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Association between coagulation function and patients with primary angle closure glaucoma: a 5-year retrospective case–control study

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ABSTRACT

Objective To evaluate the association between coagulation function and patients with primary angle closure glaucoma (PACG).

Design A retrospective, hospital-based, case–control study.

Setting Shanghai, China.

Participants A total of 1778 subjects were recruited from the Eye & ENT Hospital of Fudan University from January 2010 to December 2015, including patients with PACG (male=296; female=569) and control subjects (male=290; female=623).

Outcome measures Sociodemographic data and clinical data were collected. The one-way analysis of variance test was used to compare the levels of laboratory parameters among the mild, moderate and severe PACG groups. Multivariate logistic regression analyses were performed to identify the independent risk factors for PACG. The nomogram was constructed based on the logistic regression model using the R project for statistical computing (R V.3.3.2).

Results The activated partial thromboplastin time (APTT) of the PACG group was approximately 4% shorter (p<0.001) than that of the control group. The prothrombin time (PT) was approximately 2.40% shorter (p<0.001) in patients with PACG compared with the control group. The thrombin time was also approximately 2.14% shorter (p<0.001) in patients with PACG compared with the control group. The level of D-dimer was significantly higher (p=0.042) in patients with PACG. Moreover, the mean platelet volume (MPV) of the PACG group was significantly higher (p=0.013) than that of the control group. A similar trend was observed when coagulation parameters were compared between the PACG and control groups with respect to gender and/or age. Multiple logistic regression analyses revealed that APTT (OR=1.032, 95% CI 1.000 to 1.026), PT (OR=1.249, 95% CI 1.071 to 1.457) and MPV (OR=1.185, 95% CI 1.081 to 1.299) were independently associated with PACG.

Conclusion Patients with PACG had a shorter coagulation time. Our results suggest that coagulation function is significantly associated with patients with PACG and may play an important role in the onset and development of PACG.

Strengths and limitations of this study

- This is the first study focusing on the evaluation of the coagulation function in primary angle closure glaucoma (PACG) and its relationship with disease severity.
- The large number of studied subjects.
- The detailed demographic and clinical data of studied subjects.
- The nature of this study was a single eye centre, retrospective case–control study.
- Statistical power analysis for specificity ability was limited.
- Less than 2% of patients with PACG revealed abnormal values for activated partial thromboplastin time, prothrombin time, thrombin time and mean platelet volume that strictly limit the clinical use of such findings.

INTRODUCTION

Glaucoma, the second leading cause of blindness worldwide, is a group of heterogeneous optic neuropathies characterised by progressive retinal ganglion cell death and visual field loss.[1] Based on a population-based study, there will be 59.51 million people with glaucoma by 2020 in Asia alone, with that number expected to increase to 80.87 million patients by 2040. As primary angle closure glaucoma (PACG) appears to cause blindness more frequently than primary open angle glaucoma (POAG),[2 3] it has become an important public visual health issue.[4] Although elevated intraocular pressure is regarded as a major risk factor for glaucoma, the exact pathogenic mechanism of glaucoma is still not clearly understood. A number of studies have investigated the various risk factors that might cause glaucomatous damage, one of which includes the hypercoagulable state of ocular blood flow.[5–7]

Some have found a hypercoagulable state and elevated blood viscosity in patients with POAG or normal tension glaucoma (NTG).[8–11]For example, O'Brien *et al*[11] reported that patients with glaucoma had elevated levels of prothrombin fragments 1+2 and D-dimer compared with both NTG and controls, which could contribute to impaired blood circulation to the optic nerve and thus lead to glaucomatous damage. A hypercoagulable state and elevated blood viscosity can also reduce blood flow in eyes leading to ischaemia and dysregulation of oxygen delivery, which might be associated with the progression of visual field loss in glaucoma.[12–15] Li *et al*[16] performed a meta-analysis and showed significantly elevated endothelin-1 plasma concentrations in glaucoma which suggested that vascular dysfunction may be involved in the pathogenesis of glaucoma. Vascular dysfunction further exacerbates the hypercoagulable state and reduction of blood flow in eyes with glaucoma. Moreover, our previous study reported that the mean platelet distribution width (PDW) and mean platelet volume (MPV) were increased in patients with neovascular glaucoma.[17] There are, however, only a few published studies focusing on the relationship between coagulation function and patients with PACG.

Therefore, this study was designed to analyse the indices of coagulation function in patients with PACG, and subsequently explore whether the alteration of the blood stream state may be involved in the pathophysiological mechanism of PACG.

MATERIALS AND METHODS

Subjects

This was a retrospective case–control study. Patients with PACG were recruited from the department of ophthalmology inpatient service at the Eye & ENT Hospital of Fudan University between January 2010 and December 2015. Up to 913 age-matched and sex-matched normal controls were consecutively recruited from subjects who participated in yearly health screenings during the study period. The study was approved by the Ethics Committee of the Eye & ENT Hospital of Fudan University (EENT2015011), Shanghai, China, and was conducted according to the Declaration of Helsinki. Written informed consent for the use of any clinical data in research was obtained for all patients at the time of admission to the Eye & ENT Hospital of Fudan University. The study cohort flow diagram is shown in online supplementary figure 1. This database has been used previously to study patients with glaucoma.[18]

Inclusion criteria

Our previous study has described the inclusion criteria of PACG subjects.[18] Both newly diagnosed and referred patients with PACG were included in this study. Subjects receiving glaucoma medications and blood pressure medications were also included, except for patients who were taking medications (heparin, warfarin, and so on) which influenced their coagulation function. Control subjects had no ocular diseases, blood system diseases, active infection or major systemic diseases (acute inflammation, hyperuricaemia, cardiac, autoimmune disease and cancer) that could possibly affect their coagulation function. Moreover, those on treatment with agents affecting laboratory parameters, including patients with haematological disorders and chemotherapy treatment, were also excluded. Control subjects were also excluded if there was any family history of glaucoma.

Given the potentially higher risk of PACG blindness in women,[19–21] the PACG subjects were categorised into female and male subgroups to shed light on the role of the coagulation function in PACG development between genders. Several studies have reported that the prevalence of PACG increases with advancing age, especially in China.[22 23] Therefore, a subgroup analysis by gender across different age groups (subgroups: 0–59 years and 60+ years) was performed to shed light on the possible role of the coagulation function in PACG development with increasing age. In male and female subgroups, the patients with PACG were divided into three groups with different disease severities based on visual fields mean deviation (MD), that is, mild (MD≤6.00 dB), moderate (12 dB≥MD>6 dB) and severe (MD>12 dB).[18 24 25]

Laboratory parameters

Platelet parameters including MPV, PDW, PCT (plateletcrit) and PLT (platelet count) were measured with the Mindray BC-5500 (Shenzhen, China) automatic blood counting system. The blood samples for platelet parameters were collected in ethylenediaminetetraacetic acid tubes. Coagulation parameters including activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT) and D-dimer were measured with STAGO STA-R Evolution. The blood samples for coagulation parameters were collected in sodium citrate anticoagulation tubes.

Data analysis

The data were analysed using SPSS V.13.0 (SPSS). Normality of the data was assessed with the Kolmogorov-Smirnoff test. The independent student's t-test and χ^2 test were used for comparison of patient characteristics between the PACG and control groups. The one-way analysis of variance test was used to compare the levels of laboratory parameters among the mild, moderate and severe PACG groups. Multivariate logistic regression analyses were performed to identify the independent risk factors for PACG. ORs with 95% CIs were estimated using multivariate logistic regression analyses. The nomogram was constructed based on the logistic regression model using the R project for statistical computing (R V.3.3.2). A p value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study patients

A total of 865 patients with PACG (male=296, female=569) and 913 control subjects (male=290, female=623) were

Table 1 Demographics of the study participants by patients with PACG and controls

Factors	PACG group (n=865)	Control group (n=913)	t Value	p Value
Age	63.12±10.60	62.71±9.79	0.838	0.402
Male/female	296/569	290/623	1.213	0.271
BMI (kg/m^2)	22.80±3.47	22.71±4.27	0.378	0.705
Diabetes mellitus	72	66	0.744	0.389
Hypertension	259	312	3.647	0.056
IOP (mm Hg)	31.27±12.27	–	–	–
VCDR	0.57±0.24	–	–	–
MD (dB)	13.91±9.18	–	–	–
MS (dB)	13.58±8.14	–	–	–

Data are expressed as mean±SD. χ^2 test and independent sample t-test were used.
BMI, body mass index; IOP, intraocular pressure; MD, visual fields mean deviation; MS, visual fields mean sensitivity; PACG, primary angle closure glaucoma; VCDR, vertical cup-disc ratio.

enrolled in this study. Only one eye was selected randomly if both eyes suffered from PACG. A total of 865 eyes were selected from the patients with PACG. The PACG and control groups were closely matched in terms of mean age and sex (p=0.402 and p=0.271, respectively). The demographic and clinical characteristics are shown in table 1.

Comparison of laboratory findings in PACG and control group

The APTT of the PACG group was approximately 4% shorter (p<0.001) than that of the control group (29.83±5.08 s (PACG group) vs 31.19±5.10 s (control group)). The PT was approximately 2.40% shorter (p<0.001) in patients with PACG compared with the control group (11.68±1.11 s (PACG group) vs 11.95±1.26 s (control group)). The TT was also approximately 2.14% shorter (p<0.001) in patients with PACG compared with the control group (17.73±1.56 s (PACG group) vs 18.11±1.21 s (control group)). The level of D-dimer was significantly higher (p=0.042) in patients with PACG (0.41±0.61) than in the control group (0.36±0.36). Moreover, the MPV of the PACG group (10.42±1.42) was significantly higher (p=0.013) than that of the control group (10.24±1.70). Detailed information is shown in table 2.

According to their normal range, patients with PACG and control subjects were divided into abnormal low group, normal range group and abnormal high group, respectively. Detailed information is shown in online supplementary table 1. Moreover, the comparison of age, sex, hypertension, diabetes mellitus and body mass index was conducted between the subjects with abnormal test values in the two studied populations. Detailed information is shown in online supplementary table 1.

Comparison of APTT, PT, TT, D-dimer and MPV in PACG and control groups by age and gender

According to their age and gender, 865 patients with PACG were divided into male (20–59 years; 60+ years) and female (20–59 years; 60+ years) subgroups. Between the female subgroups aged 20–59 years and 60+ years, the levels of APTT, PT, TT, D-dimer and MPV were significantly different between the PACG and control groups. Between the male subgroups aged 20–59 years and 60+

Table 2 Laboratory findings of APTT, PT, TT, D-D and MPV in the PACG and control groups

Factors	PACG group	Control group	t Value	p Value
APTT (s)	29.83±5.08	31.19±5.10	5.616	<0.001
FIB (g/L)	2.85±0.66	2.82±0.68	1.071	0.284
PT (s)	11.68±1.11	11.95±1.26	4.790	<0.001
TT (s)	17.73±1.56	18.11±1.21	5.747	<0.001
D-D (mg/L)	0.41±0.61	0.36±0.36	2.036	0.042
MPV (fl)	10.42±1.42	10.24±1.70	2.475	0.013
PDW (fl)	15.21±2.46	15.07±2.89	1.044	0.297
PLT (10^9/L)	197.49±56.61	202.69±57.55	1.918	0.055
PCT (%)	0.28±1.05	0.25±1.42	0.429	0.668

Data are expressed as mean±SD. Independent sample t-test was used.
APTT, activated partial thromboplastin time; D-D, D-dimer; FIB, fibrinogen; MPV, mean platelet volume; PACG, primary angle closure glaucoma; PCT, plateletcrit; PDW, platelet distribution width; PLT, platelet count; PT, prothrombin time; TT, thrombin time.

years, the levels of APTT, PT and TT were significantly different between the PACG and control groups. Detailed information is shown in table 3.

Comparison of laboratory findings among mild, moderate and severe PACG

Based on the MD, the PACG subjects were categorised into three subgroups of different disease severity levels, where 257 subjects were classified as mild, 231 as moderate and 377 as severe. There was a statistical difference in the mean age (p<0.001) among the three groups. No significant differences in any other laboratory findings were observed among the three subgroups (table 4).

Multiple logistic regression analyses of associations between APTT, PT and MPV with patients with PACG and in control individuals

Stepwise multiple logistic regression analyses revealed that a shorter APTT (OR=1.032, 95% CI 1.000 to 1.026, adjusted for age, sex, PLT, PDW, PCT, hypertension, diabetes mellitus) was independently associated with patients with PACG (table 5). A shorter PT (OR=1.249, 95% CI 1.071 to 1.457, adjusted for age, sex, PLT, PDW, PLC, hypertension, diabetes mellitus) was independently associated with patients with PACG (table 5). A higher level of MPV (OR=1.185, 95% CI 1.081 to 1.299, adjusted

Table 3 Comparison of APTT, PT, TT, D-D and MPV in the PACG and control groups by age and gender

Subgroup	PACG group	Control group	t Value	p Value
Male				
APTT (s)	30.77±4.80	32.36±5.28	3.699	<0.001
20–59 years	30.96±4.88 (n=108)	33.29±5.03 (n=105)	3.250	0.001
60+ years	30.65±4.76 (n=188)	31.88±5.36 (n=185)	2.284	0.023
PT (s)	11.82±1.24	12.12±1.34	2.669	0.008
20–59 years	11.75±1.36	12.25±0.98	2.878	0.004
60+ years	11.86±1.17	12.05±1.49	1.294	0.197
TT (s)	17.74±1.58	18.14±1.27	3.294	0.001
20–59 years	17.78±1.55	17.95±1.11	0.871	0.385
60+ years	17.71±1.61	18.24±1.34	3.296	0.001
D-D (mg/L)	0.28±0.18	0.33±0.44	1.043	0.298
20–59 years	0.21±0.11	0.25±0.17	1.279	0.203
60+ years	0.32±0.21	0.37±0.52	0.669	0.504
MPV (fl)	10.24±1.42	10.30±2.44	0.326	0.744
20–59 years	10.32±1.73	10.08±1.23	1.060	0.290
60+ years	10.20±1.21	10.41±2.87	0.910	0.363
Female				
APTT (s)	29.34±5.15	30.74±4.97	4.851	<0.001
20–59 years	29.93±5.02 (n=196)	31.58±5.16 (n=208)	3.302	0.001
60+ years	29.03±5.20 (n=373)	30.31±4.81 (n=415)	3.618	<0.001
PT (s)	11.60±1.02	11.88±1.22	4.340	<0.001
20–59 years	11.53±0.97	12.12±1.36	5.015	<0.001
60+ years	11.64±1.05	11.76±1.12	1.581	0.114
TT (s)	17.72±1.56	18.10±1.18	4.718	<0.001
20–59 years	17.61±1.41	17.89±1.24	2.179	0.030
60+ years	17.78±1.62	18.21±1.13	4.258	<0.001
D-D (mg/L)	0.48±0.73	0.37±0.33	2.272	0.024
20–59 years	0.27±0.15	0.28±0.16	0.504	0.615
60+ years	0.57±0.86	0.41±0.38	3.131	0.002
MPV (fl)	10.52±1.41	10.21±1.33	3.852	<0.001
20–59 years	10.51±1.31	10.29±1.33	1.742	0.082
60+ years	10.52±1.47	10.18±1.33	3.473	0.001

Data are expressed as mean±SD. Independent sample t-test was used.
APTT, activated partial thromboplastin time; D-D, D-dimer; MPV, mean platelet volume; PACG, primary angle closure glaucoma; PT, prothrombin time; TT, thrombin time.

Table 4 Comparison of laboratory findings among mild, moderate and severe PACG

Factors	Mild PACG (n=257)	Moderate PACG (n=231)	Severe PACG (n=377)	F value	p Value
Age	61.49±9.71	65.42±10.24	62.88±10.95	7.127	0.001*‡
MD	3.78±1.43	9.41±1.56	22.51±5.23	1893.726	<0.001*†‡
APTT (s)	29.78±4.96	29.64±4.73	30.08±5.38	0.513	0.599
PT (s)	11.62±1.05	11.56±0.10	11.72±1.13	1.446	0.236
TT (s)	17.79±1.54	17.65±1.49	17.79±1.61	0.499	0.607
D-D (mg/L)	0.43±0.96	0.44±0.42	0.36±0.33	0.477	0.621
MPV (fl)	10.36±1.35	10.35±1.51	10.46±1.40	0.398	0.672

Data are expressed as mean±SD. One-way ANOVA was used.
*p<0.05 for the difference between the mild PACG group and moderate PACG group (one-way ANOVA with the LSD post hoc test).
†p<0.05 for the difference between the mild PACG group and severe PACG group (one-way ANOVA with the LSD post hoc test).
‡p<0.05 for the difference between the moderate PACG group and severe PACG group (one-way ANOVA with the LSD post hoc test).
ANOVA, analysis of variance; APTT, activated partial thromboplastin time; D-D, D-dimer; LSD, least significant difference; MD, visual fields mean deviation; MPV, mean platelet volume; PACG, primary angle closure glaucoma; PT, prothrombin time; TT, thrombin time.

for age, sex, PLT, PDW, PLC, hypertension, diabetes mellitus) was independently associated with patients with PACG (table 5).

Nomogram development

In the logistic analyses, the risk factors that predicted PACG were as follows: sex (male=0, female=1), decreased APTT, decreased PT and increased MPV. Multivariate logistic analyses demonstrated that the APTT, PT and MPV were independent risk factors for PACG (table 5). A nomogram to predict risk factors for PACG was developed (see online supplementary figure 2). As APTT, PT and MPV were independent risk factors for PACG, these variables were included in the nomogram.

DISCUSSION

The APTT and the PT reflect the function of endogenous and exogenous pathways of coagulation cascade, respectively,[26] and the TT reflects the content and structure of plasma fibrinogen to some degree.[27] In our study, it was found that the APTT, PT and TT were significantly shorter (all p<0.001) in patients with PACG when compared with the control group, which could result in a hypercoagulable state in patients with PACG. Meanwhile, D-dimer is a specific degradation product that is produced in hydrolysis of fibrin, which is able to reveal early thrombotic disease and reflect generation of thrombin and plasmin.[28] Moreover, D-dimer is a fibrin degradation product and a very useful biomarker of fibrinolysis and hypercoagulability.[28] Our results also showed that the level of D-dimer was significantly higher (p=0.042) in patients with PACG than those in the control group, which could be caused by a hypercoagulable state. These abnormal indices of coagulation function strongly indicate that there may be a hypercoagulable state in patients with PACG. At the same time, our results also discovered that the MPV of the PACG group was significantly higher (p=0.013) than that of the control group. Large platelets can result in an increased propensity to aggregate compared with small platelets, due to the increased production of thromboxane A2 and the increased expression of glycoprotein Ib and glycoprotein IIb/IIIa receptors on their surfaces.[29] This also supports the hypothesis that hypercoagulability increases in patients with PACG.

Table 5 Multiple logistic regression analyses of associations between APTT, PT and MPV with patients with PACG and in control individuals

Factors	OR	p Value	95% CI
APTT (s)	1.032	0.049*	1.000 to 1.026
PT (s)	1.249	0.005*	1.071 to 1.457
MPV (fl)	1.185	<0.001*	1.081 to 1.299

*Adjusted for age, sex, platelet count, platelet distribution width, plateletcrit, mean platelet volume, hypertension, diabetes mellitus.
APTT, activated partial thromboplastin time; MPV, mean platelet volume; PACG, primary angle closure glaucoma; PT, prothrombin time.

While various risk factors can cause a hypercoagulable state, the pathomechanism of hypercoagulability is based on an impaired blood vessel wall, a change in bloodstream state or an alteration of blood constituents. Based on the results of our study, we speculate that there may be a change in the vessel wall, blood flow and/or blood constituents in patients with PACG, which caused this state of hypercoagulability. Saccà *et al* found that there might be damage of the anterior chamber endothelium in patients with glaucoma.[30] Some studies have emphasised vascular dysregulation and endothelial dysfunction as contributing factors in patients with glaucoma.[31–33] Several studies have claimed that a reduction in ocular blood flow may occur in patients with glaucoma as well.[11 13 34 35] Meanwhile, Matsumoto *et al* reported a positive relationship between platelet hyperaggregation with NTG and/or POAG.[36] Kilic-Toprak *et al* showed that erythrocyte aggregation appears to be higher in patients with POAG.[37] All these are evidence that suggest there might be a pathological basis of hypercoagulability

in glaucoma, and provide powerful support for our hypothesis.

In 1973, Drance *et al* reported that patients with NTG had a 'greater tendency to thrombosis' and proposed the viewpoint of a 'hypercoagulable state'.[8] Once a hypercoagulable state occurs in patients with glaucoma, regardless of whether it is primary or secondary to a vascular dysregulation, it can exacerbate the reduction of ocular blood flow. This could result in ocular tissue ischaemia and hypoxia causing reduced nutritional support, a local inflammatory reaction and/or an accumulation of reactive oxygen species. In turn, this could lead to damage of the optic nerve and visual field.[38 39] An increasing number of studies have proved that reduced ocular blood flow is associated with the progression of visual field loss in glaucoma.[12 40–43] Nevertheless, some studies refute this viewpoint, finding no abnormalities in platelet function, the coagulation cascade or the fibrinolysis system.[44–46] In our study, we found an abnormality in the coagulation, fibrinolysis and platelet functions in our PACG subjects, supporting the view that patients with PACG have a greater tendency of hypercoagulability. However, diagnosis of hypercoagulability in clinical laboratory studies requires more specific indicators other than APTT, PT, TT and D-dimer. Therefore, further studies are necessary to confirm this hypothesis for a better understanding of the pathophysiological mechanism of glaucoma.

When analysing parameters of coagulation among subgroups by gender and age, a similar trend was observed between the PACG and control groups. In particular, abnormalities of the coagulation function indicators in women and the older female subgroup were more distinct than in any other subgroup. A population-based study reported that old age and female sex were risk factors for PACG.[3] Therefore, we can speculate that abnormalities of the coagulation function may be an important factor in the development of glaucoma. Analysis of the parameters of coagulation function among the mild, moderate and severe PACG subgroups showed no significant differences between different stages of the disease. This suggests that abnormalities of the coagulation function might have occurred in the early stages of PACG and do not change over the course of the disease. Therefore, this suggests that the coagulation state may serve as a potential indicator for the early detection of glaucoma.

Nomograms have been widely used for predicting the prognosis of patients with malignant cancer and quantifying the risk factors of various diseases.[47 48] The effects of several separate variables are integrated by a nomogram to give an individualised risk assessment for each patient. The benefits of this methodology compared with standard systems are clear from studies in clinical settings.[49] In this study, the patients with a shorter APTT, shorter PT and elevated MPV were high risk for PACG, as shown in online supplementary figure 2. For example, a patient with APTT=30 (34 points), PT=14 (28 points) and MPV=20 (35 points) would score 97 total points that converts to a probability risk of PACG of 63% compared with an age and sex-matched healthy control subject.

To the best of our knowledge, this is the first paper that focused on the relationship between coagulation function and PACG. Multiple logistic regression analyses also revealed that APTT, PT and MPV were independently associated with PACG. These results all suggest that abnormalities in the coagulation function, which might result in a hypercoagulable state, are significantly associated with the development of PACG. According to online supplementary tables 1 and 2, less than 2% of patients with PACG revealed abnormal values for APTT, PT, TT and MPV that may strictly limit the clinical use of such findings. Therefore, coagulation function may not be the primary cause of PACG but may be a secondary factor that could increase the risk of PACG, because coagulation function parameter values of most patients with PACG were still within the reference range. But this might provide a vital new field for researcher to study the pathophysiological mechanism of PACG. Considering that vascular dysregulation is commonly recognised as a risk factor of glaucoma, it is worth exploring the possible mechanism of vascular dysregulation in glaucoma. Moreover, a hypercoagulable state, either secondary to vascular dysregulation or resulting in vascular dysregulation, can be well monitored in a clinical laboratory. However, our study had some limitations. First, owing to the nature of this study was a retrospective case–control study, information on ocular parameters in control subjects was lacking. Second, the data were collected at a single eye centre, which may limit the generalisability of the results. Lastly, those on treatment with agents affecting coagulation parameters were excluded, but we did not consider treatment with brinzolamide eye drops, carbonic anhydrase inhibitor, mannitol and blood pressure medications and how this may affect the results and vascular physiology.

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Competing interests None declared.

Patient consent Obtained.

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