Original Article

Diagnostic Performance of Fundus Autofluorescence for Detecting Polypoidal Choroidal Vasculopathy

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Objective: To investigate the efficacy of fundus autofluorescence (FAF) for differentiating polypoidal choroidal vasculopathy (PCV) from neovascular age-related macular degeneration (nAMD), and to compare FAF and optical coherence tomography (OCT) findings.

Materials and Methods: One hundred forty-one PCV and nAMD patients were retrospectively reviewed. The FAF findings were categorized into ring pattern and patch pattern. The OCT characteristics were grouped into 1) steep pigment epithelial detachment (sPED), 2) notched PED (nPED), 3) double-layer sign (DLS), and 4) hyporeflective lumen with PED.

Results: Seventy-six PCV patients were PCV (male 44.7%) and 65 patients were nAMD (male 53.8%). The sensitivity and specificity of the ring pattern in the FAF findings were 45.7% and 76.9% while the patch pattern was 59.2% and 30.8%, respectively. The PPV and NPV were 68.1% and 56.8% for the ring pattern, and 59.2% and 39.2% for the patch pattern. The ring pattern was found more frequently in the PCV group (n=32, 68%) than in the nAMD group (n=15, 32%; OR 2.8 [1.33 to 5.90]; p=0.006). Significant associations of the FAF and OCT findings were found in the groups of ring pattern and sPED (OR 6.28 [2.89 to 13.68]; p<0.001), and of patch pattern and DLS (OR 7.00 [1.56 to 31.33]; p=0.004).

Conclusion: The sensitivity and specificity of the FAF findings were low, which precludes the use of FAF as a sole diagnostic tool for PCV. However, the significant associations between the FAF and SD-OCT emphasize the use for a multimodal approach to the non-invasive diagnosis of PCV.

Keywords: Fundus autofluorescence, Polypoidal choroidal vasculopathy, Sensitivity, Specificity, Positive predictive value, Negative predictive value

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Polypoidal choroidal vasculopathy (PCV), first described in 1990, has characteristic features of vascular dilation or polyps, and a branching vascular network (BVN) in the choroids[1,2]. At present, the gold standard investigation, which best evaluates the choroidal abnormalities, is indocyanine green angiography (ICGA)[3,4]. The ICGA findings are included in the widely-used criteria for diagnosis of PCV[5]. However, ICGA is not widely available, unlike non-invasive investigations such as optical coherence tomography (OCT) and fundus autofluorescence (FAF). This situation could make the diagnosis of PCV impossible for many ophthalmologists who do not have access to ICGA.

FAF is a non-invasive and less time-consuming technique primarily used to evaluate the retinal pigment epithelial (RPE) function by detection of lipofuscin accumulation without the need for an intravenous dye-injection, like ICGA. Maculopathy with primary RPE abnormalities shows unique patterns, such as in age-related macular degeneration (AMD)[6,7] and various inherited retinopathies[8]. The secondary changes of the FAF patterns in PCV have been described as having two distinguishable features from neovascular AMD (nAMD), which are confluent hypoautofluorescence and granular hypoautofluorescence[9]. These two

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unique patterns should have some diagnostic value in differentiating PCV from the very similar clinical phenotypes of serosanguinous maculopathy found in nAMD. Thus, the primary aim of the present study was to investigate the efficacy of FAF for differentiating PCV from nAMD. The secondary objective was to compare the FAF and OCT findings relative to the diagnosis of PCV.

Materials and Methods

The protocol for the present study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The present study complied with all of the principles set forth in the Declaration of Helsinki and its subsequent provisions.

The present study was retrospective review conducted on patients with PCV and nAMD in the outpatient unit, Ophthalmology Department, Siriraj Hospital, Mahidol University, between July 2013 and January 2015. All patients were treatment-naive cases who were aged 18 years or older. The authors excluded those cases with poor quality images, chronic fibrotic scars, massive hemorrhages obscuring the underlying retinal and choroidal pathology, or uncertain diagnoses. Diagnoses were based on the color fundus photographs, FA, and ICGA. The spectral domain optical coherence tomography (SD-OCT) and FAF had to be available on the day of the investigation. For the PCV diagnoses, the EVEREST study criteria for a definitive diagnosis were followed[5].

The data collection included best-corrected visual acuity (logMAR BCVA), intraocular pressure, and the underlying systemic diseases apparent at the same visit. The fundus investigations included color fundus photographs (Kowa nonmyd7 fundus camera, Kowa company, Nagoya, Aichi, Japan), SD-OCT, FAF and simultaneous FA, and ICGA (Heidelberg Retina Angiography 2 [HRA 2], Heidelberg Engineering, Inc., Heidelberg, Germany).

The baseline characteristics and definitive diagnoses were collected by Narongkiatikhun S. All images of the ocular investigations were reviewed blindly by Prakhunhungsit S for both groups. The authors categorized the FAF findings into two groups[9], which were ring pattern and patch pattern. Ring pattern was characterized by confluent hypoautofluorescence surrounded by a ring of hyperautofluorescence while patch pattern was characterized by a hypo/hyperautofluorescence patch or abnormal autofluorescence that could not be identified within a ring of hyperautofluorescence

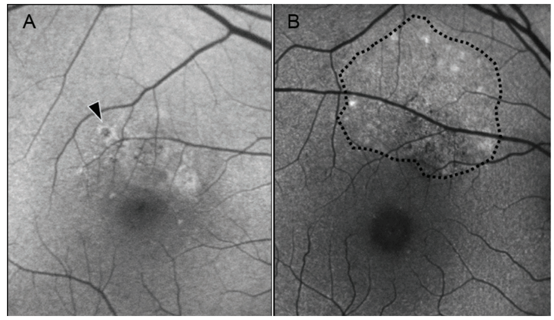

Figure 1. Fundus autofluorescence pattern showing (A) ring pattern (arrow head); hypoautofluorescence surrounded by hyperautofluorescence ring, and (B) patch pattern (dotted circle); hypo/hyper-autofluorescence patch.

(Figure 1). The definitions of the SD-OCT were 1) steep pigment epithelium (sPED), which was a steep, sharp, peak-like, and perpendicular elevation of the RPE, with underlying moderate reflectivity within the peak, 2) notched pigment epithelium detachment (nPED), which is a PED with a V-shaped depression between two PED's, 3) double-layer sign (DLS), which was two, highly-reflective, separated layers, an undulating RPE line, and a hyperreflective, straight line of Bruch membrane, with a moderate degree of hyperreflectivity between those two lines[10], and 4) a hyporeflective lumen with PED (Figure 2).

Statistical analyses were performed using SPSS Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical data were presented either as number, or as number and percentage, while continuous data were presented as mean ± standard deviation (SD). Demographic data were summarized using descriptive statistics. A univariate analysis was performed to individually evaluate the predictive significance of each factor. Student's t-test was used for normally-distributed quantitative variables, the Mann-Whitney U test was used to analyze non-normally-distributed quantitative data, and a chi-square test was used to evaluate qualitative variables. The accuracies of the FAF and SD-OCT were reported with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence interval (CI). The association between SD-OCT and FAF, the chi-square test, odds ratio, and 95% CI were used for analysis. A p-value of less than 0.05 was considered statistically significant.

Results

Seventy-six PCV patients and 65 nAMD patients

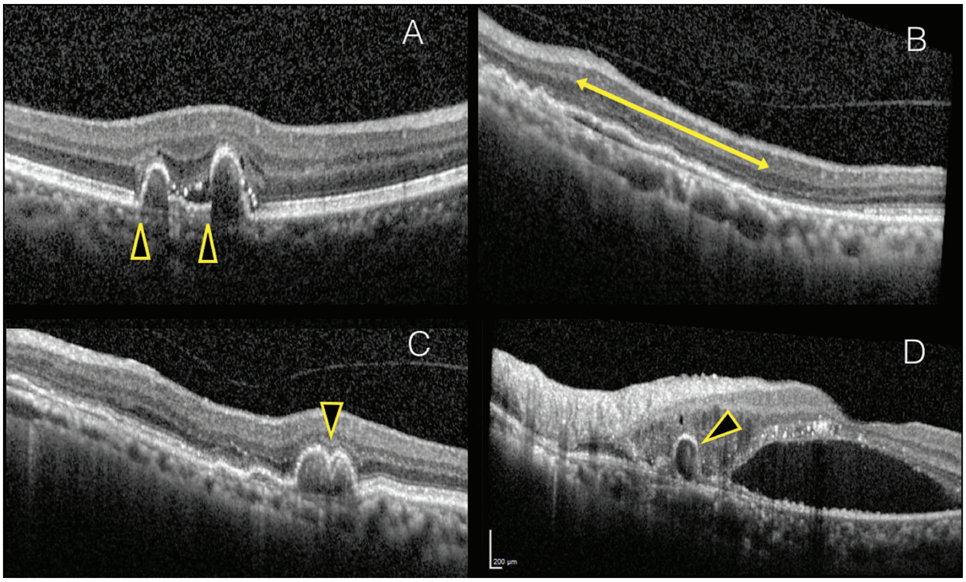

Figure 2. Optical coherence tomography of clinical signs of PCV: (A) steep pigment epithelial detachment (sPED); (B) notched pigment epithelial detachment (nPED); (C) double-layer sign (DLS); and (D) hyporeflective lumen, with retinal pigment epithelial detachment.

Table 1. Fundus autofluorescence findings in the affected eyes

FAF features	PCV group (n=76) n (%)	nAMD group (n=65) n (%)	p-value
Ring pattern	32 (68)	15 (32)	0.006
Patch pattern	45 (50)	45 (50)	0.217

FAF=fundus autofluorescence; PCV=polypoidal choroidal vasculopathy; nAMD=neovascular age-related macular degeneration

p<0.05 indicates statistical significance

were included in this study. Twenty-seven cases of equivocal findings for which a definitive diagnosis could not be made included 12 cases of poor image quality of SD-OCT, FAF, FA, and ICGA, which precluded correct interpretations, eight cases with massive hemorrhage, and seven cases with macular fibrotic scars, either resulting from advanced stage of disease or previous laser intervention.

There were more female than male patients in the PCV group (53.5% female versus 44.7% male), whereas the reverse situation in the nAMD group (53.8% male versus 46.2% female). The mean age ± SD was 66.6±8.9 years for the PCV group, and 72.7±8.41 years for the nAMD group (p<0.001). The presenting BCVA for the two groups did not differ (logMAR 0.62±0.45 in PCV versus 0.77±0.54 in nAMD).

The qualitative FAF findings showed the ring pattern was found more often in the PCV group (n=32, 68%) than the nAMD group (n=15, 32%; OR 2.8 [1.33 to 5.90]; p=0.006). In contrast, the incidence of the patch pattern in the groups did not differ significantly (p=0.217) (Table 1). The ring pattern on FAF had a sensitivity and specificity of 45.7% and 76.9%, respectively while the patch pattern showed less sensitivity and specificity than the ring pattern, with values of 59.2% and 30.8%. The PPV and NPV were 68.1% and 56.8% for the ring pattern, and 59.2% and 39.2% for the patch pattern (Table 2). The associations of FAF and SD-OCT features in PCV are described in Table 3.

Discussion

The common causes of serosanguinous maculopathy found in aging patients are PCV and nAMD. The proportions of those two diseases varies greatly among ethnicities[11,12] with a preponderance of PCV over nAMD in many Asian studies[13,14]. In general practice, the need to differentiate between PCV and nAMD is mandatory since they are vastly different in terms of their treatment modalities[5,15] and visual prognoses[12]. In the case of PCV, prompt or early photodynamic therapy is currently under investigation for the early quiescent stage of the active disease[5]. Thus, FAF may have additional

Table 2. Sensitivity, specificity, and predictive values of fundus autofluorescence in detecting polypoidal choroidal vasculopathy

FAF features	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Ring pattern	45.7 (33.7 to 58.1)	76.9 (64.8 to 86.5)	68.1 (52.9 to 80.9)	56.8 (45.8 to 67.3)
Patch pattern	59.2 (47.3 to 70.4)	30.8 (19.9 to 43.5)	59.2 (39.3 to 60.7)	39.2 (25.8 to 53.9)
Ring or patch pattern	94.3 (86.0 to 98.4)	7.69 (2.5 to 17.1)	52.38 (43.3 to 61.4)	55.56 (21.2 to 86.3)

FAF=fundus autofluorescence; CI=confidence interval; PPV=positive predictive value; NPV=negative predictive value

Table 3. The associations of fundus autofluorescence and optical coherence tomography features in polypoidal choroidal vasculopathy

OCT features	FAF features							
	Ring pattern, n (%)				Patch pattern, n (%)			
	Negative	Positive	p-value	OR (95% CI)	Negative	Positive	p-value	OR (95% CI)
sPED			<0.001	6.3 (2.89 to 13.68)			0.04	0.5 (0.24 to 0.96)
Negative	57 (64.8)	12 (22.6)			19 (37.3)	50 (55.6)		
Positive	31 (35.2)	41 (77.4)			32 (62.7)	40 (44.4)		
nPED			0.34	0.69 (0.33 to 1.47)			0.47	1.32 (0.62 to 2.81)
Negative	58 (65.9)	39 (73.6)			37 (72.5)	60 (66.7)		
Positive	30 (34.1)	14 (26.4)			14 (27.5)	30 (33.3)		
DLS			0.90	0.94 (0.37 to 2.42)			0.004	7 (1.56 to 31.33)
Negative	74 (84.1)	45 (84.9)			49 (96.1)	70 (77.8)		
Positive	14 (15.9)	8 (15.1)			2 (3.9)	20 (22.2)		

FAF=fundus autofluorescence; OCT=optical coherence tomography; sPED=steep pigment epithelial detachment; nPED=notched pigment epithelial detachment; DLS=double-layer sign; OR=odds ratio; CI=confidence interval

p<0.05 indicates statistical significance

value in performing diagnoses or, at least, in guiding ophthalmologists when to decide if there is a need for further ICGA investigation. This could lead to a reduction in the number of unnecessary dye injections in vulnerable patients.

In the current study, the proportion of male gender in the PCV group was rather low compared with that for the nAMD group and with those reported in other Asian PCV studies. A male predominance in PCV is well recognized and confirmed in Asian population[12-14,16]. The discrepancy in the proportion of males in the present study might be from variations among the different populations, or from an uneven population distribution (since the present study was not a population-based study). The presenting BCVA was relatively similar between the groups, but this does not imply that both groups had similar presenting visual impairments. In terms of BCVA, the authors cannot compare the difference between groups due to a strict exclusion criteria that might obscure the visualization of the fundus images.

In addition, the median age of patients in the PCV group was lower than that of the nAMD group with statistical significance. Many studies have shown the same trend towards a younger age for PCV subjects than nAMD subjects[15].

In terms of FAF images, the ring pattern was observed significantly more often in the PCV group than in the nAMD group (Table 1). The secondary change of RPE function, resulting from neovascularization either above or underneath the RPE or in the choroidal layers, affects the signal intensity alterations of the FAF images[17].

The present study is the first paper to study the sensitivity and specificity of FAF to detect PCV (Table 2). Unfortunately, the FAF patterns showed slightly low diagnostic efficacy for differentiating PCV from nAMD. The patch pattern had lower diagnostic values for sensitivity, specificity, PPV, and NPV. The authors observed that it was more difficult to confidently interpret whether the pattern was solely a patch pattern. Changes in FAF images could be affected by many factors, such as a pigmentary change secondary to chronic diseases, some retinal hemorrhages accumulated in the capturing area, and even the granular change to other macular abnormalities that were not seen in fundus photographs. When the authors compared the statistical values on detection of PCV with SD-OCT[2], the study showed impressively higher values for sensitivity and specificity. Consequently, for detection of PCV, the authors suggest that FAF cannot be used alone as a good diagnostic test. The difference in the diagnostic performance of these two techniques may be due to the nature of the investigations themselves. The SD-OCT can show three dimensions of retinal and choroidal pathology directly, or at least two-dimensional cross-sectional images, which can be referred to the obvious pathology. This advantage of SD-OCT may encourage the use of this technique as a more convenient tool for clinicians in their daily clinical practice. Hence, the clearer images and definitions of the SD-OCT might be the cause of the improved statistical parameters.

The present study found a significant association between the ring pattern on the FAF images and steep PED on the SD-OCT images ($p<0.001$, OR 6.3, 95% CI 2.9 to 13.7) (Table 3). This could imply local RPE damage had been caused by anterior bulging of the steep PED. Many studies have reported that the ring pattern was correlated with the protrusion of the vascular polyps[18], causing mechanical stretching of the overlying RPE[9] and resulting in a change in the FAF intensity signal. The perpendicular wall of the steep PED could form the ring of hyperautofluorescence seen in the ring pattern.

In contrast, the patch pattern was found in approximately equal proportions in the two groups. However, when the lesion with the SD-OCT findings were correlated, the authors found this pattern correlated significantly with the DLS ($p=0.004$, OR 7, 95% CI 1.56 to 31.33) (Table 3). Previous studies have reported the DLS frequently corresponds to the BVN seen on ICGA[10,19]. The widespread-patch pattern on FAF could result from the alteration of the overlying RPE caused by the exudative effect of the BVN[19]. However, as there was no BVN found in nAMD, the patch pattern found in nAMD in the present study could have arisen from the choroidal neovascularization (either type 1 or type 2) affecting the adjacent RPE[17]. The equality in the two groups downgrades the clinical value of the patch pattern for use as a distinguishing sign to suggest whether a disease is PCV or nAMD. Moreover, we also found a statistically significant correlation between sPED and patch pattern ($p=0.04$, OR 0.5, 95% CI 0.24 to 0.96) (Table 3). The weak correlation between these two findings could be from the heterogonous characteristics of the FAF images affecting images interpretation. In addition, it could be by chance that we found these two findings, ring and patch patterns, within a single image. Therefore, we encourage that FAF patterns other than these patterns should be classified, defined in detail, and further studied.

The quality of the FAF images may be affected by two capturing methods, fundus camera, and confocal scanning laser ophthalmoscope (cSLO)[17]. The present study used FAF from the cSLO technique, which has more advantages in terms of a better contrast, less scattering from opaque media, and a higher resolution. Even for the best of the imaging techniques, making a cSLO FAF interpretation may be difficult for many ophthalmologists who lack experience. Thus, the authors tried to simplify the definitions of each finding to ease the process of interpreting the images. The authors defined FAF using two easily-distinguished patterns, the ring and the patch pattern. For the definition of a patch pattern, it was a hypo/hyperautofluorescence patch, or at least an abnormal autofluorescence that could not be identified within a ring of hyperautofluorescence. The reason behind this is because the nature of the two-dimensional photographs of FAF is reader dependent. It is sometimes difficult to classify the FAF findings into the more complicated FAF patterns. Consequently, these difficulties make the FAF inconvenient to use for screening or diagnosis purposes. As a result, the FAF could make the diagnostic performance of the pattern unacceptably lower than the other investigations.

However, FAF is not of less benefit since it can give details of the overlying RPE function[20]. FAF not only gives the distinct patterns to identify an underlying pathology, but it can also be used to explain the visual prognosis of the PCV. Suzuki et al[20] reported the changes in the FAF patterns in PCV over a three-year period. This could be further applied into visual outcome prediction since the local FAF changes seen in a ring pattern reflects a small area of RPE deterioration, which could lead to a better visual prognosis. The more widespread changes in RPE in a patch pattern, resulting in the alterations of the overlying retina function, could result in a worse visual outcome for patients with this sign. Einbock et al[6] reported the changes in visual outcomes related to the pattern of FAF findings, but the study was done on patients with AMD. Thus, FAF should have some prognostic value for visual outcome predictions in patients with PCV in the future.

Therefore, the authors recommend that FAF should not be used alone due to its low diagnostic values and the limitations of interpreting its images. Nevertheless, the authors do recommend using FAF as one of the multimodal investigations for a PCV diagnosis.

Limitation

The present study had some mentionable limitations. First, consistent with the retrospective nature, some patient data may have been incomplete. Second, the size of the study population was relatively small, and this may have had the effect of underpowering the study's statistical significance of some relationships. Third, the limitation of the interpretation of the FAF images was reader dependent. The strict definition of the findings of each sign needs to be rigorously followed, and the authors stringently followed the definitions in this paper. A further study using a large sample size and a multicenter setting are needed to confirm the findings of the present study.

Conclusion

The sensitivity and specificity of FAF findings were unacceptably low, which precludes the use of FAF as a sole diagnostic tool for PCV. However, the ring pattern that was significantly found in PCV patients could be used as a valuable sign for differentiating PCV from nAMD. The significant association between the ring pattern and sPED emphasizes the need for a multimodal approach to the non-invasive diagnosis of PCV.

What is already known on this topic?

FAF is an invasive investigation aimed for RPE evaluation that is used widely in many retinal diseases. The change or loss of signal in FAF photos represents some distinguishing features in some macular disorders. Some studies investigated the unique FAF patterns found in PCV. However, this technic has never been studied to diagnose PCV from nAMD in terms of statistical value.

What this study adds?

This study shows the diagnostic and statistical performance of FAF to detect PCV. However, these parameters are quite low, and this could be due to the nature of investigation itself. This finding prevents the sole use of FAF in diagnosis of PCV.

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Conflicts of interest

The authors declare no conflict of interest.

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