic corticosteroid administration may promote the choroidal enlargement, increase the hydrostatic pressure of PED and stretches for RPE, ultimately result in a defect of RPE monolayer and the development of classic CSC. This has been indirectly proved by the OCT images of the last follow-up in both case 5 and case 10, which demonstrated the complete remission of ERD and persist dilation of the outer large choroidal layer.

In CSC, if the fluid pooled in the subretinal space couldn’t be absorbed by choroidal vasculature via the RPE pump over a long time, persistent thick outer segments may progress to permanent subretinal deposits with subsequent poor visual prognosis [15,30]. Hence, it is of paramount importance to differentiate CSC from the relapse of inflammation once dome-shaped neurosensory retinal detachment reoccurs or worsens in VKH, as the management of these two conditions is paradoxical. In our cohort, the BCVA improvement of the CSC group tended to be less than that of the non-CSC group, although there was no statistical difference due to the small sample size, indicating that the early diagnosis of CSC is important for saving vision. Therefore, to further determine the relationship between PED and CSC development in VKH patients, we proposed the PEDA, an index reflecting the PED deformation in VKH, to predict the outcomes of PED. The calculation of PEDA is simple and can be easily applied clinically. Our results revealed that PEDA in the CSC group was significantly smaller than that in the non-CSC group. Since the PEDA formed between the lifted RPE and Bruch membrane represents primarily superoinferior stretches, a smaller PEDA value indicates a smaller horizontal and a greater perpendicular PED dimension, which suggests a relatively higher hydrostatic pressure and more stretches for RPE. Therefore, patients with small PEDA may be more likely to develop defects of the RPE monolayer and fluid leakage into the sub-retina under the treatment of systemic corticosteroid. For VKH patients with small PEDA, immunomodulatory and/or biologicals could be the first choice. If the therapy of rapid and aggressive high-dose systemic corticosteroid along with immunomodulatory and/or biologicals is adopted, close follow-up will be necessary to monitor the changes in PED and the occurrence of classic CSC, and timely adjustment of the therapeutic regimen may lower the risk of vision impairment.

Discontinuation of corticosteroids is suggested as the first step in the treatment of CSC in ocular inflammatory conditions, and adding immunosuppressants and/or biological agents may be required to control inflammation [25,31]. CSC leakage points outside the fovea could be treated with continuous-wave laser photocoagulation [25]. In our series, four CSC eyes received subthreshold micropulse laser photocoagulation for foveal leakage and yielded favorable results. In contrast to the traditional continuous-wave laser, the subthreshold micropulse can provide the required activation energy of the RPE cells without damaging the retina [32,33].

The retrospective nature of the present study brings some limitations. First, these results only provided preliminary conclusions due to a small sample size and low incidence. Second, the application of PEDA were restricted since it could not be calculated in cases where severe vitreous opacities, mature cataracts, or other conditions that prevent the presence of clear OCT recordings. Despite its limitations, the study certainly adds to our understanding of the associations between PED in VKH patients and CSC development. Further research is needed to confirm the predictive value of PEDA and to clarify the mechanism of classic CSC development in VKH cases.

In conclusion, the present study provides the first assessment of PED and its relationship with CSC development in VKH patients. Our results indicate that PED predisposes to the development of CSC in selected VKH eyes, systemic corticosteroid treatment may promote the occurrence of classic CSC. We believe that PEDA is a simple parameter to present PED configuration and hydrostatic pressure, it might be an efficient predictive factor for the subsequent development of CSC.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tianjin Medical University Eye Hospital (No.2020KY (L)-37).

Consent to participate

Written informed consent was obtained from the parents.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in Figure 1, Figure 2 and Figure 3.

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Tables

Table 1 Demographics of VKH patients associated with PED

Chraterastics	Value
Number of patients / eyes	10 / 12
Number of right / left eye	7 / 5
Number of males / females	6 / 4
Prevalence of PED	2.55% (12/470)
Age (years)	49 ± 11.9
Average follow-up time (months)	10.5 ± 5.2
BCVA at baseline (LogMAR)	0.45 (0.30-1.00)
BCVA at last visit (LogMAR)	0.08 (0.00-0.45)
P value of BCVA improvement	0.02

PED, retinal pigment epithelial detachment; VKH, Vogt-Koyanagi-Harada syndrome; BCVA, best corrected visual acuity.

Table 2. Clinical Characteristics of VKH patients

Case	Age / Gender	Eye	BCVA at baseline	BCVA at final visit	Follow up (months)	The time of PED occurrence	PEDA (degree)	CSC occurrence	Time between PED and CSC	PED outcomes	Treatment
1	46 / F	OD	20/50	20/20	10	Initial visist	109.799	No	-	Regression	Routine oral steroid tapering
2	49 / F	OD	20/200	20/20	13	Initial visist	101.821	No	-	Regression	Routine oral steroid tapering & AZA
3	34 / F	OD	20/63	20/20	12	Initial visit	112.928	No	-	Regression	Routine oral steroid tapering
		OS	20/63	20/20	12	Initial visit	63.611	No	-	Regression	Routine oral steroid tapering
4	60 / F	OS	20/40	20/33	7	Initial visit	133.868	No	-	Regression	Routine oral steroid tapering
5 (Figure 2)	40 / M	OS	20/200	20/20	10	Initial visit	83.180	Yes	3 months	Persistence	Rapid oral steroid tapering & MMF subthreshold micropulse laser photocoagulation & continue-wave laser photocoagulation
6	30 / F	OD	20/40	20/40	18	During follow-up	89.597	Yes	6 months	Regression	Rapid oral steroid tapering & CsA & AZA & subthreshold micropulse laser photocoagulation
7	58 / F	OD	20/2000	0.2	6	Initial visit	125.728	No	-	Regression	Intravenous methylprednisolone & oral tapering steroid & CsA
8	62 / M	OS	20/22	20/20	6	During follow-up	100.333	No	-	Regression	Oral tapering steroid
9	64 / M	OD	20/200	20/28	9	Initial visit	59.922	Yes	2 months	Regression	Rapid oral steroid tapering & MMF
10 (Figure 3)	47 / F	OD	20/33	20/63	8	Initial visit	78.888	Yes	0	Regression	Rapid oral steroid tapering off & CsA & MMF & ADA & subthreshold micropulse laser photocoagulation
		OS	20/40	20/63	8	Initial visit	76.875	Yes	0	Regression	Rapid oral steroid tapering off & CsA & MMF & ADA & subthreshold micropulse laser photocoagulation

F, female; M, male; PED, retinal pigment epithelial detachment; PEDA, PED angle; CSC, central serous chorioretinopathy; AZA, azathioprine; CsA, ciclosporin A; ADA, adalimumab; MMF, mycophenolate mofetil.

Table 3 Parameters of CSC group and non-CSC group

Parameters	CSC group	Non-CSC group	*P* value
PEDA	77.69 ± 11.06	106.87 ± 22.62	0.03
BCVA at baseline	0.30 (0.25-1.00)	0.50 (0.30-1.00)	0.68
BCVA improvement	-0.27 ± 0.61	-0.55 ± 0.46	0.25

PEDA, retinal pigment epithelial detachment angle; BCVA, best corrected visual acuity; CSC, central serous chorioretinopathy.

Figures

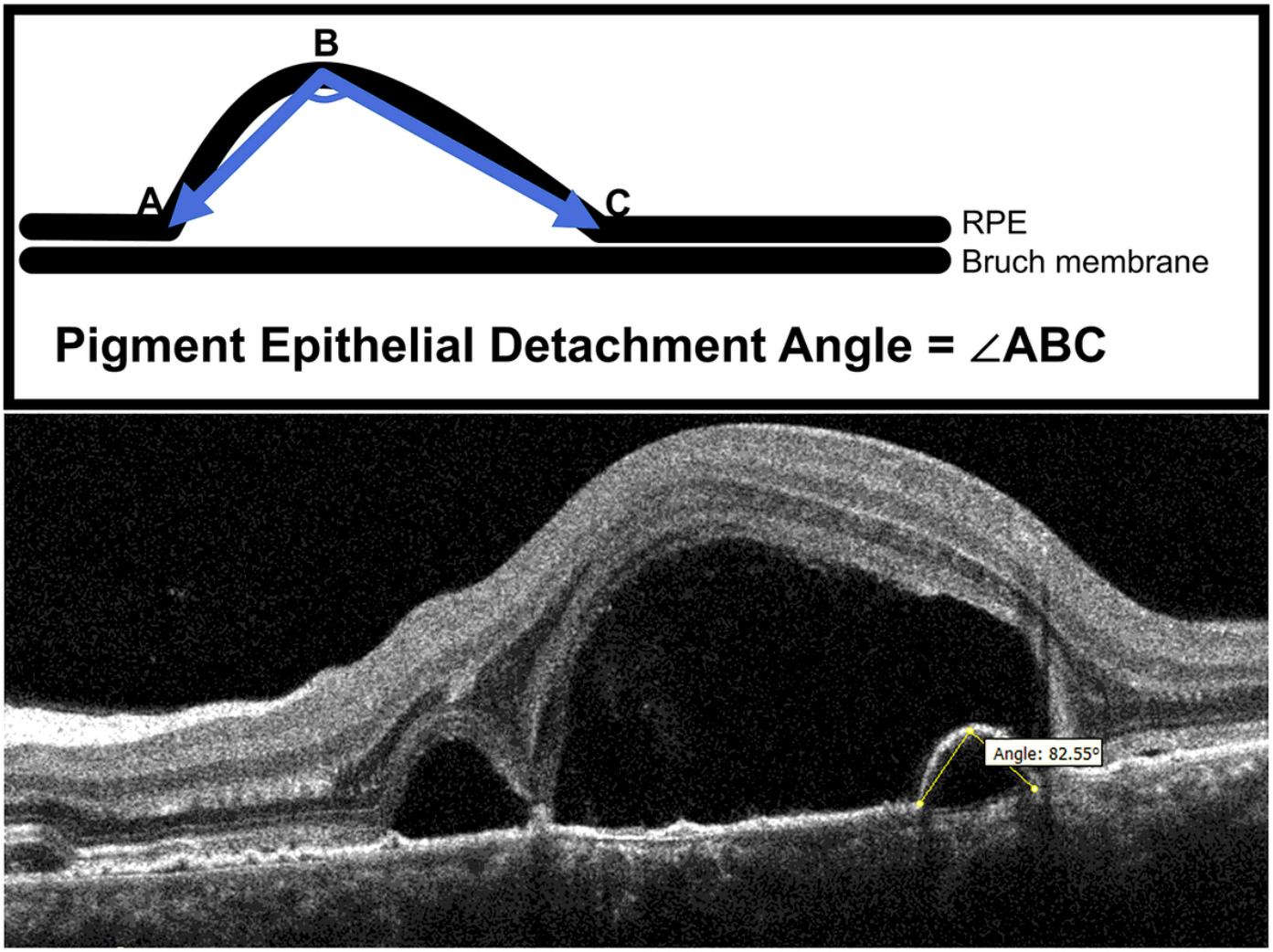

Figure 1

The retinal pigment epithelial detachment angle (PEDA). (Top) Diagram showing the PEDA, the angle between the two lines of the vertex of lifted RPE to the two edge points of the Bruch membrane. (Bottom) Optical coherence tomography (OCT) cross-sectional image of PEDA.

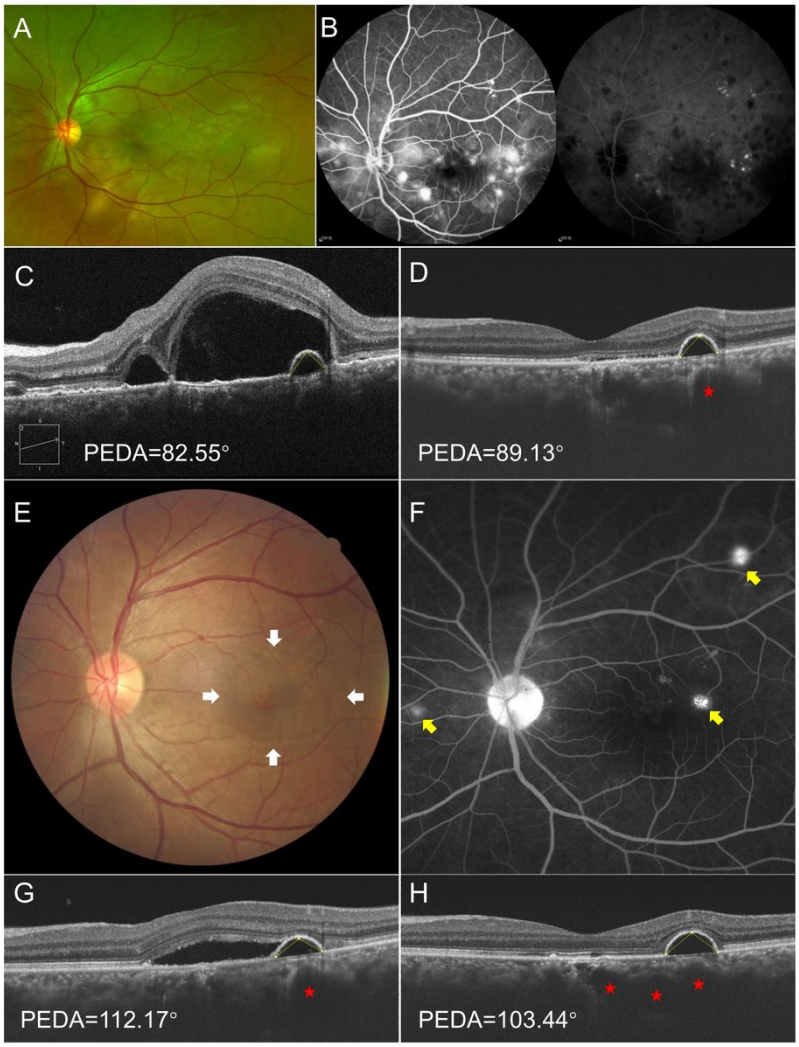

Figure 2

Disease progression and outcomes of case 5. **A-C**. Multimodal imaging examinations of case 5 at initial indicating the diagnosis of Vogt-Koyanagi-Harada disease (VKH). **A**. Wide field fundus photography demonstrated multiple exudative retinal detachment (ERD) in the left eye. **B**. Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) revealed typical acute VKH. **C**. OCT presented multilobular ERD and hyperreflective dots, a single PED, and undulating RPE. The PED angle (PEDA) was 82.55°.**D.**OCT, taken 3 weeks after systemic corticosteroid treatment, showed a quiet shallow neurosensory retinal detachment, the thinned inner choroidal layer and dilated large choroidal vessel (red pentagram) beneath the persisted PED in the left eye. The PEDA increased to 89.13°. **E-G**. Development of central serous chorioretinopathy (CSC) during the course of corticosteroids treatment. **E**. Fundus photography showed dome-shaped macular (white arrows). **F**. Multiple leakages with "ink-blot" pattern was noted on FFA (yellow arrows). **G**. OCT showed sensory retinal detachment corresponding dome-shaped macular, persisted PED, thinned inner choroidal layer and dilated large choroidal vessel (red pentagram). The PEDA increased to 112.17°. **H.** Persisted PED and dilated choroidal large vessels (red pentagrams) were noted on OCT after macular subretinal fluid of CSC resolved completely at the last follow-up. The PEDA of the persisted PED was 104.44°.

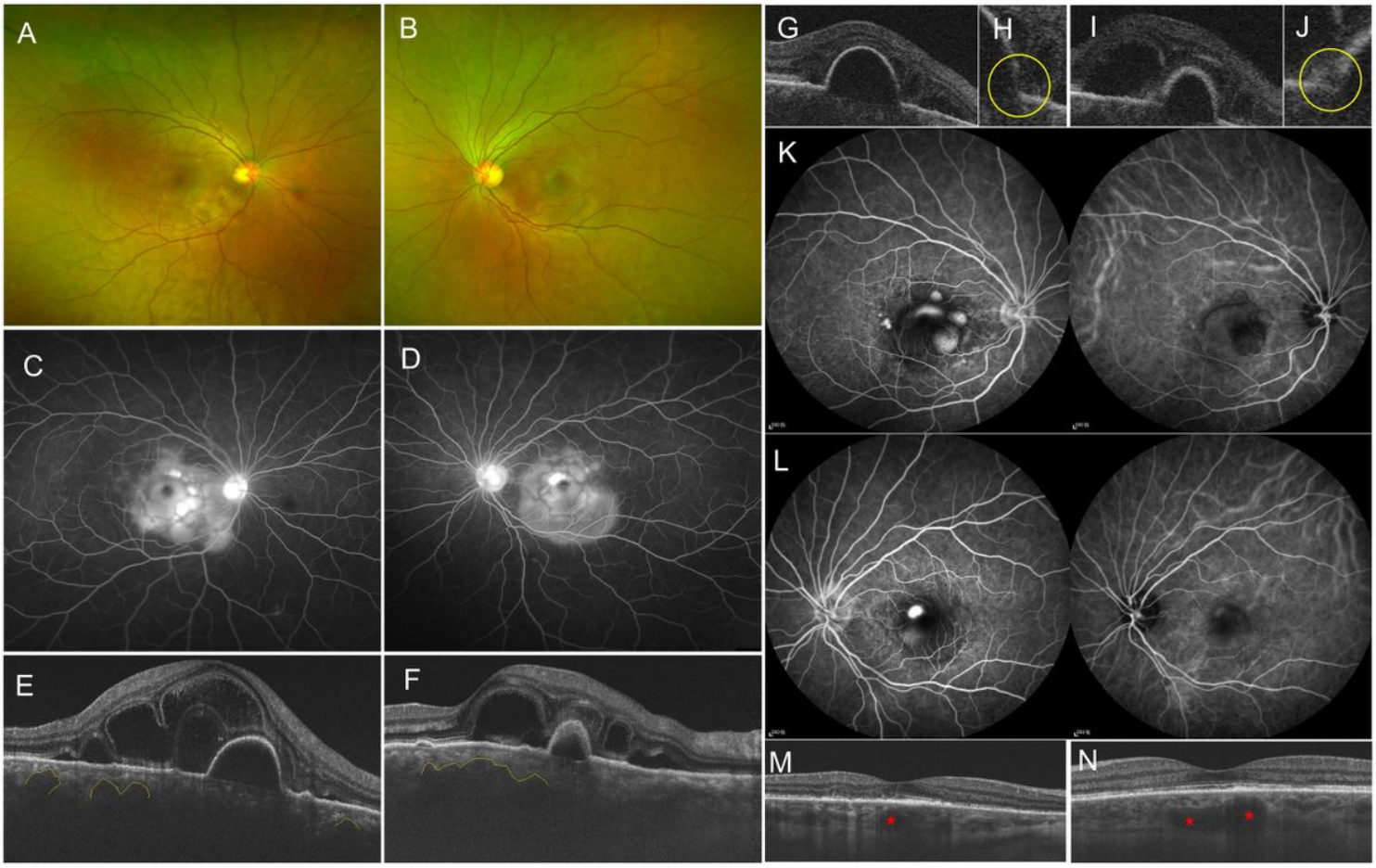

Figure 3

Disease progression and outcomes of case 10. **A-J.** Multimodal imaging examinations of case 5 at initial indicating the diagnosis of VKH and CSC. Widefield fundus photos (**A and B**) of acute VKH. Widefield late-phase fluorescein angiography of acute VKH (**C and D**). **E-J**. OCT of revealed the presence of subretinal fluid, septae, PED, dilatated large choroidal vessels (yellow polyline) and RPE microrips (yellow circle). **K-L**. Three weeks after treatment with rapid and aggressive high-dose systemic corticosteroid, adalimumab and mycophenolate mofetil, FFA demonstrated 'ink-blot' and ICGA showed large choroidal venous dilatation. **M-N**. Eight months after the presentation, OCT showed complete remission of neurosensory retinal detachment and PED, and dilated large choroidal vessels in bilateral eyes (red pentagrams)