

Elevated C-Reactive Protein Levels in Patients with Polypoidal Choroidal Vasculopathy and Patients with Neovascular Age-Related Macular Degeneration

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Purpose: To determine the relationship between systemic C-reactive protein (CRP) levels and polypoidal choroidal vasculopathy (PCV) and advanced neovascular age-related macular degeneration (AMD) in Japanese patients.

Design: Case-control study.

Participants: Ninety-seven patients with PCV, 176 with advanced neovascular AMD, and 262 control subjects without any macular abnormality were studied.

Methods: Color fundus photographs of the macular area were taken from both eyes in all subjects. Indocyanine green angiography and fluorescein angiography were performed for diagnosis. The CRP level was measured by a high-sensitivity assay using a latex aggregation immunoassay, and the levels in patients with PCV and neovascular AMD were compared with that in the control group using the Kruskal-Wallis test. Associations between CRP and PCV or neovascular AMD were compared using logistic regression analysis by computing the odds ratios (ORs) and 95% confidence intervals (CIs) after the study populations were divided into quartiles.

Main Outcome Measures: The CRP levels in patients with PCV, patients with neovascular AMD, and control subjects. Standard univariate and multivariate analyses between groups.

Results: Median CRP levels were significantly higher in cases with PCV (0.94 mg/l) or with advanced neovascular AMD (0.95 mg/l) than in control subjects (0.43 mg/l) ($P < 0.001$ for Kruskal-Wallis test). After adjusting for baseline characteristics such as age, gender, smoking status, alcohol use, body mass index, history, and use of antiinflammatory drugs, the increase in risk was significant for the highest quartile of CRP for both PCV (OR, 3.53; 95% CI, 1.49–8.40) and neovascular AMD (OR, 4.08; 95% CI, 1.94–8.56), and for the third quartile of CRP for neovascular AMD (OR, 2.29; 95% CI, 1.07–4.91). The trends for an increase in risk of disease with increase in CRP were statistically significant for both PCV ($P = 0.001$) and neovascular AMD ($P < 0.001$).

Conclusions: The significant associations between elevated serum CRP levels and PCV or neovascular AMD in the Japanese strongly suggest that inflammatory processes are involved in the pathogenesis of PCV and neovascular AMD. *Ophthalmology* 2007;114:1722–1727 © 2007 by the American Academy of Ophthalmology.

Polypoidal choroidal vasculopathy (PCV) is characterized by an inner choroidal vascular network with characteristic aneurysmal dilations at the end of the vascular network. The dilations are seen as reddish-orange, spheroidal, polypoidal structures ophthalmoscopically.^{1–3} Eyes diagnosed with PCV frequently have multiple recurrent serous and hemor-

rhagic detachments of the retinal pigment epithelium (RPE).¹ Patients with PCV complain of visual disturbance, metamorphopsia, and central scotoma. Yannuzzi et al¹ proposed that PCV is a distinct clinical entity clinically and demographically different from age-related macular degeneration (AMD).

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Indocyanine green angiography can be used to make a definitive diagnosis of PCV, because it makes the branching network of vessels and the vascular dilations clearly visible.^{4,5} Polypoidal choroidal vasculopathy has been found in all races, but more frequently in black and Asian patients than in white patients.^{1,2,6} Yannuzzi et al² found that 13 (7.8%) of 167 consecutive patients with presumed neovascularized AMD had PCV, whereas Imaizumi et al⁶ detected PCV in 96 (58.5%) of 164 eyes with retinal pigment epithelial detachment accompanied by choroidal neovascularization. Two different theories on the pathogenesis of PCV have been presented: first, the lesions are variants of choroidal neovascularization,^{7,8} or second, they are abnormalities of the inner choroidal vessels.^{9,10} However, the precise etiology of PCV is still undetermined, and the differences in the pathogenesis of PCV and AMD have not been established.

Age-related macular degeneration is a major cause of legal blindness in the elderly,¹¹ and the advanced stage of AMD is characterized by a choroidal neovascular membrane (neovascular AMD) or a geographic atrophy. The choroidal neovascular membrane appears in the macular area, which leads to subretinal hemorrhages, retinal pigment epithelial detachments, and serous retinal detachments (RDs) and/or RPE atrophy.¹² Geographic atrophy is diagnosed when sharply delineated hypopigmented areas without choroidal neovascularization are detected in the macular area.¹² The pathogenesis of AMD has been examined in a number of epidemiological, pathological, and biological studies, and several mechanisms have been put forth. Because proteins common to inflammation and immune-mediated processes are contained in ocular drusen, a typical prodromic sign of AMD, chronic inflammation has been suggested to be one of the pathogenic mechanisms for AMD.^{13–15} This is supported by the presence of leukocytes, an indicator of inflammation, in surgically excised specimens of choroidal neovascularizations.^{16,17} Moreover, elevated levels of systemic inflammatory biomarkers, such as C-reactive protein (CRP),^{18–22} interleukin 6,¹⁹ homocysteine,^{20,22,23} and fibrinogen,²¹ have been reported in AMD cases.

Seddon et al¹⁸ found that the CRP level was significantly higher among patients with advanced AMD than among those without AMD. Vine et al²⁰ reported similar findings and concluded that a higher CRP level was a risk factor for AMD. In a prospective longitudinal study, Seddon et al¹⁹ also showed that high levels of CRP were significantly associated with the progression of AMD. It was thus suggested that a similar pathway might be involved in other inflammation-associated age-related diseases such as cardiovascular disease and Alzheimer's disease,^{24–26} because the CRP levels are elevated and are considered to be a risk factor in these diseases.¹⁸ However, some other investigators could not find a significant association between serum CRP levels and AMD.^{27,28}

The purpose of this study was to examine the relationship between systemic CRP levels in Japanese patients with advanced neovascular AMD and with PCV to learn more about the pathogenesis of PCV.

Materials and Methods

Study Subjects

All case and control subjects were Japanese residents of the same area (Chubu) of Japan and were examined at the Nagoya University Hospital. The research protocol was in keeping with the Declaration of Helsinki, and this study was approved by the institutional review board of our hospital. A written informed consent was obtained from each participant for providing medical information and serum.

For all case and control subjects, color fundus photographs were taken of the macular area in both eyes. In addition, indocyanine green angiography and fluorescein angiography with the Heidelberg Retina Angiograph II (Heidelberg Engineering, Heidelberg, Germany) were performed through dilated pupils in all case subjects. Subjects were diagnosed with PCV when the characteristic polypoidal lesions were seen by indocyanine green angiography. The lesions were observed ophthalmoscopically as protruding orange–red elevated lesions in the majority of the cases. Thus, all cases met the criteria of definite cases of PCV as proposed by the Japanese Study Group of Polypoidal Choroidal Vasculopathy.²⁹ Cases diagnosed as probable²⁹ were excluded because it was difficult to distinguish such cases from AMD cases.²⁹

One hundred seventy-six neovascular AMD cases were enlisted as AMD subjects. Neovascular AMD was diagnosed when choroidal neovascularization was detected by fluorescein angiography and indocyanine green angiography. Fundus examination of these patients revealed serous or hemorrhagic retinal pigment epithelial detachment, a subretinal neovascular membrane, a subretinal hemorrhage, and/or a peroretinal fibrous scar. Thus, all cases were advanced AMD and were classified as stage 4 by the Rotterdam Study classification.³⁰ Geographic atrophy, another advanced AMD, was excluded from this study, because the number of our cases with geographic atrophy was only 18, which was not enough for the statistical analysis.

Patients with very thick macular hemorrhages were excluded because they could not be properly diagnosed. Patients with choroidal neovascularization and refractive errors of < -6.0 diopters (D) and/or with myopic fundus changes such as laquer crack lesions and chorioretinal atrophy were also excluded, because such cases were considered to have myopic choroidal neovascularization. Patients with a choroidal neovascularization associated with angioid streaks were also excluded. In addition, patients with a history of radiotherapy treatment for eyes were excluded to avoid confounding the findings with radiation-associated choroidal neovascularopathy.

The majority of the control subjects (206) were health checkup examinees at the Nagoya University Hospital.³¹ The checkup was an elective physical for persons with no particular symptom and not a regular examination. Among 476 examinees who attended a basic health checkup course with blood tests at the hospital, subjects older than 50 years were requested to participate as control subjects to match the range of ages of the case subjects. Seven subjects were excluded from this study because fundus examination revealed some abnormality, including macular drusen or macular degeneration. Forty-three participants had a history of ocular diseases other than retinal diseases. Fifty-six control subjects were recruited from patients over 50 who were examined at the same hospital for ophthalmological disorders other than degenerative or vascular retinal diseases and included patients with cataract, peripheral rhegmatogenous RD, glaucoma, esotropia, and keratopathy. They had no signs of age-related maculopathy (ARM). Thus, all control subjects (262) were classified as maculopathy stage 0 by the Rotterdam Study classification.³⁰

We excluded female subjects who used oral contraceptives or undertook hormone replacement therapies from control, PCV, and

Table 1. Baseline Characteristics of the Study Subjects

	Control (n = 262)	PCV (n = 97)*	AMD (n = 176)*
Age [mean (SD)] (yrs)	63.8 (9.2)	69.9 (6.7) [†]	73.2 (8.0) [†]
Female gender	98 (37.4)	15 (15.5) [†]	48 (27.2) [‡]
Smoking			
Never	126 (48.1)	23 (23.7) [†]	55 (31.3) [§]
Former	97 (37.0)	45 (46.4)	85 (48.3)
Current	39 (14.9)	29 (29.9)	36 (20.5)
Drinking			
Not habitual	143 (54.6)	64 (66.0)	121 (68.8) [§]
Habitual	119 (45.4)	33 (34.0)	55 (31.3)
Body mass index [mean (SD)] (kg/m ²)	23.0 (2.8)	23.3 (3.1)	22.6 (2.9)
History of			
Hypertension	64 (24.4)	38 (39.2) [§]	80 (45.5) [†]
Hyperlipemia	63 (24.1)	20 (20.6)	35 (19.9)
Diabetes mellitus	29 (11.1)	16 (16.5)	32 (18.2) [‡]
Stroke	12 (4.6)	7 (7.2)	17 (9.7) [‡]
Cardiovascular disease	29 (11.1)	10 (10.3)	18 (10.2)
Use of			
Antiinflammatory drugs	8 (3.1)	4 (4.1)	6 (3.4)

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; SD = standard deviation.

Data are n (%) unless otherwise indicated.

*P values derived from *t* tests for means and chi-square tests for proportions.

[†]P < 0.001.

[‡]P < 0.05.

[§]P < 0.01.

^{||}Not significant compared with control.

AMD groups, because such contraceptives or therapies significantly alter plasma CRP levels.

Health and Lifestyle Factors

A health and lifestyle questionnaire including questions regarding smoking and alcohol consumption was filled out by the examiners. Smoking status involved 3 categories: current smoker, former smoker, and never smoked. Body height and weight were measured while subjects wore light clothes on the same day as the ophthalmological examination. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared.

C-Reactive Protein Analysis

The CRP level was measured by a high-sensitivity assay using a latex aggregation immunoassay (Nanopia CRP, Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan) with a no. 7170 analyzer (Hitachi High-Tech Science Systems Corp., Hitachinaka, Japan).

The lower detection limit of this assay is 0.03 mg/l. The repeatability of this assay was evaluated in our institution, and coefficients of variation at concentrations of 0.49, 2.02, 11.11, and 158.80 mg/l were 2.9%, 1.0%, 0.6%, and 0.2%, respectively.

Statistical Analysis

Continuous and categorical variables in demographic and medical characteristics were compared between PCV cases or neovascular AMD cases and control subjects using *t* and chi-square tests, respectively. Differences in CRP levels between case subjects and control subjects were tested using the Kruskal–Wallis test because CRP levels were not normally distributed.

Logistic regression analysis was carried out to compute the odds ratios (ORs) and 95% confidence intervals (CIs) after dividing subjects into quartile groups based on the distribution of CRP values of the control group. Each CRP quartile was compared with the lowest quartile as the reference category. Multivariate estimates of risk were calculated, adjusted for age (50–63, 64–76, and 77–89 years), gender, smoking status (never, former, current), alcohol consumption, BMI (<18.5, 18.5–24.9, >24.9), history (hypertension, hyperlipemia, diabetes mellitus, stroke, cardiovascular disease), and use of antiinflammatory drugs.

STATA (version 8, StataCorp, College Station, TX) was used for these calculations. *P* < 0.05 was considered significant.

Results

Baseline demographic characteristics of all subjects are summarized in Table 1. Ninety-seven cases (82 men and 15 women) with PCV, 176 cases (128 men, 48 women) with advanced neovascular AMD, and 262 control subjects (164 men, 98 women) were analyzed. Mean ages were 69.9 years (range, 51–83), 73.2 (range, 50–89), and 63.8 (range, 50–89) for PCV, neovascular AMD, and control subjects, respectively. The men made up 84.5% of the PCV group and 72.7% of the neovascular AMD group. These values are consistent with earlier reports that men are more likely to have AMD in the Japanese population,^{32,33} which differs from the white population. Patients with PCV and neovascular AMD were more frequently smokers and less frequently habitual drinkers and had a higher prevalence of hypertension, diabetes mellitus, and stroke than control subjects. There were no differences in BMI, prevalence of cardiovascular disease, hyperlipemia, and use of antiinflammatory drugs between the case groups and controls. Baseline characteristics of the PCV and neovascular AMD groups did not significantly differ except for age, gender, and BMI (Table 1).

Median CRP levels were 0.94 mg/l for the PCV group and 0.95 mg/l for the neovascular AMD group. Both of these values were approximately twice that of the control groups, at 0.43 mg/l, and both were significantly higher than that of the control subjects (*P* = 0.0001, Kruskal–Wallis test) (Table 2). Geometric means

Table 2. Levels of C-Reactive Protein by Categories

	Control (n = 262)	PCV (n = 97)	AMD (n = 176)
Median (interquartile range) (mg/l)	0.43 (0.24–0.95)	0.94 (0.37–1.83)*	0.95 (0.49–1.83)*
Geometric mean (mg/l)	0.49	0.92	0.93
Overall range (mg/l)	0.06–27.40	0.09–22.27	0.06–32.18

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy.

**P* = 0.0001 for Kruskal–Wallis test (vs. control).

Table 3. Distribution of Polypoidal Choroidal Vasculopathy (PCV) Cases and Controls within Quartiles of C-Reactive Protein (CRP)

Quartile of CRP (mg/l)	Controls [n (%*)]	PCV Cases [n (%*)]	Age- and Gender-Adjusted OR (95% CI)	Multivariate-Adjusted OR (95% CI) [†]
1 (≤0.24)	65 (25)	11 (11)	1.00 (reference)	1.00 (reference)
2 (>0.24–0.43)	66 (25)	15 (15)	1.33 (0.54–3.34)	1.19 (0.46–3.12)
3 (>0.43–0.95)	67 (26)	23 (24)	1.65 (0.70–3.89)	1.63 (0.65–4.05)
4 (>0.95)	64 (24)	48 (49)	3.91 (1.75–8.74)	3.53 (1.49–8.40)
Total	262	97		

CI = confidence interval; OR = odds ratio.
 *Of total in quartile.
[†]Adjusted for age (50–63, 64–76, 77–89 yrs), gender, smoking status (never, former, current), alcohol consumption, body mass index (<18.5, 18.5–24.9, >24.9 kg/m²), history (hypertension, hyperlipemia, diabetes mellitus, stroke, cardiovascular disease), and use of antiinflammatory drugs.

were also significantly higher for the cases, although the overall ranges were similar for the PCV, neovascular AMD, and control groups. There was no significant difference in CRP levels between the PCV and neovascular AMD groups ($P = 0.746$, Kruskal–Wallis test).

Logistic regression analysis was performed because some of the baseline characteristics such as age, gender, and smoking habit differed between the case groups and the control group. Odds ratios and 95% CIs for risk of PCV and neovascular AMD according to the quartile of the CRP level are presented in Tables 3 and 4, respectively. All comparisons were made to the lowest quartile of CRP. After adjusting for age and gender, persons in the highest quartile of CRP had an approximately 4-fold increased risk of both PCV (OR, 3.91; 95% CI, 1.75–8.74) (Table 3) and AMD (OR, 4.10; 95% CI, 2.07–8.12) (Table 4). Persons in the third quartile of CRP had a 2-fold increased risk of neovascular AMD (OR, 2.18; 95% CI, 1.07–4.42) (Table 4). After adjustments for additional characteristics including smoking habit, alcohol consumption, BMI, history, and use of antiinflammatory drugs, the increase in risk was still significant for the highest quartile of CRP for both PCV (OR, 3.53; 95% CI, 1.49–8.40) (Table 3) and neovascular AMD (OR, 4.08; 95% CI, 1.94–8.56) (Table 4) and for the third quartile of CRP for neovascular AMD (OR, 2.29; 95% CI, 1.07–4.91) (Table 4). Trends for an increase in risk of disease with increase in CRP were statistically significant for both PCV ($P = 0.001$) and neovascular AMD ($P < 0.001$).

Discussion

Our results showed that there was a significant association between the CRP level, a sensitive systemic marker of inflammation, and patients with advanced neovascular AMD. This association confirms the results of previous studies^{18–22} and strongly supports the hypothesis that inflammation and immune-mediated mechanisms are involved in the pathogenesis of AMD.

However, there have been reports contradicting the association of CRP and AMD. Thus, Klein et al²⁷ found no association of any inflammatory markers including CRP with ARM, and McGwin et al²⁸ reported that although ORs in the higher CRP quartile increased after multivariate adjustments, the increases were not statistically significant. These negative results might be because the majority of cases in the AMD groups in those studies were early AMD.^{27,28} Thus, Seddon et al¹⁸ found a significant association between CRP levels and AMD using a larger number of advanced AMD cases, and Klein et al²⁷ suggested that inflammatory processes are more important in the progression from early to late stages of ARM. Odds ratios for risk of advanced AMD in our results were higher than those in the previous studies, and this may be because we compared

Table 4. Distribution of Advanced Age-Related Macular Degeneration (AMD) Cases and Controls within Quartiles of C-Reactive Protein (CRP)

Quartile of CRP (mg/l)	Controls [n (%*)]	AMD Cases [n (%*)]	Age- and Sex-Adjusted OR (95% CI)	Multivariate-Adjusted OR (95% CI) [†]
1 (≤0.24)	65 (25)	18 (10)	1.00 (reference)	1.00 (reference)
2 (>0.24–0.43)	66 (25)	18 (10)	0.95 (0.42–2.12)	0.84 (0.35–1.99)
3 (>0.43–0.95)	67 (26)	53 (30)	2.18 (1.07–4.42)	2.29 (1.07–4.91)
4 (>0.95)	64 (24)	87 (49)	4.10 (2.07–8.12)	4.08 (1.94–8.56)
Total	262	176		

CI = confidence interval; OR = odds ratio.
 *Of total in quartile.
[†]Adjusted for age (50–63, 64–76, 77–89 yrs), gender, smoking status (never, former, current), alcohol consumption, body mass index (<18.5, 18.5–24.9, >24.9 kg/m²), history (hypertension, hyperlipemia, diabetes mellitus, stroke, cardiovascular disease), and use of anti-inflammatory drugs.

only advanced neovascular AMD cases with controls that had no signs of ARM.

Evidence has been accumulating on the involvement of inflammation and immune-mediated processes in AMD from recent genetic studies. It has been shown that variations in the complement factor H (*CFH*),^{34,35} factor B (*BF*),³⁶ and complement component C (*C2*)³⁶ genes are associated with an increased risk of AMD. All of the products of these genes are regulators or activators of the complement pathway involved in inflammation and the immune system, and they are present in the choroid, ocular drusen, and Bruch's membrane.^{34–36} Factor H binds to CRP, resulting in an inhibition of CRP-dependent alternative pathway activation.^{37,38} The most reliable polymorphism of *CFH*, Y402H, is located in a region of the binding site for CRP in the gene,³⁴ and it has been shown that individuals homozygous for this variant exhibit increased levels of CRP deposition within the choroid.³⁹

The most significant finding in our study was the elevated CRP levels in patients with PCV, as was found with advanced neovascular AMD. Odds ratios for risk of PCV were similar to those of AMD for each quartile of CRP, and the risk of PCV increased significantly with an increase of CRP. To the best of our knowledge, this is the first study to demonstrate an association of the CRP values and risk of PCV that would indicate that inflammatory processes are involved in the etiology of PCV, as it most likely is in advanced AMD. This hypothesis is not too surprising because previous histopathological studies have demonstrated an infiltration of inflammatory cells in some of the excised tissues obtained during surgery or in the enucleated eyes of PCV patients.^{7,8,40,41}

Median and interquartile CRP levels among both cases and control subjects were much lower in our study than in the previous studies.^{18,20,21} These results are consistent with the previous report that basal CRP values in Japanese are lower than those in whites.⁴² This interracial difference of the CRP levels might be associated with the different incidences of AMD in the ethnicities; it has been reported that prevalences of late AMD are 0.87% in Japanese³² and 1.6% to 1.9% in whites.^{11,43,44}

One of the limitations of our study was that it was designed case-control. It should be remembered that baseline medical characteristics, including age, gender, and smoking status, were not matched between the case groups and the control group, although significant associations between CRP and the diseases were found after the potentially confounding effects were taken into account by logistic regression. Also, we cannot eliminate a possible bias in patient selection because the majority of the case individuals presented for examination and treatment for diseases, whereas the majority of the control individuals were recruited from subjects having a health checkup. Health checkup examinees might be healthier than average because they might be more concerned about their health.

Another limitation of this study is that it was cross-sectional. Because diagnosis of the disease and collection of blood samples were performed simultaneously, it is difficult to determine a causal sequence of the elevated CRP levels and the appearance or progression of PCV or AMD.

In conclusion, we found a significant association between elevated serum CRP levels and PCV or advanced AMD in a case-control study. These results strongly suggest that inflammatory processes are a common component not only in AMD but also in PCV. These findings will provide additional information for the understanding of PCV's pathogenesis. Further investigations by nested case-control or prospective studies with a larger number of participants will be needed to verify our findings.

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