Factors influencing visual acuity in patients with active polypoidal choroidal vasculopathy and imaging parameters changes

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Abstract

We performed a retrospective, observational study for 51 eyes of 51 treatment-naive patients with polypoidal choroidal vasculopathy (PCV), whose lesion ranged within the 6x6mm scope of optical coherence tomography angiography (OCTA). Patients were divided into two groups based on the pattern of branching vascular network (BVN) on OCTA: ill-defined group and well-defined group. BVN morphology was not related to baseline best-corrected visual acuity (BCVA). But the improvement of BCVA had a significant positive relationship with the pattern of BVN on OCTA ($r = 0.306, p = 0.031$). The BCVA in the ill-defined BVN group (-0.18 [interquartile range: -0.40 to 0.00]) was significantly improved after anti-vascular endothelial growth factor (VEGF) injections, compared with that (0.00 [interquartile range: -0.18 to 0.00]) in the well-defined group ($z = 2.143, p = 0.032$). Multiple logistic regression analysis showed that male sex, smaller number of injections, and presence of polypoidal lesions on OCTA images at baseline predicted a poor prognosis of polypoidal lesions on OCTA images after anti-VEGF therapy (all $p < 0.05$). Finally, BCVA at baseline and the number of injections were protective factors for BCVA after anti-VEGF therapy (all $p < 0.05$). In contrast, history of hypertension and macular edema at baseline were risk factors for BCVA after anti-VEGF injections (all $p < 0.05$).

Introduction

Polypoidal choroidal vasculopathy (PCV), a subtype of neovascular age-related macular degeneration (nAMD), is characterized by polypoidal lesions at the terminus of the branching vascular network (BVN) on indocyanine green angiography (ICGA). The increasing use of multimodal imaging, especially optical coherence tomography (OCT) and OCT angiography (OCTA), has provided cumulative evidence that PCV is vascular and originates from the type 1 neovascular network. Recently, PCV was classified into the pachychoroid disease spectrum, characterized by Haller’s layer vessel dilatation and attenuated choriocapillaris. These related choroidal changes have a relationship with the locations of BVN ingrowth, suggesting that these pachychoroidal features underlie the pathogenesis of PCV lesions. To the best of our knowledge, there have been studies on the relationship between the morphological characteristics of polypoidal lesions and visual acuity, but not on BVN. Therefore, this study investigates the relationship between BVN morphology and changes in visual acuity, as well as its associated imaging features. Given the variable size and morphology of PCV, those with massive hemorrhage or BVN extending beyond the scope of OCTA may have a different course or nature than those with PCV confined to the macular area with limited hemorrhage. As a result, we limited our study to PCV with limited hemorrhage and confined to the macula.

Anti-vascular endothelial growth factor (VEGF) monotherapy is the preferred treatment to achieve the best visual outcomes for PCV with as few injections as possible. However, to date, there are still lack of standard imaging parameters to determine visual and structural prognosis. Our study also analyzed the effect of anti-VEGF therapy for PCV patients and their morphological changes, and investigated the parameters influencing the prognosis of visual acuity.
Results

General patient information

Excluding the patients with quiescent PCV and massive hemorrhage PCV, this study enrolled fifty-one PCV eyes (26 right eyes and 25 left eyes) of 51 patients with a mean age of 65.0 years (interquartile range: 62.0–71.0 years), including 27 males and 24 females, and the average number of injections was 5 times (interquartile range: 4 to 8, Table 1). At baseline, similar best-corrected visual acuity (BCVA) was found in the ranibizumab (0.70 [interquartile range: 0.655–1.325]), conbercept (0.70 [interquartile range: 0.40-1.00]), and combined groups (0.71 [interquartile range: 0.40-1.00], F = 0.355, p = 0.703).

Compared with the baseline (0.70 [interquartile range: 0.40-1.00]), BCVA at last visit (0.60 [interquartile range: 0.40-1.00]) was significantly improved (z = 3.093, p = 0.002, Table 1). However, there was no difference in BCVA improvement between the ranibizumab (0.70 [interquartile range: 0.52–1.24]), conbercept (0.52 [interquartile range: 0.30-1.00]), and combined groups (0.56 [interquartile range: 0.375–0.82], F = 2.438, p = 0.098) at last visit. Final BCVA was positively correlated with baseline BCVA (r = 0.682, p < 0.001), medical history of hypertension (r = 0.288, p = 0.040), presence of macular edema at baseline (r = 0.540, p < 0.001), central foveal thickness (CFT) at baseline (r = 0.415, p = 0.002), pigment epithelium detachment (PED) height at baseline (r = 0.370, p = 0.007), presence of macular edema after anti-VEGF injections (r = 0.350, p = 0.012), CFT after anti-VEGF injections (r = 0.364, p = 0.009), and PED height after anti-VEGF injections (r = 0.279, p = 0.048). After adjusting for age, linear regression analysis revealed that baseline BCVA (B = 0.383, 95%CI [0.193–0.572], t = 4.087, p < 0.001), and the number of injections (B=-0.030, 95%CI [-0.058–0.002], t = 2.156, p = 0.037) were protective factors for BCVA after anti-VEGF injections. In contrast, medical history of hypertension (B = 0.222, 95%CI [0.068–0.375], t = 2.913, p = 0.006), and presence of macular edema at baseline (B = 0.297, 95%CI [0.040–0.555], t = 2.330, p = 0.025) were risk factors for BCVA after anti-VEGF injections. (Fig. 1)

Variation and correlation of OCTA images

According to OCTA profile at baseline, fifteen eyes were regarded as ill-defined type, twenty-three eyes was regarded as mulberry type, twelve eyes was regarded as medusa (or sea-fan shape) type, and one eye was regarded as dead-tree type (Fig. 2). Four participant’s BVN morphological subtypes had changed on OCTA after anti-VEGF treatment (Table 1). However, generally, the ratio of this change was statistically insignificant (z = 0.855, p = 0.393). For further analysis, mulberry type and medusa (or sea-fan shape) type are grouped together as well-defined group. Since dead-tree type is mostly found in the advanced stages of the disease, and there was only one case, it was excluded from the following comparison. Thus, fifteen eyes were assigned to the ill-defined group, while thirty-five eyes were assigned to the well-defined group. The BCVA improvement had a significant positive relationship with the classification of BVN on OCTA (r = 0.306, p = 0.031). The BCVA in the ill-defined group (-0.18 [interquartile range: -0.40 to 0.00]) was significantly improved after anti-VEGF injections, compared with that (0.00 [interquartile range: -0.18 to 0.00]) in the well-defined group (z = 2.143, p = 0.032). The improvement of CFT in the ill-defined group (–) was more significantly than that in the well-defined group (0.00 [interquartile range: -0.18 to 0.00]) (z =
2.143, p = 0.032). However, no difference was found in age, gender, the number of injections, baseline BCVA, baseline subfoveal choroidal thickness (SFCT), baseline CFT, baseline subretinal fluid (SRF), baseline PED height, SFCT improvement, SRF improvement and PED height improvement (Table 2).

Table 1

<table>
<thead>
<tr>
<th>General information and measurements</th>
</tr>
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<tbody>
<tr>
<td>At baseline</td>
</tr>
<tr>
<td>LogMAR BCVA</td>
</tr>
<tr>
<td>The total number of injections</td>
</tr>
<tr>
<td>Macular edema (OCT)</td>
</tr>
<tr>
<td>BVN(OCTA)</td>
</tr>
<tr>
<td>Mulberry type</td>
</tr>
<tr>
<td>Medusa or sea-fan shape type</td>
</tr>
<tr>
<td>Dead tree type</td>
</tr>
</tbody>
</table>

BCVA: best-corrected visual acuity; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography
Table 2
The comparison of imaging parameters between ill-defined and well-defined groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ill-defined group (n = 15)</th>
<th>Well-defined group(n = 35)</th>
<th>z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>221.000</td>
<td>851.000</td>
<td>0.880</td>
<td>0.379</td>
</tr>
<tr>
<td>Gender</td>
<td>210.000</td>
<td>330.000</td>
<td>1.287</td>
<td>0.198</td>
</tr>
<tr>
<td>The number of injections</td>
<td>233.000</td>
<td>353.000</td>
<td>0.640</td>
<td>0.522</td>
</tr>
<tr>
<td>Baseline BCVA, logMAR</td>
<td>23.80</td>
<td>-0.03</td>
<td>0.117</td>
<td>0.907</td>
</tr>
<tr>
<td>Baseline SFCT</td>
<td>207.500</td>
<td>837.500</td>
<td>1.164</td>
<td>0.244</td>
</tr>
<tr>
<td>Baseline CFT</td>
<td>205.000</td>
<td>835.000</td>
<td>1.048</td>
<td>0.295</td>
</tr>
<tr>
<td>Baseline SRF</td>
<td>258.000</td>
<td>378.000</td>
<td>0.097</td>
<td>0.923</td>
</tr>
<tr>
<td>Baseline PED height</td>
<td>225.500</td>
<td>345.500</td>
<td>0.810</td>
<td>0.418</td>
</tr>
<tr>
<td>BCVA improvement, logMAR</td>
<td>163.500</td>
<td>283.500</td>
<td>2.143</td>
<td><strong>0.032</strong></td>
</tr>
<tr>
<td>SFCT improvement</td>
<td>213.000</td>
<td>843.000</td>
<td>1.048</td>
<td>0.295</td>
</tr>
<tr>
<td>CFT improvement</td>
<td>150.500</td>
<td>780.500</td>
<td>2.371</td>
<td><strong>0.018</strong></td>
</tr>
<tr>
<td>SRF improvement</td>
<td>183.000</td>
<td>813.000</td>
<td>1.711</td>
<td>0.087</td>
</tr>
<tr>
<td>PED height improvement</td>
<td>231.500</td>
<td>861.500</td>
<td>0.675</td>
<td>0.500</td>
</tr>
</tbody>
</table>

Wilcoxon-Mann-Whitney test, bold face values indicate P < 0.05

The polypoidal lesions on OCTA images after anti-VEGF injections were positively correlated with male patients (r = 0.367, p = 0.008), the presence of polypoidal lesions on OCTA images (r = 0.331, p = 0.018) at baseline, and the presence of polypoidal lesions on OCT images (r = 0.478, p < 0.001) after anti-VEGF injections. After adjusting for age, multiple logistic regression analysis showed that male sex (p = 0.005), the presence of polypoidal lesions on OCTA at baseline (p = 0.008), and fewer injections (p = 0.033) predicted a poor prognosis of polypoidal lesions on OCTA after anti-VEGF injections (Table 3).
Table 3
The influential factors for the prognosis of polyps on OCTA

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>OR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.050</td>
<td>1.051</td>
<td>0.962–1.148</td>
<td>0.274</td>
</tr>
<tr>
<td>Gender</td>
<td>2.577</td>
<td>13.153</td>
<td>2.187–79.100</td>
<td>0.005</td>
</tr>
<tr>
<td>PLs on OCTA at baseline</td>
<td>2.364</td>
<td>10.637</td>
<td>1.840-61.485</td>
<td>0.008</td>
</tr>
<tr>
<td>The number of injections</td>
<td>-0.412</td>
<td>0.663</td>
<td>0.454–0.967</td>
<td>0.033</td>
</tr>
</tbody>
</table>

PLs: polypoidal lesions; OCTA: optical coherence tomography angiography

Comparison of the incidence of imaging parameters at baseline

In the early stages of ICGA, 68.6% of eyes with PCV showed BVN, which was lower than the detection rate of double-layer sign (DLS) on OCT (96.1%, z = 3.5, p < 0.001). Similarly, 60.8% of eyes with PCV showed late geographic hyperfluorescence (LGH) in the late stage of ICGA, which was lower than the detection rate of choroidal pachyvessels on OCT (96.1%, z = 4.025, p < 0.001). According to the non-invasive detection of polypoidal lesions, OCTA had a relatively lower detection rate (20/51) than OCT (35/51, z = 3.441, p = 0.001). OCTA had a similar detection capability for BVN (70.6%) with ICGA (68.6%, z = 0.243, p = 0.808).

Variation and correlation of imaging parameters

At baseline, the SFCT was 287 (interquartile range: 187.0-370.0) µm, which had a positive relationship with BVN (r = 0.352, p = 0.011) and LGH (r = 0.349, p = 0.012) on ICGA, as well as polypoidal lesions (r = 0.314, p = 0.025) and pachyvessels (r = 0.295, p = 0.036) on OCT, respectively.

After anti-VEGF therapy, the CFT was decreased significantly from 431.0 (interquartile range: 341.0-698.0) µm at baseline to 350.0 (interquartile range: 242.0-580.0) µm (z = 3.923, p < 0.001) at last visit. Similarly, there was a reduction in SRF from 140.0 (interquartile range: 0.0-257.0) µm at baseline to 0.0 (interquartile range: 0.0-165) µm (z = 3.137, p = 0.002). However, no difference was found in PED height between the baseline (61.0 [interquartile range: 0.0-234.0] µm) and the last visit (55.0 [0.0-215.0] µm; z = 1.356, p = 0.175). There was no difference in SFCT between the baseline and the last visit. (275.0 [interquartile range: 220.0-358.0] µm; z = 0.244, p = 0.807).

In addition, the proportion of polypoidal lesions on OCT was 51.0% after anti-VEGF injections, which was significantly lower than that at baseline (z = 2.183, p = 0.029). The reduction in pachyvessels on OCT was also observed from the baseline (49/51) to last visit (40/51, z = 3.0, p = 0.003). However, the change of
DLS (96.1%), macular edema on OCT (23.5%), and polypoidal lesions on OCTA (35.3%) after anti-VEGF injections were insignificant compared with baseline (all p > 0.05).

Comparing the incidence of baseline imaging parameters, we found that the detection rate of the DLS on OCT was higher than BVN on ICGA. In our study, BVN (68.6%) had a similar incidence with previous study. The term BVN is commonly used to describe the whole network area or the relatively large vessels in PCV eyes, which is now considered type 1 macular neovascularization. Previous histology studies showed that the space within the DLS contained macular neovascularization as well as serous fluid, exudation, thickened extracellular matrix material, or was thickened beneath the basal laminar deposits. A previous study indicated that the extent of the DLS on OCT was larger than BVN on ICGA in some cases. Therefore, the detection probability of DLS is greater than BVN, although DLS usually spatially represents the area of the BVN, even though they are not identical. We found that the detection rate of pachyvessels on OCT was higher than that of LGH on ICGA, although LGH and pachyvessels are thought to be related to choroidal vascular hyperpermeability. LGH was defined as a well-demarcated geographic hyperfluorescent lesion in the late phase of ICGA. Our results were similar with those of a previous study in which LGH was noted in most PCV eyes. Kim et al found that all eyes that developed active PCV had LGH at baseline, and vice-versa. Vessel dilation may be derived from vortex venous engorgement and anastomosis, and macular choroidal vessels could not modulate pressure by vortex vein outflow, so that the regional vessel pressure could be abnormally high, which may result in vascular remodeling. Therefore, pachyvessels may be an early change that appears before the clinical manifestation of PCV, which coincides with a report by Siedlecki et al. We assessed two non-invasive examinations to detect polypoidal lesions and found OCTA had a relatively lower detection rate than OCT. Our study showed similar detection rates of polypoidal lesions with previous studies on OCT and OCTA. Ring-like or bubble-like changes on OCT are highly suggestive of polypoidal lesions and are characteristic of PCV. Although slow and turbulent flow within polypoidal lesions or circulation at the periphery of an aneurysmal dilation might contribute to poor detection on OCTA, these cannot fully replace ICGA. In this regard, the Asia Pacific Ocular Imaging Society PCV workgroup recently provided recommendations for the non-invasive diagnosis of PCV.

On OCT imaging, SRF height, CFT, polypoidal lesions and pachyvessels were decreased significantly after treatment, similar to previous studies. Additionally, SFCT was positively related to the presence of BVN and LGH on ICGA, as well as to polypoidal lesions and pachyvessels on OCT. LGH and pachyvessels are representative signs of choroidal vascular hyperpermeability, which can increase extravascular volume, leading to higher SFCT. The presence of hyperpermeability is a significant risk factor for the development of active PCV. Cheung et al indicated that polypoidal lesions tended to be larger in eyes with increasing SFCT, similar to our results.

This study had several limitations. This was a retrospective, single-center study with a limited sample size. Patients with large hemorrhage or PEDs were excluded so that all parameters could be compared in the same individual, therefore, the findings may primarily refer to PCV eyes with limited hemorrhage.
These patients have minimal bleeding and are small in extent. Also, Pachyvessels did not have a size criterion, thus we just conducted a qualitative analysis based on their appearance on OCT. We abandoned the analysis of choroidal vascular density because its measurements were interfered too much by artifacts and hemorrhage. All limitations should be considered in future research.

**Conclusion**

In conclusion, our results revealed the visual and morphological changes of patients with active subfoveal circumscribed PCV. The baseline BCVA and the number of injections were protective factors for final BCVA, whereas history of hypertension and macular edema were risk factors. This study also highlighted that male sex, a smaller number of injections and the presence of polypoidal lesions on OCTA images at baseline were risk factors for the prognosis of polypoidal lesions on OCTA images. This is the first study to morphologically categorize BVN. PCV patients with ill-defined BVN pattern presented better vision improvement.

**Methods**

**Eligibility criteria and anti-VEGF treatment**

This was a retrospective study based on real-world evidence. A medical record review of patients who were first diagnosed with PCV using ICGA was performed from January 2019 to May 2022 at the Department of Ophthalmology, the Fourth People's Hospital of Shenyang, China Medical University. This study was approved by the Institutional Review Board/Ethics Committee of the Fourth People's Hospital of Shenyang in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

The inclusion criteria were as follows: 1) Treatment-naive PCV diagnosis based on EVEREST criteria; 2) PCV activity was confirmed by both leakage on fluorescein angiography (FA) and exudation on OCT; 3) PCV lesion was ranged within OCTA 6x6 macular examination range; 4) macular hemorrhage did not affect BVN morphological recognition; 5) received three-plus pro re nata (3 + PRN, PRN dosing with that of 3 initial monthly injections followed by PRN) intravitreal injections of anti-VEGF treatment and were followed up at one month after each injection; 6) the study eye did not reactive for 6 months or more after the last injection. No reactivation meant no intraretinal or subretinal fluid on OCT, and no need for further anti-VEGF therapy or other treatment.

The exclusion criteria were as follows: 1) any other fundus diseases that could confuse the results, such as retinal angiomatous proliferation, retinal arterial microaneurysms, retinal artery or vein occlusion; 2) previous ophthalmic intervention (such as laser, vitrectomy, or photodynamic therapy); 3) refractive medium turbidity affecting BVN morphological recognition or image discrimination; 4) patients with high PED that influences the measurement of choroidal parameters; 5) quiescent PCV and massive hemorrhage PCV (Quiescent PCV is characterized by the presence of one or several polyps in the absence of any intraretinal or subretinal fluid or hemorrhage,
and usually does not need treatment.\textsuperscript{32} Massive hemorrhage PCV was defined as four or more disc areas with subretinal or sub-RPE hemorrhaging.\textsuperscript{33} 6) and patients with serious systemic diseases (such as heart or brain infarction, liver or kidney failure, infectious diseases, rheumatic diseases, blood diseases, etc.)

In total, 51 eyes of 51 patients satisfied all the inclusion and exclusion criteria. All patients received anti-VEGF intravitreal injections using ranibizumab, conbercept, or both. Medication alterations resulted from inadequate responses defined as persistence of SRF on OCT after 3 times of the loading phase injection.\textsuperscript{34}

**Clinical measurements**

All patients underwent examinations including BCVA in decimal form, fundus photography (TRC-50DX; Topcon, Tokyo, Japan), FA, ICGA (Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany), enhanced depth imaging OCT (Spectralis HRA + OCT; Heidelberg Engineering), and OCTA (RTVue AngioVue System, Optovue, Inc, Fremont, CA) of a macular cube (6 × 6 mm), centred at the fovea. All data were measured by two masked retinal specialists and the average value was used for evaluation. In case of disagreement, a third senior retinal specialist made the final judgement.

We recorded the PCV-related parameters including: LGH on ICGA; polypoidal lesions on OCT and OCTA;\textsuperscript{35} BVN on ICGA and OCTA; DLS and pachyvessels on OCT; macular edema on OCT including intraretinal fluid and intraretinal cystoid regions; CFT; SRF height; SFCT; and PED height. According to the injected medicine, subgroup analysis categorized all enrolled patients into three groups: ranibizumab, conbercept, and combined groups. According to OCTA flow maps, BVN was divided into four subtypes based on previous nAMD studies,\textsuperscript{12,36} including ill-defined type, Medusa (or sea-fan shape) type, mulberry type, and dead tree type. Alteration among these subtypes was counted. Furthermore, mulberry type and medusa (or sea-fan shape) type are more likely to be active, whereas the rest two types are more likely to be less active. Since dead tree type is mostly the latest phase in the course of the disease, which is essentially different from the other types, it was excluded from the following comparison. We divided the remaining patients into ill-defined group and well-defined group, the latter including mulberry type and medusa (or sea-fan shape) type patients. And the differences in the parameters between the two groups were compared. The medical history of hypertension was also documented.

**Statistical analyses**

Statistical analyses were performed using SPSS (version 23.0; IBM Inc., Chicago, IL, USA). Data are expressed as the median (interquartile range). Decimal BCVA was converted to the logMAR form for statistical analysis. Differences in BCVA were analyzed using one-way ANOVA tests. Wilcoxon matched-pair signed-rank tests were used to investigate the differences between quantitative data and ranked data. Spearman's correlation coefficient was used to investigate the factors influencing SFCT, and the prognosis of BCVA and polypoidal lesions on OCTA. Wilcoxon-Mann-Whitney test were used to investigate the differences between ill-defined group and well-defined group. Moreover, the factors
influencing the prognosis of BCVA and polypoidal lesions on OCTA were calculated using linear regression analysis and multiple logistic regression analysis, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was defined as a P-value < 0.05.

**Declarations**

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**Contributions**

F.X. and R.H. designed the study, analyzed the data and wrote the manuscript. P.X. and H.Z. collected the data. T.N. supervised the study and edited the manuscript.

**Ethics declarations**

**Competing interests**

The authors declare no competing interests.

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**Data availability**

The data proving the main findings of the study are contained within the manuscript. Data are however available from the authors upon reasonable request and with appropriate permissions of the Fourth People's Hospital of Shenyang.

**Additional Information**

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**References**


**Figures**
Figure 1

Experimental procedure
Figure 2

Well-defined subtypes of BVN on OCTA.