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ORIGINAL RESEARCH

# Morphological and Functional Outcomes in the Long-Term Natural Course of Peripapillary Pachychoroid Syndrome

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## ABSTRACT

***Introduction*:** This study investigated the long-term natural history of peripapillary pachychoroid syndrome (PPS), analyzing both morphological and functional outcomes.

***Methods*:** This retrospective study included 24 eyes from 14 participants diagnosed with PPS. No interventions were administered. Baseline and follow-up assessments comprised best-corrected visual acuity (BCVA), measured on the LogMAR scale, inner nasal (IN) and outer nasal (ON) macular thickness measured using the ETDRS (Early Treatment Diabetic Retinopathy Study) subfields. To account for repeated measures and the hierarchical structure of eyes nested within participants, and to appropriately handle incomplete longitudinal data, linear mixed-effects models were utilized for all statistical analyses.

***Results*:** The mean age was 74 ± 7 years, and 71% of patients had bilateral PPS. All patients had peripapillary atrophy at baseline. The mean baseline BCVA was 0.05 and showed only small variations over time. ON macular thickness showed a significant decrease at 2 years ($\Delta = -36.9$ µm, $p = 0.034$), whereas IN macular thickness decreased significantly at both 2 years ($\Delta = -40.75$ µm, $p = 0.023$) and 3 years ($\Delta = -39.97$ µm, $p = 0.042$). One-quarter of participants developed a serous pigment epithelium detachment with subretinal fluid, suggesting an overlapping PPS/CSC (central serous chorioretinopathy) phenotype.

***Conclusions*:** Peripapillary atrophy appears to be an important anatomical predisposition for PPS. Waxing and waning of intraretinal fluid were observed during the natural course

Christina Karakosta and Peter Kiraly contributed equally to this work and designated as co-first authors.

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of PPS, with a significant reduction at 2 years. Most patients remained asymptomatic and maintained stable BCVA throughout long-term follow-up, indicating a generally favorable prognosis in the absence of intervention.

**Keywords:** Peripapillary pachychoroid syndrome; PPS; Pachychoroid; Peripapillary atrophy; Central serous chorioretinopathy; CSC

| **Key Summary Points** |
|---|
| *Why carry out this study?* |
| Understanding the natural course of peripapillary pachychoroid syndrome (PPS) is essential for determining if and when treatment is necessary. |
| This study evaluated morphological and functional parameters and assessed natural, long-term outcomes in patients with PPS. |
| *What was learned from the study?* |
| All patients with PPS at baseline had peripapillary atrophy (PPA), suggesting that PPA could be an important anatomical predisposition for PPS. |
| Most patients were asymptomatic at baseline and maintained good best-corrected visual acuity (BCVA) over the follow-up period. |
| Waxing and waning of intraretinal fluid was observed in eyes with PPS. |
| Favorable morphological and functional outcomes suggest that treatment should be reserved for patients with persistent foveal involvement (intra- or sub-retinal fluid) or those exhibiting an overlapping PPS/CSC (central serous chorioretinopathy) phenotype. |

## INTRODUCTION

Peripapillary pachychoroid syndrome (PPS) is a relatively new entity, first described by Phasukkijwatana et al. in 2018 [1]. It is part of the pachychoroid disease spectrum (PDS), which is characterized by a thick choroid and includes central serous chorioretinopathy (CSC), pachychoroid neovasculopathy, pachychoroid pigment epitheliopathy, focal choroidal excavation, and polypoidal choroidal vasculopathy [2]. The underlying pathophysiology of PDS involves choroidal vascular hyperpermeability in combination with disruption of the retinal pigment epithelium (RPE) [3]. Although a thick and hyperpermeable choroid is a common morphological parameter in the PDS spectrum, intra/subretinal findings differ significantly, leading to a wide range of natural courses, treatment modalities, and morphological and functional outcomes. Therefore, in each PDS entity, long-term morphological and functional outcomes and therapeutic approaches need to be determined.

PPS is characterized by intraretinal fluid (IRF) originating from the peripapillary region, which is hypothesized to result from intervortex venous anastomosis hyperpermeability around the optic nerve head [3]. In CSC, elevated hydrostatic pressure in the choroid can lead to pigment epithelium detachments (PEDs) and/or RPE bumps, which manifest as leakage on fluorescein angiography. By contrast, most patients with PPS show no leakage, with only a small number demonstrating mild leakage [3]. It has been hypothesized that peripapillary atrophy is an anatomical predisposition that allows fluid to gently seep from the choroid into the retina, which would not be possible with an intact peripapillary RPE barrier [4]. PPS can also develop PED and subretinal fluid, findings more commonly associated with CSC. In the literature, only a handful of PPS studies have been published, mostly examining morphological and functional parameters at baseline and outcomes after treatment [1, 4–6]. Therefore, a study of the natural course of PPS is essential to determine outcomes without intervention, which could be critical to determine whether or when treatment is needed.

In our study, we aimed to evaluate morphological and functional parameters at presentation and the changes observed during natural, long-term follow-up. We also aimed to

determine the number of asymptomatic participants referred to the eye department due to incidental optical coherence tomography (OCT) findings. Moreover, we aimed to evaluate leakage on angiography, the presence of peripapillary atrophy at baseline, and the percentage of patients with an overlapping PPS/CSC phenotype. In addition, we aimed to determine whether intraretinal fluid follows a waxing and waning course similar to that seen in CSC. Lastly, we aimed to assess long-term best-corrected visual acuity (BCVA) outcomes without any intervention.

## METHODS

The retrospective data were collected for a period between 2015 and 2024 from the Oxford Eye Hospital, and included PPS diagnoses confirmed by a medical retinal specialist. Inclusion criteria encompassed patients demonstrating choroidal thickening or choroidal hyperpermeability, as well as intraretinal fluid originating from the optic disc. Exclusion criteria encompassed macular oedema from other causes (inflammatory, diabetic, or secondary to vein occlusion or medication), vitreomacular traction, epiretinal membrane, macular neovascularization, ocular surgery within the past six months, any ocular therapy for PPS, optic disc pit maculopathy, glaucomatous optic neuropathy with peripapillary neurosensory retinal detachment, nanophthalmos with uveal effusion, and drug-induced uveal effusion, including topiramate, flucloxacillin, carbamazepine, venlafaxine, trimethoprim/sulfamethoxazole, hydrochlorothiazide, chlorthalidone, bupropion, indapamide, and escitalopram [7, 8].

This retrospective study adhered to the tenets of the Declaration of Helsinki. Since all investigations and imaging were performed as part of routine clinical care, no ethical approval was required nor consent in accordance with local/national guidelines of the Oxford Eye Hospital Ethical Review Board [9].

At baseline, participants underwent a comprehensive ophthalmological examination, which included slit-lamp evaluation, fundoscopy, OCT, and blue fundus autofluorescence (BAF). Fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed in some patients. Multimodal imaging was performed using the Spectralis imaging platform (Heidelberg Engineering, Heidelberg, Germany).

Participants were examined at baseline and, when possible, at 6 months, 12 months, 1.5 years, 2 years, 2.5 years, 3 years, and 3.5 years. The use of steroids and the presence of symptoms were recorded at baseline. Best-corrected visual acuity (BCVA) in LogMAR, the thickness in the inner nasal (IN) and the outer nasal (ON) macula using the ETDRS subfields were recorded at every visit. Intraocular pressure (IOP) and axial length (AL) were measured at baseline. Choroidal thickness (CT) was measured at baseline as the distance between the outermost part of the RPE and the sclerochoroidal junction using the OCT caliper tool at 1.5 and 3.0 mm from the foveal center. Peripapillary atrophy was evaluated on BAF, and its temporal extension from the optic disc was measured on the OCT scan using a 1:1 µm scale. Foveal involvement, defined as either subretinal or intraretinal fluid, was also assessed.

Participant characteristics were described using means and standard deviations (SD) for normally distributed continuous variables.

To analyze longitudinal changes in ON, IN, and BCVA measurements collected from both eyes of each subject over 3.5 years, we employed linear mixed-effects models using the *lme4* package in R. These models included fixed effects for time, categorized into 6-month intervals, and random intercepts for subjects, with eyes nested within subjects, to appropriately account for the hierarchical data structure and correlated repeated measurements. Model assumptions were initially assessed visually using the *performance* package in R, which provides comprehensive diagnostic plots such as Q–Q plots and residuals-versus-fitted plots to evaluate normality, linearity, and homoscedasticity of residuals. To complement these visual assessments, the *DHARMa* package was utilized to simulate residuals and conduct formal model diagnostics through both graphical checks and statistical tests. These diagnostics included the Kolmogorov–Smirnov test for evaluating residual

uniformity as an indicator of overall model fit, a nonparametric dispersion test that compares the variance of the observed residuals to the variance expected under the fitted model by simulating residuals, and Levene's test to detect group-level heterogeneity in residual variance [10]. When minor deviations from normality or homoscedasticity were observed visually using the *performance* package, but *DHARMa*'s simulation-based tests indicated no significant violations, the model was considered adequately specified.

Due to the bounded and skewed nature of the BCVA data, which exhibited substantial zero inflation with 41% of observations recorded as zero, we applied a monotonic transformation using the arccosine (inverse cosine) of the square root to stabilize variance and improve model assumptions. This transformation was selected over alternatives (e.g., square root, arcsine square root) based on improved residual diagnostics and its ability to effectively address zero inflation [11].

Estimated marginal means (EMMs) with 95% confidence intervals (CI) were computed for each time point using the *emmeans* package. These EMMs represent adjusted means at each time point, accounting for both subject-level and eye-level variability. To evaluate time-related differences, we used two types of contrasts: (1) contrasts comparing each follow-up time point to baseline, and (2) consecutive pairwise contrasts to assess changes between successive time points. Both types of comparisons were adjusted for multiple testing using the Šidák method [12]. The Kenward–Roger approximation [13] was used to estimate degrees of freedom and standard errors, as it offers improved control over Type I error rates in linear mixed models, particularly under unbalanced designs and small sample sizes. For BCVA, estimated marginal means and confidence intervals were backtransformed to the original scale to facilitate clinical interpretation.

As this was an observational study without interventions or treatment comparisons that could systematically influence dropout patterns, attrition was assumed to result from routine clinical processes (e.g., scheduling conflicts, limited patient availability, loss of interest, or unrelated health issues). All available data were analyzed using a linear mixed-effects modeling framework, which effectively handles incomplete observations without requiring complete data from every participant. Imputation was not performed due to the relatively small sample size and the increasing proportion of missing values over time, conditions under which a high proportion of imputed data could severely compromise both validity and interpretability of results.

All analyses were performed using the R programming language Version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

In total, 24 eyes from 14 patients were included in the study. Four participants were female and 10 were male. Mean age was 74 years (SD 7 years, range 57–88 years). At baseline, only two participants reported previous use of steroids. Three participants were symptomatic (metamorphopsia and/or central shadow), while the remaining 11 participants did not report any visual symptoms. Ten patients had PPS in both eyes, whereas four patients had PPS in only one eye. Mean intraocular pressure was 13 mmHg (SD 2.5 mmHg) and mean axial length was 22.34 mm (SD 1.30 mm). Baseline data for all participants are summarized in Table 1.

All participants had peripapillary atrophy, and the mean atrophy size was 560 µm (range 157–1135 µm) (Fig. 1). The number of eyes assessed at each follow-up visit was as follows: 6 months ($n=23$), 12 months ($n=17$), 1.5 years ($n=15$), 2 years ($n=15$), 2.5 years ($n=13$), 3 years ($n=14$), and 3.5 years ($n=10$).

Fluorescein and indocyanine green angiography were available in seven participants (14 eyes) and showed no leakage in the area of intraretinal fluid in the peripapillary atrophy region; these eyes also displayed no subretinal fluid. In Fig. 2, the multimodal imaging of participant with hypermetropia, short axial length (AL = 20.94 mm), chorioretinal folds, enlarged/thickened ocular coats is shown [14]. The IOP was normal (15mmHg), with no signs of hypotony. Two eyes had subfoveal retinal pigment

**Table 1** Demographic, morphological and functional characteristics of patients with peripapillary pachychoroid syndrome (PPS)

| Variable | Value |
|---|---|
| Age (years), mean ± SD | 74 ± 7 |
| Sex ratio (male: female) | 10:4 |
| Patients using steroids | 4 out of 14 |
| Patients with visual symptoms | 3 out of 14 |
| Presence of PPA | 14 out of 14 |
| Intraocular Pressure (mmHg), mean ± SD | 13 ± 2.5 [range: 10–19] |
| Axial length (mm), mean ± SD | 22.34 ± 1.30 |
| IN macular thickness (µm), mean ± SD | 365.25 ± 53.50 |
| ON macular thickness (µm), mean ± SD | 352.04 ± 57.57 |
| CT at 1.5 mm from foveal center (µm), mean ± SD | 321.5 ± 72.24 |
| CT at 3.0 mm from foveal center (µm), mean ± SD | 204.38 ± 103.30 |
| Number of eyes with concurrent CSC | 5 out of 24 |

*SD* standard deviation, *PPA* peripapillary atrophy, *IN* inner nasal, *ON* outer nasal, *CT* choroidal thickness, *CSC* central serous chorioretinopathy

epitheliopathy, two eyes had intraretinal fluid involving the center of the fovea and four eyes had foveal subretinal fluid at some point during the observation period (Fig. 3).

Linear mixed-effects models were fitted to assess longitudinal changes in ON and IN over time, accounting for random intercepts at the subject and eye levels. Model assumptions were met based on statistical tests and the graphs that are shown in the supplementary material (Figures S1, S2, S3, and S4). The estimated marginal means showed a progressive decline in both ON and IN across follow-up visits when compared to baseline (Figs. 4A, B, 5A, B). Pairwise contrasts of each follow-up time point against baseline are shown in Table 2. Specifically, ON macular thickness showed a significant decrease at 2 years ($\Delta = -36.9$ µm, $p = 0.034$), whereas IN macular thickness decreased significantly at both 2 years ($\Delta = -40.75$ µm, $p = 0.023$) and 3 years ($\Delta = -39.97$ µm, $p = 0.042$). Spaghetti plots illustrating greater fluctuations in both inner and outer macular thickness in eyes with higher inner/outer macular thickness at baseline are shown in Fig. 6. Pairwise comparisons between consecutive time points were not statistically significant for both ON and IN (Table S1, Supplementary material).

Linear mixed effects model assumptions for the transformed BCVA are shown in the supplementary material (Figures S5 and S6). The back-transformed marginal means of BCVA over time, presented in Fig. 7, indicate a baseline value of 0.05. Although the contrast comparing the 1-year follow-up to baseline showed a statistically significant change ($\Delta = 0.133$, $p = 0.038$), overall changes from baseline across time points remained small (Table 2). Consecutive contrasts of the transformed estimated marginal means for BCVA revealed no statistically significant differences.

An example of spontaneous intraretinal fluid fluctuations in a patient with PPS over a 15-month follow-up is shown in Fig. 8.

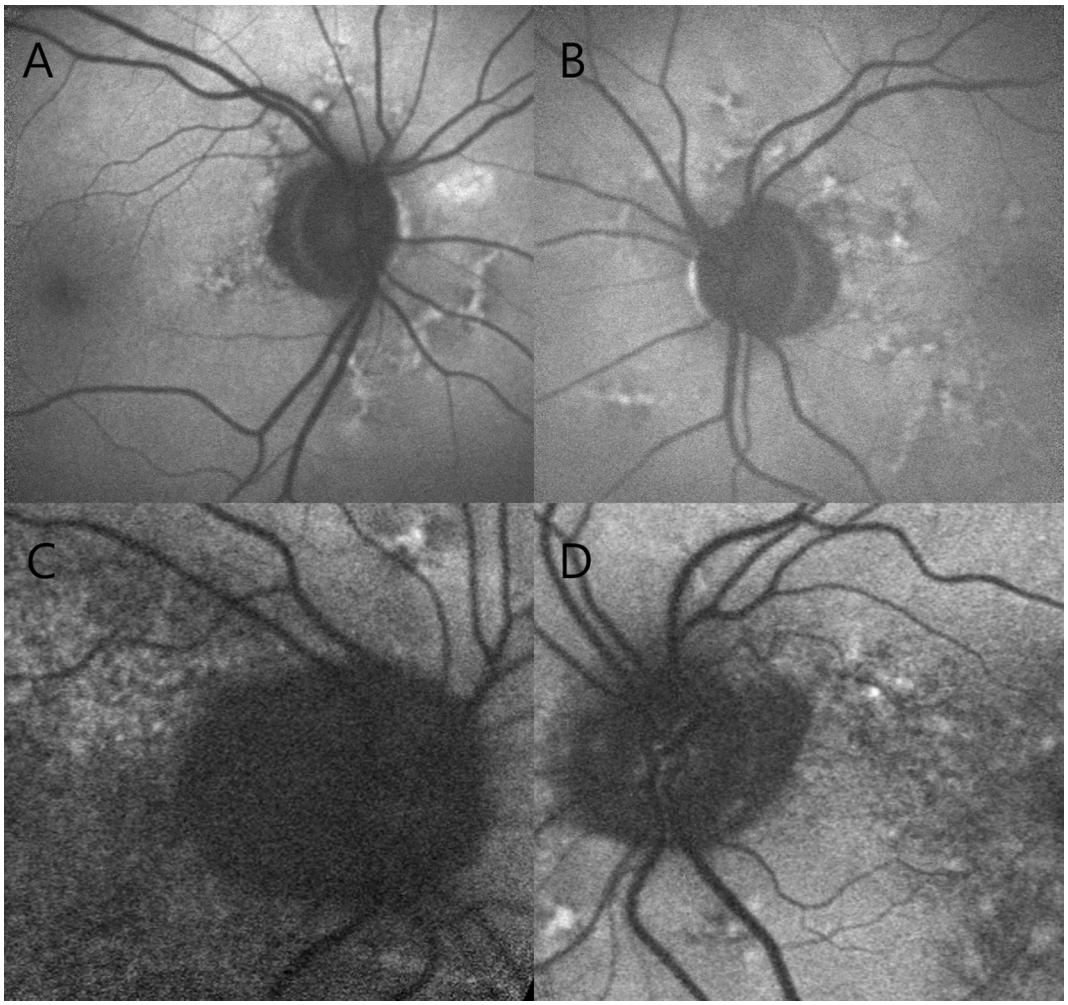


**Fig. 1** Peripapillary atrophy (PPA) was observed in all patients with peripapillary pachychoroid syndrome (PPS). Examples of four different eyes (**A**–**D**) with PPA and PPS

## DISCUSSION

A major contribution of this study is reporting the morphological and functional long-term outcomes in patients with PPS without intervention. Our study showed that patients with PPS were older than patients with CSC. PPA was evident in all participants, with no leakage on FFA in the PPA area. Most participants remained asymptomatic, maintaining very good BCVA at both presentation and last follow-up. Patients with PPS rarely developed sub- or intraretinal fluid or RPE changes in the fovea. Nonetheless, in one-quarter of patients, a serous PED with subretinal fluid was observed, suggesting an overlap between PPS and CSC. Although some fluctuations in intraretinal fluid thickness appeared in the nasal macula, these were not statistically significant. In our study, 72% of patients were male, which is similar to other PPS studies [1, 5, 6, 15] and only slightly higher than in patients with CSC (63%) [16]. In our study, 70% of patients presented with bilateral PPS, exceeding the 50% previously reported by Kumar et al. [17].

The mean age of patients with PPS in our cohort was 74 years, which is significantly older than the 45 years reported for CSC [16]. This finding is in concordance with other

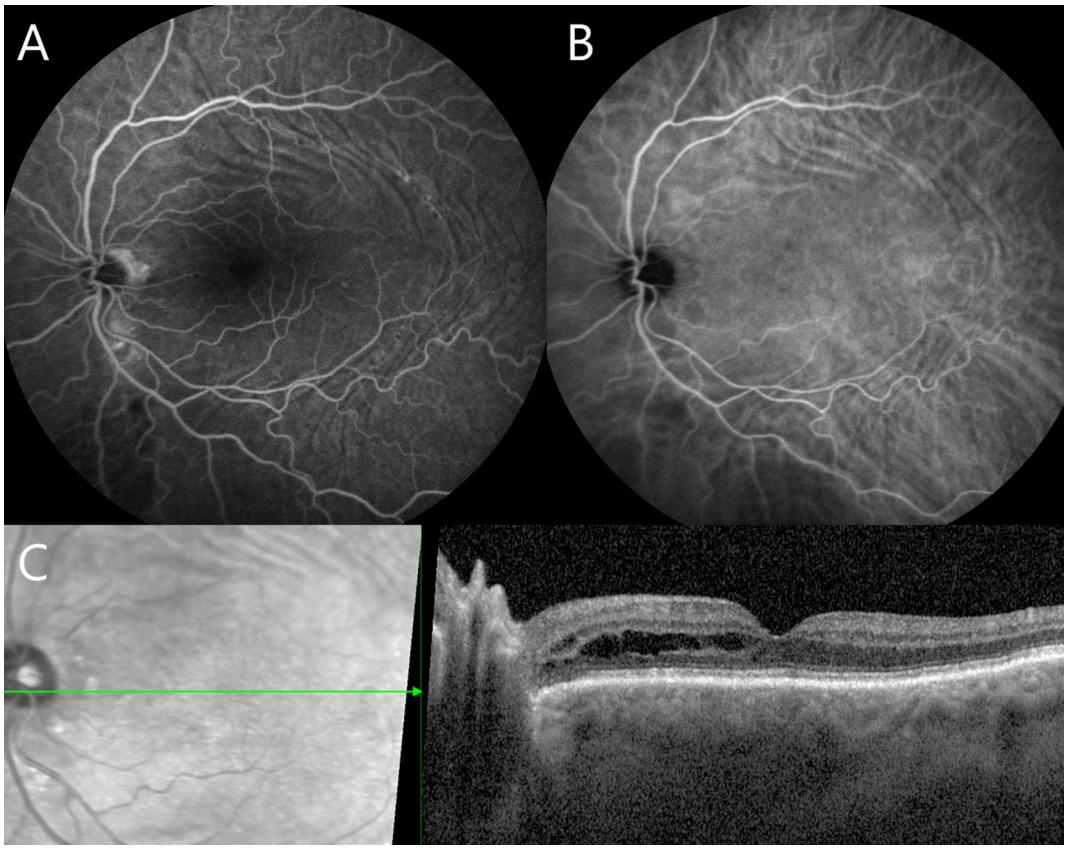


**Fig. 2** No leakage on fluorescein (**A**) and indocyanine green (**B**) angiography was observed in the area of peripapillary atrophy in patients with intraretinal fluid but no subretinal fluid (**C**)

studies showing a mean age of 64–71 years in patients with PPS [1, 5, 15], with only one study reporting a mean age of 52 years [6]. Previous studies have shown that CT decreases with age [18], and PPA size increases with age [19]. Therefore, the older average age in PPS compared with patients with CSC could be explained by a thinner choroid, leading to low blood flow conditions and an increasingly disrupted RPE outer blood–retina barrier around the optic disc, seen as developing PPA. PPA was observed in all our patients, indicating that it may be an anatomical predisposition required for PPS to develop. Additionally, the majority of patients in our study showed no to minimal leakage on FA from the PPA area. Therefore, the development of intraretinal fluid in patients with PPS could follow low-flow oozing of fluid from the choroid, which requires a breakdown of the outer blood–retina barrier—such as RPE atrophy in the PPA area. This process may be analogous to the development of intraretinal cysts in chronic CSC, where RPE atrophy secondary to chronic CSC leads to intraretinal cyst formation—something not characteristic of acute CSC. In PPS, however, PPA itself could be the anatomical predisposition for intraretinal cysts to form, whereas in chronic CSC, RPE atrophy develops as a consequence of CSC. Conversely, in acute CSC, presumably higher blood-flow conditions result in RPE bumps or PED, which lead to subretinal fluid but not intraretinal fluid. In one quarter of our participants with PPS, serous PED/RPE bumps with surrounding subretinal fluid developed away from the peripapillary area, suggesting an overlap between PPS and CSC (Fig. 3). Kumar et al. reported that 52.4% of patients with PPS presented with RPE gravitational tracks, serous PEDs, and outer retinal atrophy, indicating a

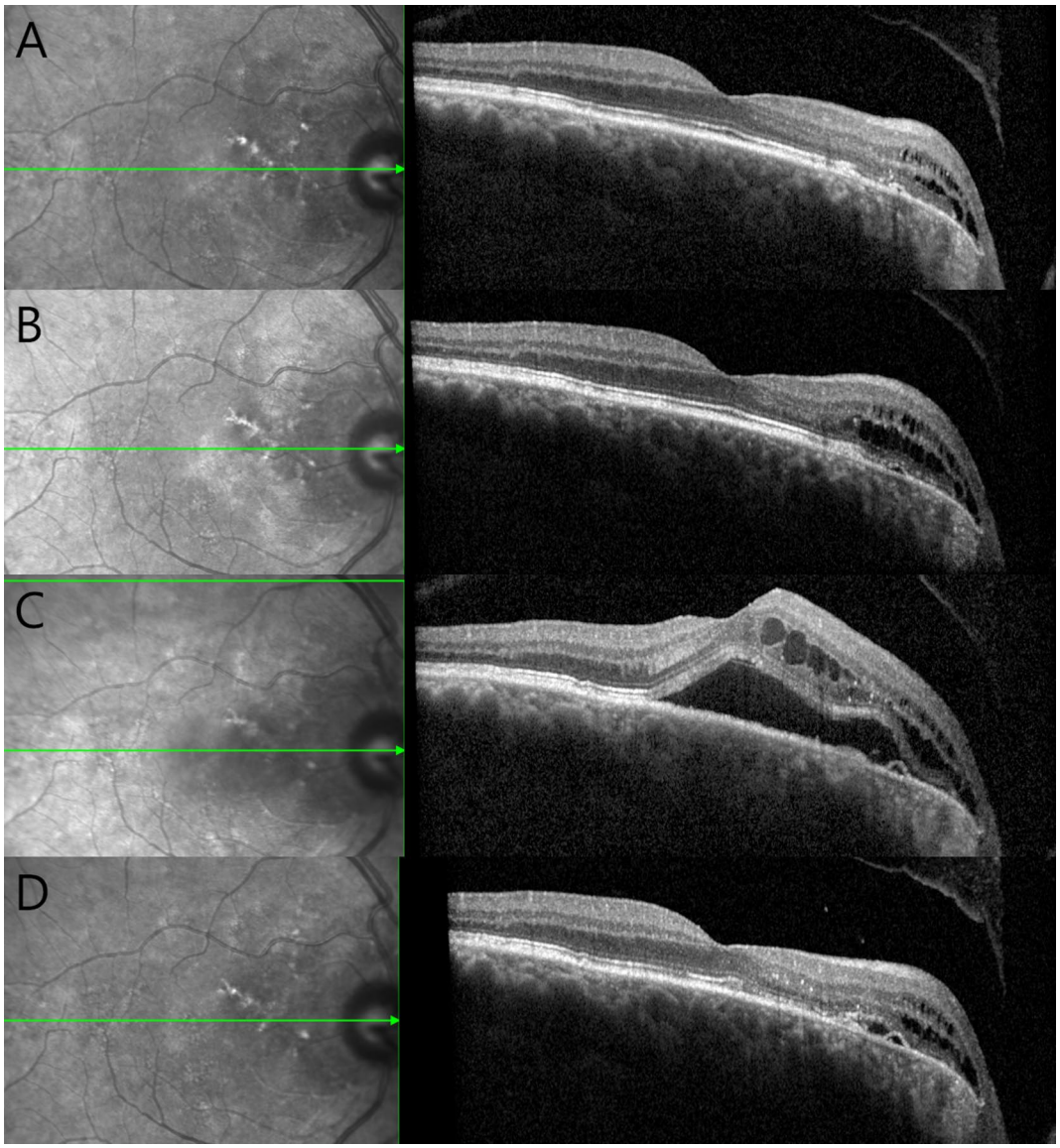


**Fig. 3** A patient with peripapillary pachychoroid syndrome (PPS) presented with intraretinal fluid at baseline (**A**), which increased after 6 months (**B**). At 8 months, the patient developed a serous pigment epithelial detachment and subretinal fluid accumulation (**C**), which almost completely resolved by month 9 (**D**)

greater overlap between PPS and CSC than we observed in our study [6].

Of the 14 patients with PPS in our study, only three were symptomatic at baseline. They were referred by community optometrists due to incidental findings on OCT scans. Considering the cohort's baseline age of 74 years, the average BCVA was very good at baseline and even though there was a statistically significant change at 1 year, there were overall only small variations from baseline. This could be explained by the fact that only six patients developed foveal intra- or subretinal fluid at any point, and only two eyes developed subfoveal RPE epitheliopathy. Phasukkijwatana et al. reported similarly good BCVA in patients with PPS [1], consistent with our findings, whereas other studies have reported significantly worse BCVA [6, 15]. Such differences in baseline BCVA among patients with PPS could be attributed to

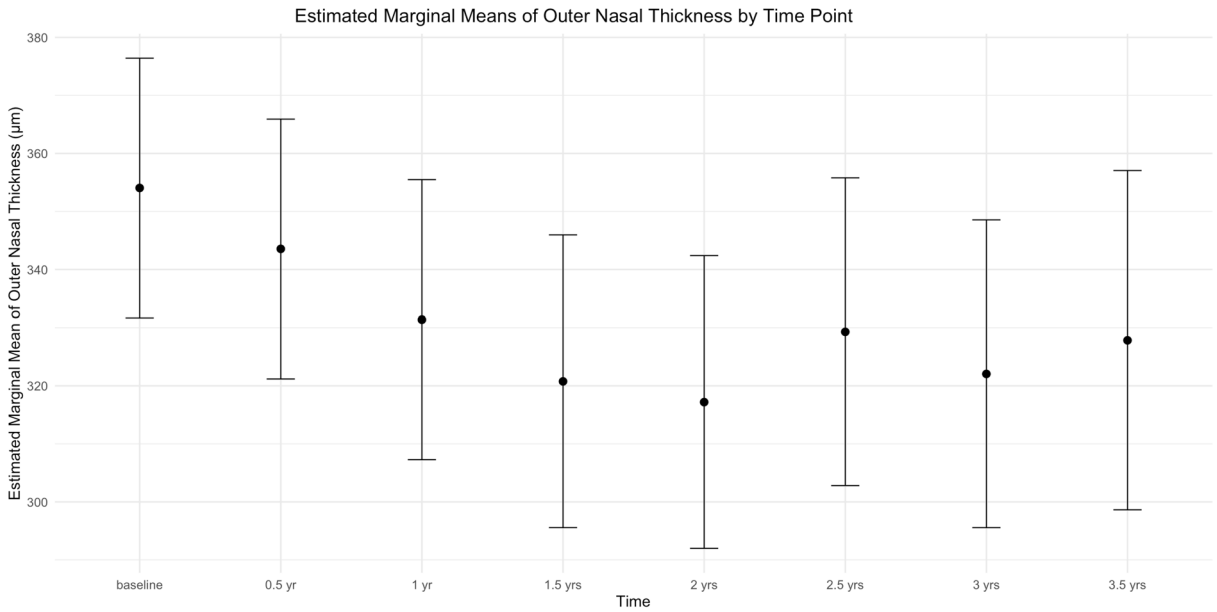


**Fig. 4** Marginal means with error bars (95% confidence interval) of the outer nasal macular thickness over time

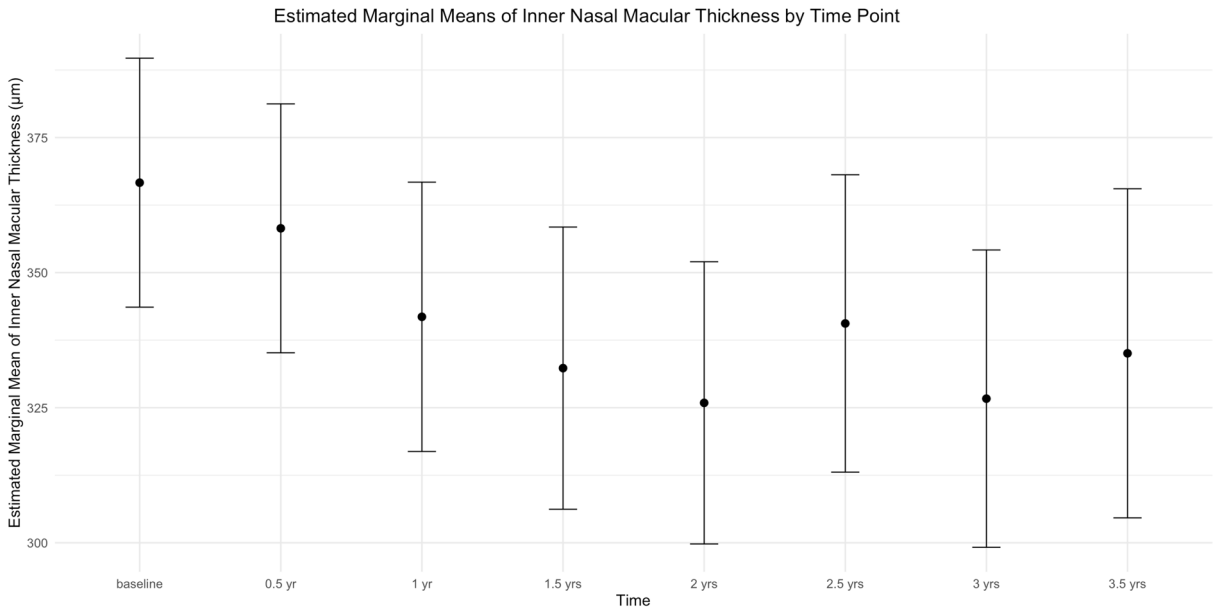


**Fig. 5** Marginal means with error bars (95% confidence interval) of the inner nasal macular thickness over time

varying referral thresholds in different countries and to the proportion of referred patients with an overlapping PPS/CSC phenotype. In the UK, asymptomatic patients commonly undergo regular OCT scans, thereby leading to referral of the full spectrum of patients with PPS. In other countries, however, OCT scans may not be as widely available, so only symptomatic patients with more severe phenotypes tend to be referred. Secondly, patients with an overlapping PPS/CSC phenotype may also contribute to worse BCVA.

**Table 2** Pairwise contrasts of outer nasal and inner nasal macular thickness (μm) and best-corrected visual acuity (LogMAR) vs. baseline (Sidak-adjusted)

| Contrast | Estimate (Δ mean) | SE | *df* | *t* value | Adjusted *p* value | |
|---|---|---|---|---|---|---|
| Outer nasal macular thickness | | | | | | |
| 0.5 year—baseline | − 10.5 | 11.3 | 90.3 | − 0.930 | 0.953 | |
| 1 year—baseline | − 22.7 | 12.2 | 93.0 | − 1.856 | 0.383 | |
| 1.5 years—baseline | − 33.3 | 12.8 | 93.7 | − 2.602 | 0.073 | |
| 2 years—baseline | − 36.9 | 12.8 | 93.7 | − 2.881 | 0.034 | |
| 2.5 years—baseline | − 24.7 | 13.5 | 93.9 | − 1.836 | 0.396 | |
| 3 years—baseline | − 32.0 | 13.5 | 93.9 | − 2.374 | 0.130 | |
| 3.5 years—baseline | − 26.2 | 14.9 | 93.9 | − 1.760 | 0.449 | |
| Inner nasal macular thickness | | | | | | |
| 0.5 year—baseline | − 8.45 | 11.9 | 90.6 | − 0.707 | 0.999 | |
| 1 year—baseline | − 24.83 | 12.9 | 93.4 | − 1.922 | 0.340 | |
| 1.5 years—baseline | − 34.33 | 13.5 | 94.1 | − 2.536 | 0.087 | |
| 2 years—baseline | − 40.75 | 13.5 | 94.1 | − 3.011 | 0.023 | |
| 2.5 years—baseline | − 26.06 | 14.3 | 94.3 | − 1.828 | 0.402 | |
| 3 years—baseline | − 39.97 | 14.3 | 94.3 | − 2.804 | 0.042 | |
| 3.5 years—baseline | − 31.59 | 15.7 | 94.5 | − 2.006 | 0.290 | |
| **Best-corrected visual acuity** | | | | | | |
| **Contrast** | **Estimate (Δ mean) (transformed data)** | **SE** | ***df*** | ***t* value** | **Adjusted *p* value** | **Estimate (Δ mean) (back-transformed estimate)** |
| 0.5 year—baseline | − 0.05 | 0.07 | 91.4 | − 0.636 | 0.995 | 0.021 |
| 1 year—baseline | − 0.22 | 0.08 | 93.4 | − 2.837 | 0.038 | 0.133 |
| 1.5 years—baseline | − 0.01 | 0.08 | 93.9 | − 0.158 | 1.000 | 0.006 |
| 2 years—baseline | 0.03 | 0.08 | 93.9 | 0.324 | 1.000 | − 0.011 |
| 2.5 years—baseline | − 0.15 | 0.08 | 94.0 | − 1.759 | 0.450 | 0.083 |
| 3 years—baseline | − 0.04 | 0.08 | 94.0 | − 0.418 | 1.000 | 0.017 |
| 3.5 years—baseline | − 0.003 | 0.09 | 94.8 | − 0.036 | 1.000 | 0.002 |

*Δ Mean* mean difference, *SE* standard error, *df* degrees of freedom

In our cohort, waxing and waning of intraretinal cysts were observed during the follow-up period, which is consistent with previous studies [4]. Our linear mixed effects model showed a progressive decline in the macular thickness of the outer and inner nasal ETDRS Subfield across follow-up visits when compared to baseline. A statistically significant reduction of the

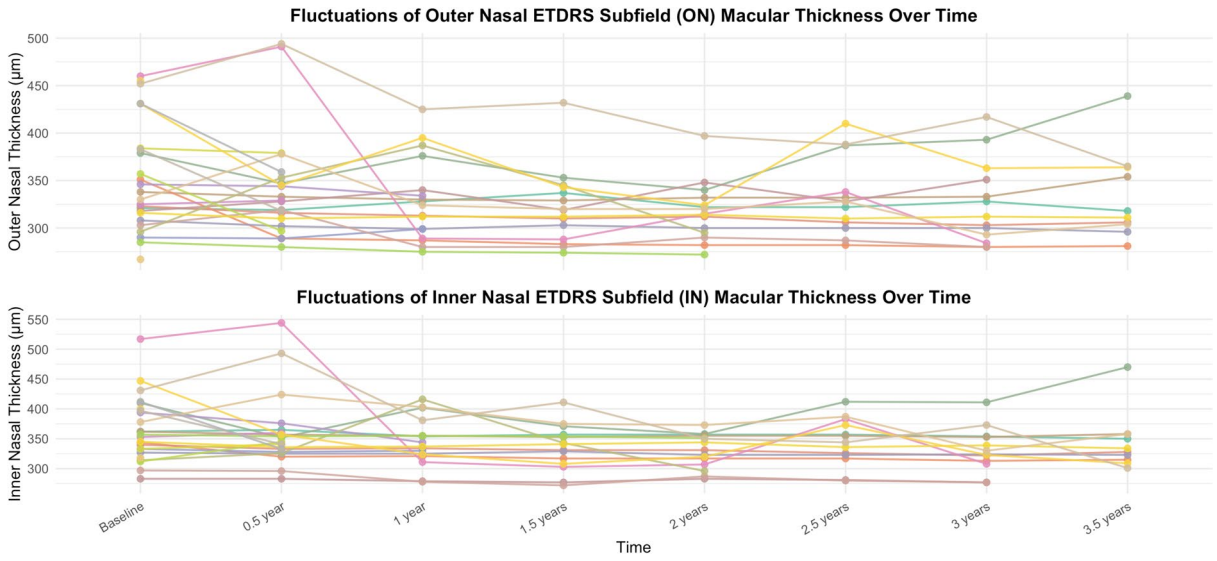


**Fig. 6** Spaghetti plots illustrating fluctuations in the thickness of both inner nasal (*bottom*) and outer nasal (*top*) ETDRS (Early Treatment Diabetic Retinopathy Study) subfield

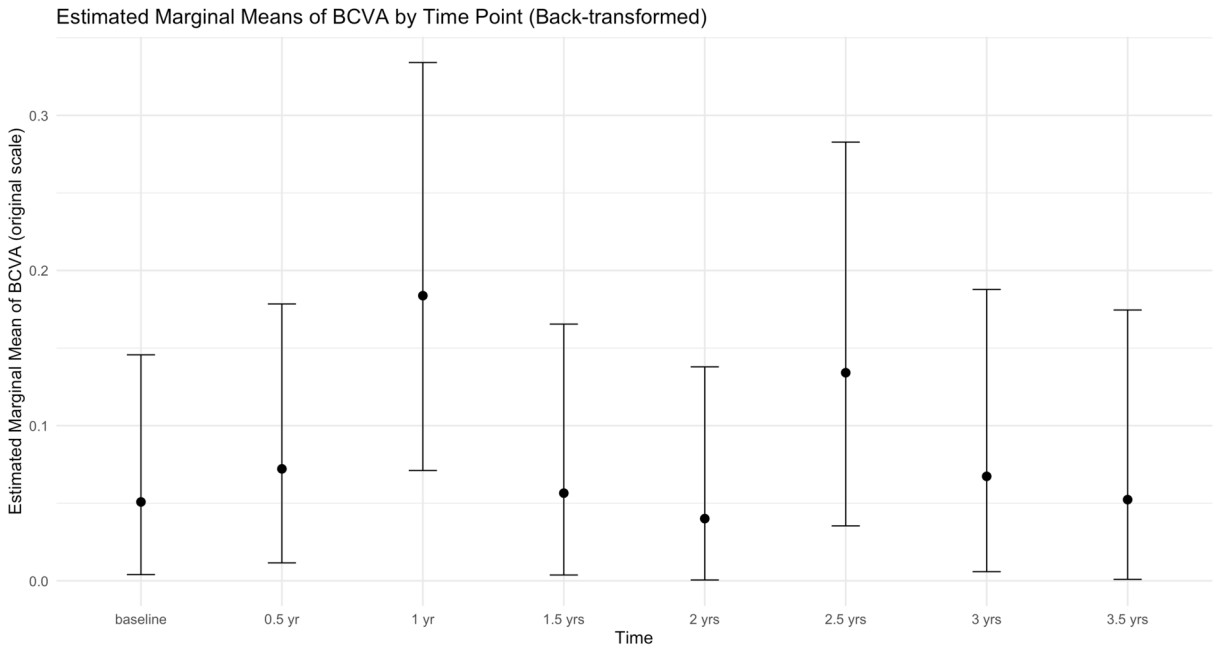


**Fig. 7** Marginal means with error bars (95% confidence interval) of best-corrected visual acuity (BCVA) over time, derived from the back-transformation of the model estimates

outer nasal and inner nasal macular thickness was observed at 2 years compared to baseline. Changes in retinal thickness may not accurately represent intraretinal fluid fluctuations since intraretinal fluid comprises only a small proportion of overall retinal thickness. Therefore, AI algorithms that quantify intraretinal fluid volume [20] might better determine intraretinal fluctuations in future studies. However, Figs. 3 and 8 clearly demonstrate

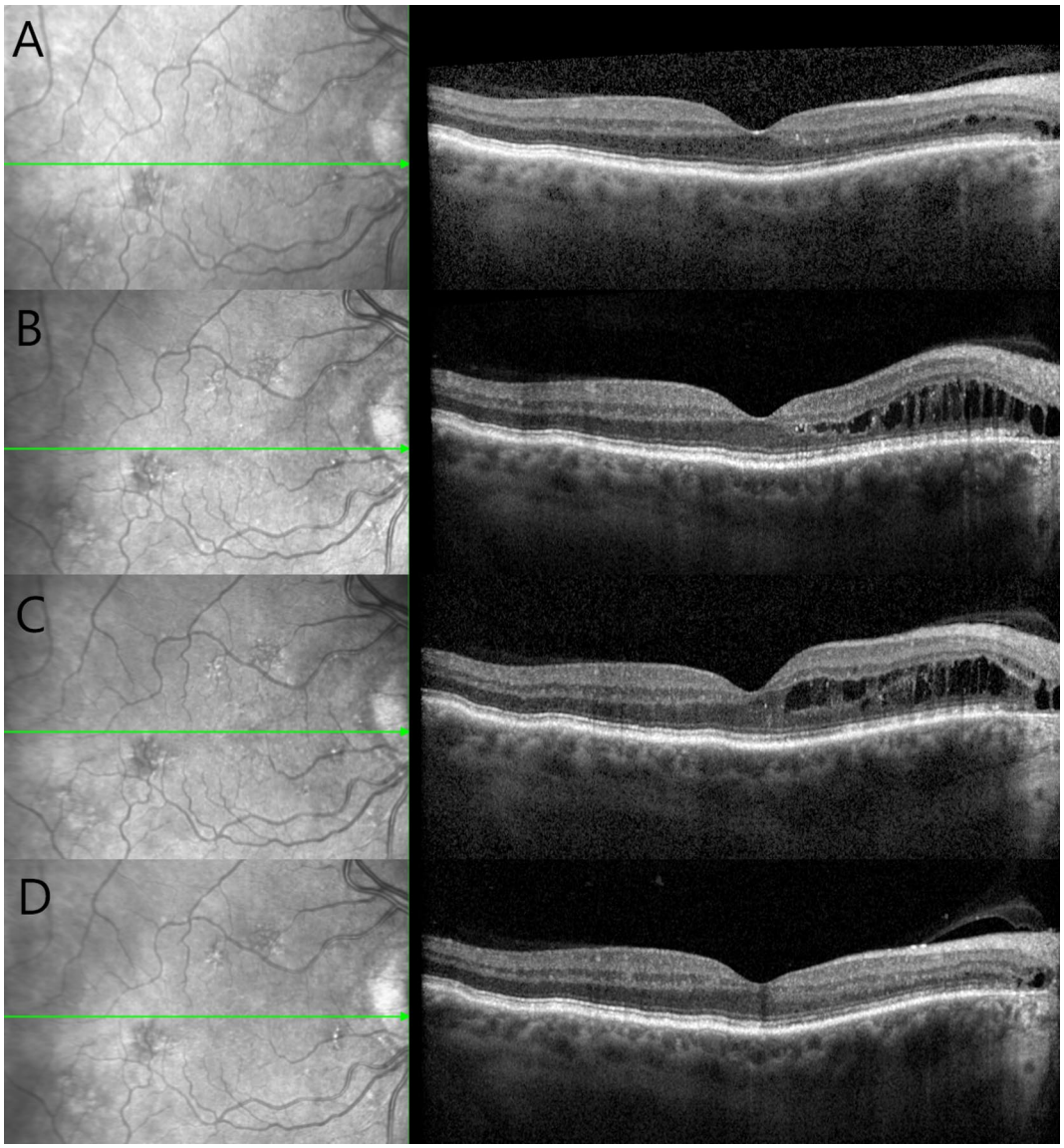


**Fig. 8** Spontaneous intraretinal fluid fluctuations in a patient with peripapillary pachychoroid syndrome over a 15-month follow-up (A = baseline, B = 6 months, C = 9 months, D = 15 months)

spontaneous intra- and subretinal fluid fluctuations in two different patients with PPS. Additionally, the spaghetti plots in Fig. 6 illustrate greater fluctuations in the IN and ON in eyes with higher baseline inner and outer macular thickness.

In chronic CSC, photodynamic therapy (PDT) is considered the gold-standard treatment [21]. Similarly, Iovino et al. reported that PDT produced a favorable response in 64% of patients with PPS, reducing both SRF height and central-subfield thickness three months after treatment [22]. Few studies have evaluated subthreshold micropulse laser or topical prednisolone, and because they lacked control groups, any apparent improvement may just mirror the condition's natural course rather than a true therapeutic effect [19–21].

Our study is important for determining how proactively we should treat patients with PPS. In our cohort, BCVA was very good at baseline and remained overall stable during follow-up visits,

suggesting that monitoring may be sufficient for many of these patients. We believe treatment should be offered to patients with PPS who have intra/subretinal fluid at the fovea for more than 3 months and to those with an overlapping PPS/CSC phenotype featuring subretinal fluid originating outside the peripapillary area. If intervention is needed, PDT has demonstrated good safety and efficacy in patients with PPS [15].

The results of this study should be interpreted within the context of its limitations. First, this was a retrospective study with a relatively small sample size and uneven number of eyes at each time point, with a progressive loss of cases over the 3.5-year follow-up. Although sample attrition increased over time, the use of a linear mixed model with time as a factor allowed for the inclusion of all available data and provided a robust approach to handling the unbalanced longitudinal dataset. Additional studies with larger patient cohorts and longer follow-up periods are needed to confirm our findings. Moreover, the relatively small sample size did not allow for co-variants testing, and future studies should focus on co-founders, including systemic risks factors.

## CONCLUSIONS

In conclusion, our study showed that all participants who developed PPS had PPA, suggesting that PPA could be an important anatomical predisposition for PPS. Most patients were asymptomatic at baseline and maintained good BCVA over the follow-up period. Therefore, the generally favorable morphological and functional outcomes indicate that treatment may be reserved for those with long-term foveal involvement (intra/subretinal fluid) and for patients with an overlapping PPS/CSC phenotype.

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***Data Availability.*** All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

### *Declarations*

***Conflict of Interest.*** Christina Karakosta, Peter Kiraly, Anastasios Bisoukis and Konstantinos I. Bougioukas have nothing to disclose. Professor M. Dominik Fischer is or has been (last 3 years) on the advisory board of and/or consulting and/or receiving honoraria/grant money/travel support from the following companies: Aavantgarde, AbbVie, Adverum, Alder Therapeutics, BlueRock, Coave Therapeutics, DORC, Janssen Research & Development, MedScape, Novartis, NMD, PeerVoice, Physicians Education Resource, Roche, RegenxBio, Sovinnova Partners, Sparing Vision, SpliceBio, STZeyetrial, THEA.

***Ethical Approval.*** This retrospective study adhered to the tenets of the Declaration of Helsinki. Since all investigations and imaging were performed as part of routine clinical care, no ethical approval was required nor consent in accordance with local/ national guidelines of the Oxford Eye Hospital Ethical Review Board.

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