

Primary Open-Angle Glaucoma with Progressive Synechial Angle Closure in Senior Chinese: A Retrospective Two-Center Cohort Study

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Abstract

Background: This study aims to compare a unique subtype of combined-mechanism glaucoma (CMG), primary open-angle glaucoma (POAG) with progressive synechial angle closure, with chronic primary angle-closure glaucoma (PACG) in the Chinese senior population.

Methods: In this two-center retrospective cohort study, 30 eyes with POAG plus primary angle closure suspect (PACS) or primary angle closure (PAC) were included in the CMG group, and 30 chronic PACG eyes with matched extent of glaucomatous optic neuropathy (GON) were included in the control group. Clinical features and detailed disease development histories were investigated and compared between the two groups.

Results: No statistical significances were found in age, anterior chamber depth (ACD), axial length (AL), cup-to-disc (C/D) ratio, average retinal nerve fiber layer (RNFL) thickness, and mean deviation (MD) of visual field (VF) between the two groups ($P > 0.05$). Compared to CMG group, higher preoperative maximum intraocular pressure (IOP) and more extensive synechial angle closure were found in PACG group (both $P < 0.001$). Pearson correlation analysis revealed significant correlations in the CMG group between C/D ratio and MD of VF ($P < 0.001$). However, the synechial angle closure degree in the CMG group did not show a significant correlation with any of the other parameters. In the PACG group, the extent of synechial angle closure has a linear relationship with the maximum IOP, C/D ratio, and MD of VF (all $P < 0.05$).

Conclusion: The study highlights the importance of recognizing CMG, particularly NTG with progressive synechial angle closure, in the Chinese senior population. Future studies with more comprehensive medical records may provide further evidence to clarify the characteristics and prevalence of this condition.

Keywords: Normal Tension Glaucoma; Progressive Synechial Angle Closure; Combined-Mechanism Glaucoma; Glaucomatous Optic Neuropathy

Abbreviations: PACG: Primary angle-closure glaucoma; ACD: Anterior chamber depth; AL: Axial length; IOP: Intra-ocular pressure; C/D: Cup-to-disc; RNFL: Retina nerve fiber layer; MD: Mean deviation; VF: Visual field; CMG: Combined-mechanism glaucoma; PACG: Primary angle-closure glaucoma; IOP: Intra-ocular pressure

Introduction

Primary glaucoma in adults can be classified into open-angle glaucoma and angle-closure glaucoma based on morphology of iridocorneal angle. Essentially, primary open-angle glaucoma (POAG) is defined as "a chronic and progressive optic neuropathy characterized by an acquired atrophy of the optic nerve and a loss of retinal ganglion cells (RGC)", as described in the latest Preferred Practice Pattern (PPP 2016) [1]. Primary angle-closure glaucoma

(PACG) is characterized by elevated intraocular pressure (IOP) due to mechanical obstruction of the trabecular meshwork. Importantly, mechanical angle closure is the pathophysiological basis in PACG, so that the range of the angle closure determines the extent of IOP elevation. IOP rising to a certain extent and maintaining for a certain period of time would be the direct cause leading to glaucomatous optic neuropathy (GON). The nomenclature of primary angle closure suspect (PACS, defined

as appositional contact between the peripheral iris and posterior trabecular meshwork) and primary angle closure (PAC, defined as synechial angle closure) is proposed when evidence of characteristic glaucomatous structural and/or functional damage is not present [2,3].

POAG is the most common type of glaucoma in Asian [4] while normal-tension glaucoma (NTG) constitutes the majority of POAG in Asian population-based studies [5-7], which is one of the distinctive characteristics of glaucoma in Asians compared with other races. In China, the overall pooled prevalence of NTG among POAG patients is 69.8% [5]. At the same time, it should be noted that Chinese eyes are prone to developing creeping angle closure due to shallow anterior chamber depth and high rates of plateau iris configuration [8-10]. Approximately 20% Chinese people aged 50 years and older develop a certain form of angle closure over a 10-year period [11]. Therefore, the prevalence of NTG with PACS/PAC in Chinese elderly people may far exceed our expectations. In our clinical settings, approximately 50% POAG patients over 60 years old present with some extent of narrow angle, and quite a lot of these senior patients have normal or close to normal IOP. These cases are defined as PACG according to the ISGEO and PPP2016 guidelines, but they are quite different from classic PACG. In classic PACG [12], clinical development follows from PACS to PAC, and PACG. Generally, only when synechial angle closure progresses to more than 50% of the entire angle [13,14], compromised aqueous outflow system leads to gradual IOP elevation which is in proportion to the extent of synechial angle closure and finally cause GON. In our scenario, the degree of GON in many patients is not proportion to the extent of synechial angle closure and IOP elevation, which suggested other underlying pathogenesis in GON progression. The possible explanation for these cases might be that GON occurs prior to extensive synechial angle closure. POAG might be the primary diagnosis, and the narrow anterior segment structure leading to progressive synechial angle closure is a coexisting pathology. We define this glaucoma as a unique type of combined-mechanism glaucoma (CMG) [15,16]. We believe that this subtype of CMG is quite common among senior Chinese population, but the lack of recognition and systematic medical data analysis leads to underdiagnosis. In the current study, we have retrospectively inspected many glaucoma cases, from which we found 30 eyes with solid evidence supporting the existence of POAG with progressive synechial angle closure. We would emphasize the importance of a complete medical database, especially records of series of gonioscopy, UBM and evaluations of GON, as well as IOP in every clinical patient with narrow angle.

Methods

Ethical approval

In this retrospective study, patients with complete out-patient medical records were selected from Zhongshan Ophthalmic Center between November 2015 and November 2020, and from Beijing Tongren Hospital between November 2020 and November 2024. Institutional approval for this study was obtained from

the Ethics committee of the Zhongshan Ophthalmic Center (No. 2020KYPJ103) and Beijing Tongren Hospital (TREC2022-KY109). All procedures were conformed to the tenets of the Declaration of Helsinki.

Study population

Two groups were included in this study. The CMG group consisted of patients with POAG and progressive synechial angle closure, while the PACG group consisted of patients with chronic PACG and matched severity of GON. The diagnosis of PACG, POAG, and CMG followed the guidelines from PPP 2016. Patients were included in the CMG group if they met the following criteria: (1) Confirmed POAG diagnosis with functional and/or structural evidence of GON, together with various extent of synechial angle closure; (2) Complete clinical records, including IOP records (measured by Goldmann applanation tonometry), Optical Coherence Tomography (OCT), anterior chamber depth (ACD), axial length (AL), visual field (VF), and optic nerve imaging with vertical cup-to-disc (C/D) ratios were available; (3) the severity of GON was not consistent with the extent of synechial angle closure (less than 180 degrees) and IOP elevation.

Patients were included in the PACG group if they met the following criteria:

- a) Classic diagnosis of chronic PACG.
- b) Complete medical records, showing a progressive synechial angle closure, developing from PACS, PAC to PACG.
- c) Severity of GON was in proportion to the extent of synechial angle closure and IOP elevation with extended period of time.

Specifically, detailed gonioscopy examination was performed on each patient's eyes using standard procedures. Briefly, the angle recess was evaluated using a 2-mm high, narrow slit beam in the least possible illumination, with the eye in primary gaze. Manipulative and indentation gonioscopy were carried out to visualize all possible angle structures. The presence and extent of PAS, trabecular pigmentation, and any other angle abnormalities were recorded. PAS is defined as abnormal adhesions of the iris to the angle which is at least half of a clock hour in width and is present to the level of the anterior trabecular meshwork or higher [17]. The number of clock hours of PAS was recorded. Besides, angles are graded based on Spaeth's classification, repeated and confirmed by a senior glaucoma specialist, Dr. Zhigang Fan (FZG).

Exclusion criteria in two group was included as follows.

- a. angle synechiae was secondary to other conditions, such as inflammation, neovascularization, and iridocorneal endothelial syndrome (ICE);
- b. Systemic or other ocular conditions that affect aqueous outflow function, including Posner-Schlossman syndrome (PSS), trauma or tumor etc.

c. developmental anomaly of the anterior ocular segments.

A complete medical record for each patient was examined and confirmed by one glaucoma specialist (FZG), including ophthalmic examinations, demographic data, systemic health condition and eye disease history. Statistical analysis. Statistical analyses were performed using SPSS software version 22.0 (SPSS, Inc., Chicago, IL, USA). All continuous data that conformed to a normal distribution were recorded as mean ± standard deviation (SD). The comparisons of clinical data between the two groups were performed using Student t test after the confirmation of homogeneity of variance with an F test. Pearson correlation analysis was used to explore the relationships between various clinical parameters in different groups. Pearson correlation coefficients (r) were calculated to quantify the strength and direction of linear relationships between pairs of continuous variables. The assumptions for Pearson correlation analysis were met, including the normal distribution of variables and the linearity of relationships. For all test, P-values < 0.05 was

considered to be statistically significant.

Results

Recruitment and Demographics

Consecutive patients meeting the criteria were selected in the CMG group and consecutive patients diagnosed with PACG during the same period were used as controls. A total of 60 eyes from 51 patients were included in this study, comprising 30 eyes (27 patients) in the CMG group and 30 eyes (24 patients) in the PACG group. In the CMG group, 12 eyes (12 patients) recruited from the Zhongshan Ophthalmic Center and 18 eye (15 patients) from the Beijing Tongren Hospital. In the PACG group, 11 eyes (11 patients) recruited from the Zhongshan Ophthalmic Center and 19 eye (13 patients) from the Beijing Tongren Hospital. There were 15 males and 12 females in the CMG group, 7 males and 17 females in the PACG group. The age of patients in CMG group and PACG group was 62.0 ± 8.9 and 58.8±10.0 years (P = 0.2389), respectively. Details are shown in (Table 1).

Table 1: Statistical information of patients in the two groups.

| Items | Age (year) | IOP in clinical time (mmHg) | Maximum IOP (mmHg) | ACD (mm) | AL (mm) | C/D ratio | Average RNFL thickness (µm) | MD of VF (dB) | Synechia degree |
|-------|------------|-----------------------------|--------------------|-----------|------------|-----------|-----------------------------|---------------|-----------------|
| CMG | 62.0 ± 8.9 | 19.3±5.6 | 27.3±5.1 | 2.33±0.48 | 22.59±0.86 | 0.85±0.07 | 54.2±15.6 | -24.6±7.6 | 3.5±1.5 |
| PACG | 58.8± 10.0 | 20.8±5.5 | 43.0±5.5 | 2.21±0.35 | 22.64±0.83 | 0.85±0.07 | 56.7±13.1 | -23.8±6.2 | 9.0±2.0 |
| P | 0.2389 | 0.2998 | <0.001 | 0.3067 | 0.805 | 0.725 | 0.4677 | 0.6879 | <0.001 |

CMG: Combined-mechanism glaucoma; PACG: Primary angle-closure glaucoma; IOP: Intro-ocular pressure; ACD: Anterior chamber depth; AL: Axial length; C/D: Cup-to-disc; RNFL: Retina nerve fiber layer; MD: Mean deviation; VF: Visual field

Disease information

In the CMG group, 27 eyes (90%) were in the advanced stage of glaucoma, and 3 eyes (10%) were in the middle stage of glaucoma. In the PACG group, 29 eyes (96.7%) were in the advanced stage of glaucoma, and 1 eye (3.3%) was in the middle stage of glaucoma. No statistical significances were found between the CMG and PACG group including IOP in clinical time (19.3 ± 5. 6 vs. 20.8 ±5.5 mmHg), ACD (2.33 ± 0.48 vs. 2.21 ± 0.35 mm), and AL (22.59 ± 0.86 vs. 22.64 ± 0.83 mm) (all P > 0.05). After an in-depth inquiry into medical history, higher maximum IOP was found in the PACG group than that in the CMG group (43.0 ± 5.5 vs. 27.3 ± 5.1 mmHg, P < 0.001). Although the severity of GON in two groups was comparable (C/D ratio: 0.85 ± 0.07 vs. 0.85 ± 0.07, MD of VF: -24.6 ± 7.6 vs. -23.8 ± 6.2 dB; average RNFL thickness: 54.2 ± 15.6 vs. 56.7 ±13.1 µm; all P > 0.05), the extent of synechial angle closure was more extensive in the PACG group than that in CMG group (9.0 ± 2.0 vs. 3.5 ± 1.5 clock hours, P < 0.001). This indicates that angle closure contributes only part of the GON defect in CMG patients.

Pearson Correlation Analysis

In the CMG group, Pearson correlation analysis revealed several significant correlations among the variables (Table 2). ACD showed a significant positive correlation with average RNFL thickness (r = 0.457, P < 0.05). The C/D ratio showed a significant negative correlation with MD of VF (r = -0.861, P < 0.001). Notably, the synechial angle closure degree did not show a significant correlation with any of the other parameters (P > 0.05). In the PACG group, Pearson correlation analysis revealed the following significant correlations (Table 3). Maximum IOP showed a significant negative correlation with average RNFL thickness (r = -0.481, P < 0.01) and MD of VF (r = -0.658, P < 0.001), and a significant positive correlation with synechial angle closure degree (r = 0.572, P < 0.01). The C/D ratio showed a significant positive correlation with average RNFL thickness (r = 0.441, P < 0.05) and synechial angle closure degree (r = 0.364, P < 0.05), and a significant negative correlation with MD of VF (r = -0.397, P < 0.05). Average RNFL thickness showed a significant positive

correlation with the MD of VF ($r = 0.478, P < 0.01$). The MD of VF showed a significant negative correlation with synechial angle closure degree ($r = -0.613, P < 0.001$). These correlation analyses highlight the extent of synechial angle closure have a linear relationship with the maximum IOP, C/D ratio, and MD of VF.

Table 2: Pearson correlation analysis results in CMG groups.

| Variables | ACD (mm) | AL (mm) | Maximum IOP (mmHg) | C/D ratio | Average RNFL thickness (μm) | MD of VF | Synechia degree |
|--|----------|---------|--------------------|-----------|--|-----------|-----------------|
| ACD (mm) | 1 | -0.25 | -0.162 | -0.035 | 0.457* | -0.001 | -0.202 |
| AL (mm) | | 1 | -0.191 | -0.001 | -0.311 | 0.031 | 0.028 |
| Maximum IOP (mmHg) | | | 1 | 0.263 | 0.063 | -0.191 | 0.091 |
| C/D ratio | | | | 1 | -0.248 | -0.861*** | 0.287 |
| Average RNFL thickness (μm) | | | | | 1 | -0.219 | -0.238 |
| MD of VF | | | | | | 1 | -0.234 |
| Synechia degree | | | | | | | 1 |

CMG: Combined-mechanism glaucoma; ACD: Anterior chamber depth; AL: Axial length; IOP: Intra-ocular pressure; C/D: Cup-to-disc; RNFL: Retina nerve fiber layer; MD: Mean deviation; VF: Visual field; * <0.05 ; ** <0.01 ; *** <0.001 .

Table 3: Pearson correlation analysis results in PACG groups.

| Variables | ACD (mm) | AL (mm) | Maximum IOP (mmHg) | C/D ratio | Average RNFL thickness (μm) | MD of VF | Synechia degree |
|--|----------|---------|--------------------|-----------|--|-----------|-----------------|
| ACD (mm) | 1 | 0.041 | 0.021 | 0.161 | -0.136 | -0.147 | 0.121 |
| AL (mm) | | 1 | 0.205 | -0.135 | 0.159 | 0.049 | 0.162 |
| Maximum IOP (mmHg) | | | 1 | 0.279 | -0.481** | -0.658*** | 0.572** |
| C/D ratio | | | | 1 | 0.441* | -0.397* | 0.364* |
| Average RNFL thickness (μm) | | | | | 1 | 0.478** | -0.272 |
| MD of VF | | | | | | 1 | -0.613*** |
| Synechia degree | | | | | | | 1 |

PACG: Primary angle-closure glaucoma; ACD: Anterior chamber depth; AL: Axial length; IOP: Intra-ocular pressure; C/D: Cup-to-disc; RNFL: Retina nerve fiber layer; MD: Mean deviation; VF: Visual field; * <0.05 ; ** <0.01 ; *** <0.001 .

Discussion

The study highlights the importance of recognizing CMG, particularly POAG with progressive synechial angle closure, in the Chinese senior population. The clinical features and disease progression differ from classic PACG, and accurate diagnosis is crucial for appropriate treatment. In the CMG group, the degree of GON damage was severe, but not proportional to the extent of synechial angle closure, which is vital to distinguish from classic PACG. If we do not deliberately scrutinize this special condition from the dynamic course of disease development, a misdiagnosis of PACG could be made with pictures in a single disease section.

In general, in classic PACG patients, the extent and period of IOP elevation is proportional to the extent of synechial angle closure. The severity of GON is also consistent with the duration of IOP elevation together with the extent of synechial angle closure. A discrepancy between these three index alerts clinicians to consider the possibility of POAG/NTG complicated with PACS/PAC/PACG, namely the CMG. There might be three types of CMG, the high-IOP POAG complicated with PACG, the PACG with secondary open-angle glaucoma (OAG) and NTG complicated with PACG. For the high-IOP POAG complicated with PACG, in which the IOP was high mainly due to increase outflow resistance at trabecular meshwork with in proportional extent of synechial angle closure, and GON

damage is much earlier and more severe in consideration of the extent of synechial angle closure. For the PACG with secondary OAG, the high IOP was also in proportionated with the extent of synechial angle closure.

According to our clinical experience, this situation may exist. The hypothesis is that repeated episodes of angle closure attacks cause permanent damage to the corneoscleral trabecular meshwork even without formation of peripheral anterior synechiae (PAS) and that they could in this way induce a form of permanent OAG3. As presented in Sihota's study, which included CMG patients with elevated IOP and angle closures less than 90 degrees with a sectional picture of the disease stage, they confirmed that both high-IOP POAG and PACG elements are present in each case 16. However, there is no history to distinguish which element happens first or both happen simultaneously. Our study also found a typical patient who had a range of synechial angle closure extending to 2, 3, or 4 clock-hours in the presence of an IOP in the 40-mmHg range. If tomography is taken, it may indicate an impairment of facility of outflow consistent with the IOP, but disproportionate to the extent of angle closure 3. This was frequently misdiagnosed as POAG with PAC/PACS/PACG, but if we investigate into the medical history, no initial GON, a progressive synechial angle closure and gradual elevation of IOP would be identified, which helps to make correct diagnosis. However, no matter which subtype it was, the treatment for these high-IOP CMG follows common POAG treatment protocol [18]. Simultaneously, these patients also need treatment for accompanying PACS/PAC that follows exactly the same strategy and protocol as in a classic PACS/PAC/PACG situation, including iridotomy, iridopathy or cataract extraction.

The third type of CMG, NTG complicated with PACG was a more complex situation. In these cases, the IOP might elevated to related or absolute high level during the development of synechial angle closure, which could potentially accelerate the progression of GON by aggravating ischemia. As defined by the International Society Geographical and Epidemiological Ophthalmology (ISGEO), PACG was PAC plus glaucomatous damage (optic disc/visual field), and PAC was defined as non-visibility of posterior trabecular meshwork in three or more quadrants under static gonioscopy and plus raised IOP and/or PAS. This means high IOP, and extensive synechial angle closure were not necessary for the diagnosis of PACG. Actually, PACG patients might be presented with normal IOP in clinic time, since the repeated episodes of sub-clinical acute or sub-acute angle closure attacks, which may be resolved naturally, and may not be serious enough to alert patients seeking immediate medical attention, could possibly cause GON as well [19]. Therefore, normal-IOP CMG patients might easily misdiagnosis as PACG when no complete records to make a definitive differentiation. In our study, IOP in clinic time has no statistical significance between the CMG and PACG group. While after an in-depth inquiry into medical history, higher maximum IOP was found in the PACG group than that in the CMG

group. Besides, the synechial angle closure degree did not show a significant correlation with any of the GON related parameters. However, if only through sectional data presented at a later disease stage when an extensive synechial angle closure was already present, our CMG cases would have been indistinguishable to chronic PACG. More importantly, for this type of CMG, target IOP and treatment strategy were quite different from PACG or high-IOP CMG. The mainstream treatment for NTG is IOP reduction [20] and aggressive lowering of IOP by 30% below the baseline can be beneficial [21]. Long-term topical ocular hypotensive agents, incisional surgery, trabeculectomy or tube shunt, and, rarely, laser trabeculoplasty could be selected based on the severity of GON and target IOPs, while the coexisting narrow angle and progressive synechial angle closure should also be addressed simultaneously.

In this study, we aim to highlight that ophthalmologists should become well-acquainted with this specific subtype of CMG, NTG with progressive synechial angle closure. When considering a diagnosis of PACG, a thorough examination is essential to assess the consistency between the extent of IOP elevation, angle closure and GON. The most definitive evidence differentiating these two categories of patients is GON appears prior to synechial angle closure and elevated IOP in NTG. Therefore, our studies repeatedly address the importance in reporting and investigating the entire disease course. Considering the significantly higher incidence of NTG and narrow angle in Asian population, NTG with narrow angle and progressive synechial angle closure is probably a very common form of glaucoma in Chinese patients. Estimates of its exact incidence is not possible at this moment, due to vastly incomplete medical record due to the current lack of historical medical data system that incorporate medical history with all the imaging examinations. We included cases from the two leading ophthalmic centers in China to alert, as much as possible, that this type of CMG deserves our attention.

Conclusion

Conclusion with complete scientific evidence demands a longitudinal multi-center clinical trial. Some limitations in this study should be considered. First, it was a retrospective case series with a limited size. Ideally, identification of CMG would be better based on randomized clinical trials with large sample size. Subsequent RCT studies will be conducted to include more patients to verify this point of view. Second, the degree of PAS was evaluated based on the subjective judgment, which might be less helpful for wider interpretation and application to identify the CMG. However, the number of clock hours of PAS, are graded based on Spaeth's classification, repeated and confirmed by a senior glaucoma specialist, Dr. FZG. Thirdly, only Chinese patients were recruited in this study, which may limit its application to other ethnic groups. In conclusion, this study highlights the importance of recognizing CMG, particularly NTG with progressive synechial angle closure, in the Chinese senior population. Scrutinizing medical records to build an entire clinical picture is

important for making correct diagnosis. Appropriate therapeutic strategies primarily focus on NTG should be administered supplemented by treatments on PAC/PACS. We look forward to conducting longitudinal multicenter clinical trials to improve our understanding.

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