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GLAUCOMA

Long-term structural and functional outcomes of primary congenital glaucoma

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Abstract

Purpose To investigate the clinical characteristics and long-term outcomes of primary congenital glaucoma (PCG) patients.

Methods In this retrospective, longitudinal, cohort study, PCG patients with reliable visual field (VF) tests and optical coherence tomography (OCT) were included. Disease progression was detected using guided progression analysis with OCT and the change analysis of mean deviation (MD) slope with VF tests. Factors associated with the disease progression and visual prognosis were analyzed.

Results Twenty-nine eyes from 11 bilateral and 7 unilateral PCG patients were enrolled. LogMAR visual acuity declined (0.15 vs. 0.40, $P<0.001$). The change rate of the average retinal nerve fiber layer thickness was -0.83 ± 1.45 μm/year, and 28% of eyes showed glaucoma progression on OCT. The median of the MD slope was 0.16 (− 1.19 to 1.07) dB/year, and 14% of eyes showed glaucoma progression on the VF test. Higher average intraocular pressure (IOP) ($P=0.046$) and IOP fluctuation ($P=0.031$) predicted disease progression. None of the fellow eyes of unilateral PCG patients developed glaucoma during the follow-up. At last, 59% of eyes had visual acuity > 20/70, and 31% had MD > − 6 dB. Patients with worse baseline visual acuity ($P=0.027$), worse baseline MD ($P<0.001$), and smaller neuroretinal rim area ($P<0.001$) showed worse final MD values.

Conclusions Aggressive IOP control is necessary to prevent structural and functional decline in PCG patients. Their fellow eyes are not at risk of glaucoma. Baseline neuroretinal rim area can predict the functional outcome.

Keywords Primary congenital glaucoma · Optical coherence tomography · Visual field test · Glaucoma progression

Key messages

What was known before:

- Primary congenital glaucoma patients had visual field defects and decreased retinal nerve fiber layer thickness.

What this study adds:

- Primary congenital glaucoma patients had comparable change rate of retinal nerve fiber layer thickness and mean deviation slope to adulthood glaucoma patients.
- The fellow eyes of primary congenital glaucoma patients remained free of glaucomatous damage during long-term follow-up.

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Introduction

Primary congenital glaucoma (PCG) is the most common type of childhood glaucoma and is potentially a sight-threatening condition [1, 2]. Most patients need surgical intervention and require life-long management [2, 3]. Even if successful surgical control of intraocular pressure (IOP), the visual acuity may be impaired due to glaucomatous optic neuropathy, high myopia, corneal complications, and amblyopia [2, 4, 5].

Several studies reported the long-term outcomes in PCG patients [4–8] and found that a second surgical intervention may be required at any time and the probabilities increased during follow-up [6, 7]. Most studies used conventional outcome measurements, such as elevated IOP ≥ 21 mmHg [7] or an increase of 0.2 in the cup-to-disc ratio, to define the disease progression or surgical failure. These outcome measurements might fail to detect early signs of progression [2, 4, 6]. The optical coherence tomography (OCT) scanning and visual field (VF) test could play a role in detecting the structural and functional progression more precisely and earlier if reliable test results can be obtained [9–11]. However, there is a paucity of long-term OCT and VF test data from the PCG patients in the literature.

In the current study, we retrospectively reviewed the clinical characteristics and long-term visual outcomes of PCG patients using VF test and OCT data. We also analyzed the factors associated with structural and functional progression and visual outcomes. We aimed to understand the long-term progression of PCG patients and provide a reference for a life-long treatment plan.

Patients and methods

In this retrospective, longitudinal, and observational study, we enrolled patients who had the diagnosis of PCG and had been followed up in the glaucoma clinic at the National Taiwan University Hospital between 2010 and 2018. This study was approved by the Institutional Review Board of the National Taiwan University Hospital and adhered to the tenets of the Declaration of Helsinki. A diagnosis of PCG was made if the patient had an elevated IOP or other suggestive clinical features, including glaucomatous optic disc, Haab's striae, and increased cornea diameter [10, 12, 13]. We excluded patients with other associated ocular and systemic anomalies, congenital cataract, juvenile open-angle glaucoma, and other secondary glaucoma and those who had received intraocular surgeries other than glaucoma surgery. Patients with insufficient or nonreliable VF tests and OCT data were excluded. The medical records of all the patients from their first visits were retrospectively reviewed. The follow-up duration was calculated as the time interval between the first and the last follow-up. The age at the first visit, methods and times of surgical treatment, and the number of antiglaucoma medications used were recorded. The first and last available records of autorefraction, axial length, anterior chamber depth, lens thickness, central corneal thickness, corneal diameter, and corneal endothelial cell density were also documented. Since the visual acuity would improve under the amblyopia treatment, the best visual acuity achieved after the commencement of amblyopia treatment was indicated as the baseline visual acuity. IOP was measured with pneumotonometry (CT-80 Non-Contact Computerized Tonometer; Topcon Corp, Tokyo, Japan). IOP at initial visit, average IOP, and inter-visit IOP fluctuation (defined as the standard deviation of the IOP at all visits) [14] were recorded and calculated. A patient with any IOP measurement ≥ 21 mmHg was defined as having unstable IOP.

Optical coherence tomography

Optic nerve head scanning was performed using spectral domain OCT (Cirrus HD-OCT 4000, Carl Zeiss Meditec Inc., Dublin, CA, USA). The OCT follow-up duration was calculated as the time interval between the acquirement of the first and the last reliable OCT results. The average retinal nerve fiber layer (RNFL) thickness, RNFL thickness at each quadrant, rim area, disc area, cup-to-disc ratio, and cup volume were recorded. The progression was detected using the guided progression analysis (GPA). The average RNFL change rate (μm/year) was documented. There are three RNFL progression parameters—RNFL thickness map progression, RNFL thickness profile progression, and average RNFL thickness progression. If there were at least two " Likely Loss" among the three parameters, structural progression was considered [15].

Visual field test

The VF test (Husmphrey VF analyzer, Carl Zeiss Meditec, Dublin, CA, USA) was performed using the 24–2 SITA-fast program. The VF follow-up duration was calculated as the time interval between the acquirement of the first and the last reliable VF results. Reliable VF test result was defined as false positive < 33%, false negative < 33%, and fixation loss < 20%. Mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) were recorded. The MD change per year (dB/year), the MD slope, was obtained by linear regression analysis using the HFA Statpac 2 program. If the MD slope was significant (< 5%), VF progression was considered [16]. Fast progressor was defined as patients with MD slope worse than − 1 dB/year.

Visual outcome measurements

The final visual acuity was classified according to the World Health Organization classification of the severity of visual impairment [17]. Eyes with visual acuity ≥ 20/70 were considered to have no or mild visual impairment, those with visual acuity < 20/70 to ≥ 20/200 were considered to have moderate visual impairment, those with visual acuity < 20/200 to ≥ 20/400 were considered to have severe visual impairment, and those with visual acuity < 20/400 were considered to have blindness. The final VF test results were classified as early (MD ≥ − 6.0 dB), moderate (− 6 dB > MD ≥ − 12 dB), and severe glaucoma defect (MD < − 12 dB), according to the Hoddap-Parrish-Anderson criteria [18].

Statistical analysis

The statistical analyses were performed using R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). For descriptive statistics, the mean and standard deviation were calculated for the parametric numerical data, the median and range were calculated for non-parametric numerical data, and percentages were calculated for the categorical variables. Best-corrected visual acuity was converted to the logarithm of the minimal angle of resolution (LogMAR) equivalents for statistical analyses. Non-optotype visual acuities were converted to LogMAR with the following values: counting fingers = 1.9, hand motion = 2.3, light perception = 2.7, and no light perception = 3 [4, 12]. A generalized estimating equation (GEE) model was used to assess the difference of the baseline characteristics between unilateral and bilateral PCG eyes and the change of clinical features at baseline and the last follow-up. Logistic regression analysis using the GEE model was performed to analyze the factors associated with structural or functional progression. Factors predicting visual outcomes (final visual acuity and final MD of the VF test) were assessed using univariable linear regression analysis with the GEE model. Variables with *P*-value < 0.1 were included in the multivariable regression analysis with the GEE model. *P*-value < 0.05 was considered statistically significant.

Results

Baseline clinical characteristics

The medical chart of 61 patients was reviewed, but 43 patients had to be excluded due to lack of adequate VF tests and OCT exams. Therefore, we enrolled 18 patients (12 males and 6 females). The median follow-up period was 17.8 years (range, 12.4–46.0). Seven patients had unilateral PCG, while 11 patients had bilateral PCG. Twenty-nine glaucomatous eyes and seven fellow eyes were included for analysis. The median patient age of the first visit was 1.75 years old (range, 0.25–13). The mean IOP at presentation was 30.4 ± 16.7 mmHg. The average IOP during follow-up was 17.2 ± 7.0 mmHg. Table 1 shows the baseline clinical features of bilateral and unilateral PCG eyes and the fellow eyes of unilateral PCG. Unilateral PCG eyes had lower inter-visit IOP fluctuation than the bilateral PCG eyes. Compared to the fellow eyes of the unilateral PCG patients, PCG eyes had a higher baseline IOP, higher inter-visit IOP fluctuation, worse visual acuity, larger corneal diameter, lower corneal endothelial density, more negative value of spherical equivalent, deeper anterior chamber depth, longer axial length, thinner average RNFL thickness, smaller rim area, larger cup-to-disc ratio, larger cup volume, and worse VF test results.

Long-term clinical characteristics and visual outcomes

During the follow-up, the affected eyes received 0.8 ± 1.0 antiglaucoma medications and underwent 1.5 ± 1.3 glaucoma surgeries. Thirteen (44.8%) eyes underwent trabeculectomy, four (13.7%) eyes underwent goniotomy, five (17.2%) eyes underwent trabeculotomy, one (3.4%) eye underwent shunt surgery, and two (6.8%) eyes underwent trans-scleral cyclophotocoagulation.

Table 2 shows the comparison of the baseline and last follow-up clinical characteristics. The mean follow-up duration of OCT and VF tests was 7.2 ± 2.0 years (7.9 ± 3.0 exams) and 7.1 ± 2.5 years (9.1 ± 3.4 exams), respectively. The average age of taking the first OCT and VF test was 12.4 ± 4.7 and 12.9 ± 4.5 years, respectively. In the affected eyes, IOP decreased significantly to 17.2 ± 7.3 mmHg ($P < 0.001$), and 13 (44.8%) eyes were free of antiglaucoma medications. Visual acuity deteriorated significantly ($P < 0.001$). The value of spherical equivalent became more negative ($P = 0.004$) and axial length increased ($P < 0.001$), while other ocular biometric parameters and corneal endothelial cell density showed no significant change from baseline. Average RNFL thickness ($P = 0.001$) along with RNFL thickness at the superior ($P = 0.005$), inferior ($P = 0.005$), and temporal ($P = 0.006$) quadrants decreased, while other parameters of optic nerve head were stable. Among the fellow eyes, only refractive error ($P < 0.001$), anterior chamber depth ($P = 0.003$), axial length ($P = 0.003$), and RNFL thickness at the inferior quadrant ($P < 0.001$) significantly changed from baseline.

At the last follow-up, of the affected eyes, 17 (58.6%) eyes had mild or no visual impairment (≥ 20/70), six (20.7%) eyes had moderate visual impairment (< 20/70 to ≥ 20/200), one (3.4%) eye had severe visual impairment (< 20/200 to ≥ 20/400), and five (17.2%) eyes had blindness (< 20/400). Twenty-five (86.2%) affected eyes developed

Table 1 Baseline clinical characteristics of bilateral and unilateral primary congenital glaucoma patients and their fellow eyes

	All PCG eyes	Fellow eyes	*P*-value[a]	Bilateral PCG	Unilateral PCG	*P*-value[a]
Number (eyes/patients)	29/18	7/7		22/11	7/7	
Gender (male)	12 (66.7)	4 (57.1)	0.500	8 (72.7)	4 (57.1)	0.500
Median age at first visit (years)[b]	1.75 (0.25–13)	2 (0.25–6)	0.348	1.5 (0.25–13)	2 (0.25–6)	0.350
Intraocular pressure at first visit (mmHg)	30.4 ± 16.7	15.7 ± 3.5	< 0.001	31.7 ± 17.2	25.8 ± 15.7	0.410
Average intraocular pressure (mmHg)	17.2 ± 7.0	17.9 ± 3.4	0.670	18.1 ± 7.7	14.4 ± 3.8	0.101
Unstable IOP (%)	13 (44.8)	3 (42.9)	0.848	11 (50)	2 (28.6)	0.260
IOP fluctuation during follow-up (mmHg)	3.2 ± 2.3	2.2 ± 0.4	0.031	3.5 ± 2.5	2.1 ± 0.7	0.016
LogMAR visual acuity	0.15 (0–1.90)	0 (0–0.10)	< 0.001	0.10 (0–1.90)	0.40 (0.05–1.90)	0.293
Corneal diameter (mm)	13.2 ± 1.0	11.5 ± 0.5	< 0.001	13.3 ± 1.1	13.1 ± 0.8	0.710
Corneal endothelial cell density (cells/mm^2)	1434.5 ± 696.2	2844.0 ± 536.1	< 0.001	1343.0 ± 692.1	1630.0 ± 716.4	0.379
Spherical equivalent (D)	− 6.46 ± 5.88	− 0.86 ± 2.37	< 0.001	− 6.51 ± 5.35	− 6.30 ± 7.64	0.870
Average corneal curvature (D)	41.51 ± 2.80	42.69 ± 1.69	0.091	41.57 ± 2.75	41.36 ± 3.13	0.876
Anterior chamber depth (mm)	3.95 ± 0.40	3.25 ± 0.39	< 0.001	3.93 ± 0.37	4.00 ± 0.42	0.690
Lens thickness (mm)	3.61 ± 0.33	3.98 ± 0.42	0.010	3.59 ± 0.34	3.67 ± 0.31	0.540
Axial length (mm)	24.64 ± 2.64	21.98 ± 2.01	0.002	24.52 ± 2.55	24.97 ± 3.08	0.720
Central corneal thickness (μm)	556.4 ± 69.7	570.3 ± 30.2	0.630	520.4 ± 62.2	570.4 ± 69.0	0.077
Average retinal nerve fiber layer thickness (μm)	71.6 ± 15.6	100.0 ± 12.9	< 0.001	72.4 ± 15.1	69.6 ± 17.8	0.710
Rim area (mm^2)	0.87 ± 0.31	1.29 ± 0.11	< 0.001	0.84 ± 0.28	0.94 ± 0.38	0.494
Disc area (mm^2)	1.85 ± 0.45	2.06 ± 0.30	0.120	1.83 ± 0.51	1.91 ± 0.25	0.630
Cup-to-disc ratio	0.68 ± 0.16	0.55 ± 0.13	0.010	0.68 ± 0.16	0.67 ± 0.17	0.940
Cup volume (mm^3)	0.472 ± 0.400	0.219 ± 0.128	0.001	0.480 ± 0.381	0.450 ± 0.481	0.870
Mean deviation (dB)	-10.92 ± 9.44	-2.42 ± 1.69	< 0.001	-11.29 ± 10.36	-9.63 ± 5.57	0.640
Pattern standard deviation (dB)	4.67 ± 3.20	1.67 ± 0.38	< 0.001	4.33 ± 2.96	5.89 ± 3.98	0.347
Visual field index (%)	76.7 ± 28.1	98.6 ± 1.3	0.002	73.8 ± 31.3	85.3 ± 13.5	0.270

[a]If the Bonferroni correction was applied for multiple comparisons, the *P*-value was required to be less than 0.003 to achieve statistical significance

[b]Four patients were treated at other hospitals and visited our hospital at the age of 6, 6, 12, 13, respectively

VF defects—eight (32%) eyes had general depression, two (8.0%) eyes had nasal step scotoma, eight (32%) eyes had a single arcuate defect, and seven (28%) eyes had double arcuate scotoma. Of the affected eyes, nine (31.0%) eyes met the criteria of early glaucoma, seven (24.1%) eyes had moderate glaucoma, and 13 (44.8%) eyes had severe glaucoma [18]. None of the fellow eyes of the unilateral PCG patients developed visual impairment or a glaucomatous VF defect.

Structural and functional progression

Among the affected eyes, the average RNFL change rate was − 0.83 ± 1.45 μm/year and the median of the MD rate was 0.16 (− 1.19 to 1.07) dB/year. Two (6.9%) eyes from one patient met the criteria of fast progressor. With event-based analysis, eight (27.6%) PCG eyes showed progression by the GPA of OCT and four (13.8%) PCG eyes showed progression in the change analysis of the VF tests. Univariate logistic regression analysis using the GEE model showed that higher average IOP ($P = 0.016$) and inter-visit IOP fluctuation ($P = 0.048$) were associated with structural progression identified by OCT. Higher average IOP ($P = 0.001$) was associated with functional progression identified by VF tests. (Table 3). Multivariable regression analysis using the GEE model showed that higher inter-visit IOP fluctuation ($P = 0.031$, OR = 2.59 (1.27–8.48)) remained associated with OCT progression, while higher average IOP ($P = 0.046$, OR = 1.79 (1.01–3.16)) remained associated with VF progression. Among the fellow eyes, the average RNFL change rate was − 0.32 ± 0.43 μm/year and the median of the MD rate was 0.15 (0.01 to 0.31) dB/year. None of them had progression by the GPA of OCT or the MD slope.

Factors associated with visual outcomes

Univariable linear regression analysis using GEE model showed that final MD was negatively associated with baseline LogMAR visual acuity ($P = 0.028$), corneal diameter ($P = 0.041$), axial length ($P = 0.005$), cup volume ($P = 0.007$), and cup-to-disc ratio ($P < 0.001$) and positively associated with RNFL thickness ($P < 0.001$), baseline MD ($P < 0.001$), and rim area ($P < 0.001$) (Table 4). Multivariable linear regression analysis showed that poor baseline LogMAR visual acuity ($P = 0.027$,

Table 2 Clinical characteristics of at baseline and at last follow-up

	Affected eyes			Fellow eyes		
	Baseline	Last follow-up	*P*-value[a]	Baseline	Last follow-up	*P*-value[a]
Intraocular pressure (mmHg)	30.4 ± 16.7	17.2 ± 7.3	< 0.001	15.7 ± 3.5	17.2 ± 2.8	0.120
LogMAR visual acuity	0.15 (0–1.90)	0.40 (0–2.30)	< 0.001	0 (0–0.10)	0.02 (0–0.10)	0.400
Corneal endothelial cell density (cells/mm^2)	1434.5 ± 696.2	1467.9 ± 674.1	0.710	2844.0 ± 536.1	3011.0 ± 558.7	0.160
Spherical equivalent (D)	− 6.46 ± 5.88	− 7.96 ± 6.56	0.004	− 0.86 ± 2.37	− 2.45 ± 2.82	< 0.001
Average corneal curvature (D)	41.51 ± 2.80	41.52 ± 2.45	0.970	42.69 ± 1.69	42.57 ± 1.47	0.420
Anterior chamber depth (mm)	3.95 ± 0.40	4.07 ± 0.36	0.210	3.25 ± 0.39	3.46 ± 0.36	0.003
Lens thickness (mm)	3.61 ± 0.33	3.65 ± 0.28	0.520	3.98 ± 0.42	3.83 ± 0.44	0.130
Axial length (mm)	24.64 ± 2.64	27.95 ± 2.85	< 0.001	21.98 ± 2.01	25.59 ± 1.90	0.003
Central corneal thickness (μm)	556.4 ± 69.7	558.5 ± 64.3	0.730	570.3 ± 30.2	566.0 ± 47.7	0.860
Average RNFL thickness (μm)	71.6 ± 15.6	63.1 ± 15.0	0.001	100.0 ± 12.9	95.3 ± 13.9	0.058
Superior quadrant RNFL thickness (μm)	81.0 ± 26.3	68.7 ± 22.8	0.005	128.9 ± 19.7	121.9 ± 24.8	0.076
Temporal quadrant RNFL thickness (μm)	61.8 ± 18.6	55.7 ± 14.7	0.006	82.0 ± 20.2	86.9 ± 28.4	0.420
Inferior quadrant RNFL thickness (μm)	84.8 ± 26.2	67.8 ± 21.3	0.005	122.3 ± 12.5	109.9 ± 10.9	< 0.001
Nasal quadrant RNFL thickness (μm)	61.6 ± 11.6	59.8 ± 17.3	0.803	65.7 ± 6.6	63.1 ± 6.4	0.280
Rim area (mm^2)	0.87 ± 0.31	0.87 ± 0.38	0.880	1.29 ± 0.11	1.37 ± 0.23	0.230
Disc area (mm^2)	1.85 ± 0.45	1.82 ± 0.40	0.690	2.06 ± 0.30	1.96 ± 0.25	0.015
Cup-to-disc ratio	0.68 ± 0.16	0.67 ± 0.18	0.840	0.55 ± 0.13	0.48 ± 0.12	0.040
Cup volume (mm^3)	0.427 ± 0.400	0.463 ± 0.434	0.850	0.219 ± 0.128	0.149 ± 0.107	0.017
Mean deviation (dB)	− 10.92 ± 9.44	− 12.49 ± 10.25	0.150	− 2.42 ± 1.69	− 1.83 ± 1.03	0.200
Pattern standard deviation (dB)	4.67 ± 3.20	4.49 ± 4.05	0.540	1.67 ± 0.38	1.47 ± 0.21	0.073
Visual field index (%)	76.7 ± 28.1	78.2 ± 26.2	0.730	98.6 ± 1.3	98.9 ± 0.7	0.390

[a]If the Bonferroni correction was applied for multiple comparisons, the *P*-value was required to be less than 0.003 to achieve statistical significance

RNFL, retinal nerve fiber layer

beta-coefficient = − 7.08), worse MD ($P < 0.001$, beta-coefficient = 0.71), and smaller rim area ($P < 0.001$, beta-coefficient = 20.97) predicted worse final MD (Table 5).

Univariable linear regression analysis showed that final LogMAR visual acuity was positively associated with the number of surgeries ($P = 0.020$), baseline LogMAR visual acuity ($P < 0.001$), axial length ($P = 0.016$), cup volume ($P < 0.001$), and cup-to-disc ratio ($P < 0.001$) and negatively associated with baseline RNFL thickness ($P = 0.012$), MD ($P = 0.002$), and rim area ($P < 0.001$) (Table 4). Multivariable linear regression analysis showed that worse baseline visual acuity ($P = 0.003$, beta-coefficient = 0.80), smaller rim area ($P = 0.027$, beta-coefficient = − 1.78), and more surgeries ($P = 0.046$, beta-coefficient = 0.13) predicted worse final visual acuity (Table 5).

Discussion

Different types of pediatric glaucoma may have distinct clinical characteristics and outcomes [8]. The current study focused on PCG patients, who had better outcomes than patients with other childhood glaucoma types [12, 19, 20]. We demonstrated the clinical characteristics and the long-term structural and functional progression of these patients. Twenty-eight percent of eyes had structural progression detected by OCT, while 14% of eyes had functional progression detected by VF tests. Higher average IOP during follow-up could predict VF progression, while higher inter-visit IOP fluctuation was associated with OCT progression. The fellow eyes of unilateral PCG patients were not at risk of developing glaucoma. At the last follow-up, although only 20% of patients met the criteria of severe visual impairment, about half of the patients met the severe glaucoma criteria, which impaired the quality of their visual function. Baseline visual acuity, MD of the VF test, and neuroretinal rim area predicted the final functional status.

In the literature, unilateral cases accounted for about 30% of PCG cases [10]. It is unclear if the laterality of the PCG affects the visual outcome [5, 8, 10, 19, 20]. Srinivasan et al. reported that the unilateral cases had thinner optic nerve head and ganglion cell complex parameters than bilateral cases [10]. The delayed diagnosis of unilateral cases and the more profound amblyopia may contribute to the worse visual prognosis [8, 21]. However, our data showed that there was no difference in most of the clinical characteristics, such as ocular biometry, corneal profile, optic nerve

Table 3 Logistic regression analysis using generalized estimating equation for factors associated structural and functional progression

	Structural progression		Functional progression	
	Odds ratio (95% CI)	*P*-value[a]	Odds ratio (95% CI)	*P*-value[a]
Gender	1.23 (0.19 ~ 8.10)	0.832	0.62 (0.04 ~ 9.08)	0.726
Age	0.64 (0.37 ~ 1.09)	0.101	0.41 (0.15 ~ 1.13)	0.084
Laterality[b]	0.75 (0.11 ~ 5.21)	0.772	Not available[d]	
Intraocular pressure[c]	0.99 (0.94 ~ 1.05)	0.900	1.01 (0.89 ~ 1.36)	0.427
Average intraocular pressure	1.12 (1.02 ~ 1.23)	0.016	1.33 (1.12 ~ 1.58)	0.001
Unstable IOP	1.83 (0.32 ~ 10.50)	0.501	Not available[d]	
IOP fluctuation during follow-up	1.77 (1.01 ~ 3.11)	0.048	8.55 (0.91 ~ 80.3)	0.060
Number of surgeries	0.47 (0.22 ~ 1.03)	0.060	0.48 (0.19 ~ 1.18)	0.109
Number of anti-glaucoma medication	0.57 (0.24 ~ 1.32)	0.187	0.61 (0.18 ~ 2.12)	0.439
Corneal endothelial cell density[c]	1.01 (1.00 ~ 1.02)	0.052	1.01 (1.00 ~ 1.02)	0.440
LogMAR visual acuity[c]	0.29 (0.05 ~ 1.90)	0.196	0.02 (0.01 ~ 10.5)	0.174
Corneal diameter[c]	0.36 (0.08 ~ 1.05)	0.099	0.61 (0.16 ~ 2.02)	0.420
Axial length [c]	0.86 (0.60 ~ 1.19)	0.380	0.99 (0.63 ~ 1.51)	0.950
Retinal nerve fiber layer thickness [c]	1.05 (0.99 ~ 1.14)	0.150	0.99 (0.92 ~ 1.08)	0.900
Mean deviation [c]	1.15 (1.01 ~ 1.43)	0.110	1.10 (0.95 ~ 1.45)	0.340
Rim area [c]	0.82 (0.05 ~ 14.70)	0.890	0.08 (0.01 ~ 2.79)	0.180
Disc area [c]	0.22 (0.01 ~ 1.98)	0.240	0.32 (0.01 ~ 3.48)	0.400
Cup volume [c]	1.30 (0.13 ~ 10.74)	0.810	7.65 (0.62 ~ 127.96)	0.120
Cup-to-disc ratio [c]	0.30 (0.01 ~ 7.73)	0.660	17.10 (0.01 ~ 94,432)	0.460

[a]If the Bonferroni correction was applied for multiple comparisons, the *P*-value was required to be less than 0.003 to achieve statistical significance

[b]Reference: unilateral case

[c]Measured at baseline

[d]Number of events is too small to perform logistic regression analysis

head parameters of OCT, and VF test results between the bilateral and unilateral cases. The laterality of the disease also did not predispose to functional or structural progression and did not affect the visual outcomes. Worth to be noted, bilateral PCG eyes had higher inter-visit IOP fluctuation. On the other hand, the fellow eyes of unilateral cases were reported to have higher IOP and larger cup-to-disc ratio than healthy subjects' eyes [1]. In the present study, the fellow eyes had a better structural and functional status than the PCG eyes. During follow-up, none of the fellow eyes met the criteria of glaucoma or had a functional and structural decline. The average RNFL change rate (− 0.32 μm/year) was comparable to age-related RNFL thinning (− 0.2 to − 0.5 μm/year). The RNFL thinning in these eyes could also be attributed to significant axial length elongation (from 21.98 to 25.59 mm) [22]. However, the RNFL thickness at the inferior quadrant decreased significantly, which might be an early sign of glaucoma.

In very young patients, it was almost impossible to measure the optotype visual acuity upon diagnosis. The present study compared the first best available visual acuity to that at the final visit and found significant deterioration. Similarly, previous studies, especially in studies with longer follow-up, have found that the visual acuity may decline over time [5, 8]. However, nearly 60% of our patients still maintained good visual outcome at the last follow-up, in line with the results in the literatures (41–79%) [4–6, 20]. Several studies reported the presence of VF abnormalities ranging from 27 to 83% in PCG patients, with arcuate defect being the most common [9, 23]. The present study showed that approximately half of patients suffered from VF loss meeting the severe glaucoma criteria at the final visit. Therefore, preservation of visual acuity did not directly translate into a good functional status overall. In previous studies, female sex, large cup-to-disc ratio, repeated surgeries, higher baseline IOP, and disease onset < 1 month were associated with a greater VF loss [9, 23]. The current study analyzed the association between OCT parameters and visual outcome in PCG patients, which have not previously been studied. We found that baseline rim area and visual acuity could predict both the final visual acuity and MD.

In most of the adulthood glaucoma patients, the disease status was monitored by OCT and VF tests. However, owing to the young age of the PCG patients and the disease's rarity, only a few studies have reported the relevant data [10, 11, 24]. In previous studies, OCT provided reproducible data; the data showed that the optic nerve head and ganglion cell parameters of PCG eyes were worse than those of normal

Table 4 Univariable regression analysis using generalized estimating equations for factors associated with visual outcomes

	Final mean deviation of visual field test		Final LogMAR visual acuity	
	β coefficient (95% CI)	*P*-value[a]	β coefficient	*P*-value[a]
Gender	−0.51 (−8.57 ~ 7.55)	0.901	−0.11 (−0.74 ~ 0.51)	0.720
Age of first visit	0.57 (−0.18 ~ 1.32)	0.240	−0.03 (−0.08 ~ 0.02)	0.300
Laterality [b]	−5.97 (−11.30 ~ −0.63)	0.055	−0.33 (−1.04 ~ 0.22)	0.309
Baseline Intraocular pressure [c]	−0.21 (−0.44 ~ 0.03)	0.099	−0.01 (−0.02 ~ 0.01)	0.776
Average IOP during follow-up	−0.06 (−0.64 ~ 0.51)	0.838	−0.02 (−0.05 ~ 0.02)	0.410
Unstable IOP	−2.34 (−10.50 ~ 5.79)	0.578	−0.01 (−0.52 ~ 0.50)	0.976
Inter-visit IOP fluctuation	−1.17 (−2.88 ~ 0.53)	0.190	0.01 (−0.08 ~ 0.15)	0.600
Number of surgeries	−2.11(−5.11 ~ 0.90)	0.170	0.22 (0.05 ~ 0.36)	0.020
Number of anti-glaucoma medication	−1.90 (−6.33 ~ 2.53)	0.401	0.03 (−0.29 ~ 0.39)	0.835
Corneal endothelial cell density [c]	0.002 (−0.005 ~ 0.008)	0.612	−0.0002 (−0.0006 ~ 0.0001)	0.241
LogMAR visual acuity [c]	−9.51 (−18.10 ~ −0.89)	0.028	1.14 (0.97 ~ 1.35)	< 0.001
Corneal diameter [c]	−4.54 (−8.58 ~ −0.50)	0.041	0.26 (−0.01 ~ 0.53)	0.075
Axial length [c]	−2.03 (−3.33 ~ −0.74)	0.005	0.12 (0.03 ~ 0.21)	0.016
RNFL thickness [c]	0.48 (0.27 ~ 0.68)	< 0.001	−0.02 (−0.04 ~ 0.01)	0.012
Mean deviation [c]	0.89 (0.75 ~ 0.99)	< 0.001	−0.04 (−0.06 ~ −0.02)	0.002
Rim area [c]	26.29 (17.20 ~ 34.90)	< 0.001	−1.49 (−2.07 ~ −1.03)	< 0.001
Disc area [c]	−3.56 (−12.20 ~ 5.05)	0.430	0.47 (−0.05 ~ 0.99)	0.094
Cup volume [c]	−14.40 (−23.90 ~ −4.89)	0.007	1.01 (0.54 ~ 1.49)	< 0.001
Cup-to-disc ratio [c]	−39.44 (−59.40 ~ −19.40)	< 0.001	2.55 (1.35 ~ 3.76)	< 0.001

[a]If the Bonferroni correction was applied for multiple comparisons, the *P*-value was required to be less than 0.003 to achieve statistical significance

[b]Reference group: unilateral primary congenital glaucoma

[c]Measured at baseline

IOP, intraocular pressure; *RNFL*, retinal nerve fiber layer

eyes [10, 11, 24]. Our data showed that the PCG eyes had worse optic nerve head parameters on OCT compared to fellow eyes of unilateral PCG. Although OCT examinations could not be performed upon diagnosis, we demonstrated a 7.2 ± 2.0 years of OCT follow-up data after the reliable examinations could be obtained. Despite having the similar average IOP value during follow up, the PCG eyes had thinner final RNFL (63.1 ± 15.0 μm) compared to the fellow eye of unilateral PCG patients (95.3 ± 13.9 μm). This finding could be attributed to the higher inter-visit IOP fluctuation and the damage caused by highly elevated initial IOP. The RNFL thickness decreased significantly and the average

Table 5 Multivariable regression analysis using generalized estimating equations for factors associated with visual out

	Final mean deviation of visual field test			Final LogMAR visual acuity	
	β coefficient	*P*-value		β coefficient	*P*-value
LogMAR visual acuity[a]	−7.08 (−13.70 ~ −1.52)	**0.027**	LogMAR visual acuity[a]	0.80 (0.43 ~ 1.16)	**0.003**
Cornea diameter[a]	−2.42 (−4.07 ~ 0.64)	0.337	Cornea diameter[a]	−0.08 (−0.24 ~ 0.09)	0.395
Axial length[a]	0.77 (−0.98 ~ 2.52)	0.421	Axial length[a]	−0.01 (−0.06 ~ 0.06)	0.929
RNFL thickness[a]	−0.10 (−0.49 ~ 0.29)	0.626	RNFL thickness[a]	0.01 (−0.01 ~ 0.02)	0.488
Mean deviation[a]	0.71 (0.36 ~ 1.01)	**< 0.001**	Mean deviation[a]	−0.01 (−0.03 ~ 0.01)	0.378
Rim area[a]	20.97 (10.70 ~ 30.70)	**< 0.001**	Rim area[a]	−1.78 (−3.08 ~ −0.49)	**0.027**
Cup volume[a]	−0.96 (−17.10 ~ 15.10)	0.911	Cup volume[a]	−0.57 (−1.31 ~ 0.17)	0.169
Cup-to-disc ratio[a]	−16.51 (−56.30 ~ 23.30)	0.477	Cup-to-disc ratio[a]	−1.01 (−2.80 ~ 0.79)	0.303
Intraocular pressure[a]	0.04 (−0.27 ~ 0.34)	0.821	Number of surgeries[a]	0.13 (0.02 ~ 0.23)	**0.046**
Laterality	−0.34 (−13.8 ~ 13.1)	0.962	Disc area[a]	1.09 (0.14 ~ 2.05)	0.075

Statistically significant values are already indicated in bold

[a]Measured at baseline

RNFL, retinal nerve fiber layer

RNFL change rate (−0.83 μm/year) was worse than the age-related thinning (−0.2 to −0.5 μm/year) [25, 26], and was comparable to that of open-angle glaucoma patients (−0.7 to −1.0 μm/year) [27, 28]. More than one-quarter of our patients had progression identified by the GPA of OCT. Most of the previous studies defined progression by conventional outcome measurements, such as elevated IOP ≥ 21 mmHg or an increase of 0.2 in cup-to-disc ratio [2, 4, 6, 7]; however, in our cases, among the eight patients with progression on OCT, only one of them would meet the above criteria. The application of OCT could help to detect the glaucoma progression earlier and more precisely. In the longitudinal observation of the VF change, the MD slope (0.16 dB/year) was slightly better than that of the adult glaucoma patients (0 to −1.1 dB/year) [29]. It may be explained by the fact that younger patients had a larger neuronal reserve [30]. Similar to adulthood glaucoma, higher inter-visit IOP fluctuation and average IOP were identified as risk factors of disease progression in PCG patients [14, 31]. Because only one of the patients with disease progression had an average IOP ≥ 21 mmHg and possible functional decompensation at an older age, more aggressive IOP control and frequent follow-up are warranted. Since PCG is essentially a surgical disease, around half of the affected PCG eyes in our cohort were free of antiglaucoma medication postoperatively, which was comparable to the literature [5, 12, 32, 33]. Therefore, there was still a room for medication adjustment for tighter IOP control.

Normal cornea only loses 0.6% of the central endothelial cell density annually [34]. However, corneal endothelial cell density could substantially decrease in PCG eyes due to several reasons, including elevated IOP, damage from intraocular surgeries, toxicity of antiglaucoma medications, enlarged and stretched cornea tissue, and the presence of Haab's striae [34–36]. Good IOP control may halt the progressive endothelial cell loss. In our cohort, although the baseline corneal endothelial cell density was lower than that in the normal population [34], the density remained stationary during the long-term follow-up.

This study had several limitations. Since we aimed to present the long-term follow-up data of OCT and VF tests, we had to exclude patients with limited test results. Besides, many cases involved very young patients, visual acuity measurement, OCT, and VF tests could not be performed. Therefore, the cases enrolled in the present study were limited. Moreover, patients with very poor visual acuity at baseline could not cooperate with VF tests; hence, our data presented the long-term outcomes of patients with relatively good baseline visual acuity. Due to its retrospective nature, the age of the first available OCT or VF test result and the follow-up interval were inconsistent among patients. Some patients received the examination later in the clinical course, which might have missed the possible progression that occurred at an earlier time point. However, the follow-up duration of both examinations was up to 7 years and could still provide valuable information about long-term functional and structural outcomes. Because we would like to find the factors associated with outcome and the change of clinical characteristics during follow-up, we analyzed many parameters from OCT, VF, and ocular biometry. However, multiple comparisons had the risk of increasing type I error; therefore, we listed the adjusted *P*-value with Bonferroni correction in the tables with multiple comparisons for the reader's interpretation. We still discussed based on the results without Bonferroni correction since the results with Bonferroni correction were conservative and may increase the type II error [37].

In conclusion, this study highlighted the long-term results of OCT and VF tests in PCG patients and their fellow eyes. PCG patients had structural and functional decline comparable to adulthood glaucoma patients, while their fellow eyes remained free of glaucomatous damage. Higher IOP during follow-up and more significant inter-visit IOP fluctuation were associated with disease progression. Despite the preservation of visual acuity, most of the patients had significant VF defects. Larger neuroretinal rim area and better baseline visual acuity could predict better final visual acuity and the MD of the VF. The application of OCT and VF tests as early as the patient could cooperate can help to detect disease progression timely and predict the visual outcome. Considering the thinner RNFL at baseline caused by the highly elevated initial IOP and longer life expectancy in these young patients, diligent long-term follow-up and more aggressive control of IOP value and inter-visit fluctuation were suggested.

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Data availability Data is available upon reasonable request.

Code availability Not applicable.

Declarations

Ethical approval This study was approved by the Institutional Review Board of National Taiwan University Hospital and adhered to the tenets of the Declaration of Helsinki.

Consent to participate Informed consent was waived by the Institutional Review Board of National Taiwan University Hospital due to its retrospective nature

Consent for publication Not applicable

Conflict of interest The authors declare no competing interests.

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