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Bilateral asymmetry improved accuracy when assessing glaucomatous vision-related quality of life impairment

Li Yang, MD[a,b,c], Xin Tang, MD, PhD[a,b,c,*]

Abstract

Bilateral asymmetry has been used in optical coherence tomography tests to find early damage to the optic nerve. However, limited studies have quantitatively evaluated bilateral asymmetry in electrophysiological disorders in patients with glaucoma. The aim of the study was to evaluate bilateral asymmetry in pattern visual evoked potentials (PVEPs) and conventional clinical markers as well as its potential use in detecting glaucomatous impairment. After investigating 60 glaucomatous patients (120 eyes) and 65 age and sex-matched normal control subjects (130 eyes) using uni- and multivariable analysis, we found that vision-related quality of life (VRQOL) impairment was significantly associated with larger bilateral asymmetry index (BAI) of clinical markers. Rasch-calibrated National Eye Institute Visual Function Questionnaire-25 scores were significantly associated with the BAI in PVEPs latency in 15 minutes check size ($\beta = -0.478$, 95% confidence interval [CI], -0.708 to -0.248, $P < .001$) and the BAI in visual field mean deviation ($\beta = -0.249$, 95% CI, -0.454 to -0.044, $P = .018$) according to multivariable analysis. Bilateral asymmetry in objective and subjective functional measurements was quantitatively associated with glaucomatous VRQOL impairment. This finding may help bridge the gap in understanding between patients and clinicians, and increase awareness of how glaucomatous neuropathic progression may interfere with patients' daily life.

Abbreviations: BAI = bilateral asymmetry index, BE = better eye, CACG = chronic angle-closure glaucoma, CI = confidence interval, CS = contrast sensitivity, logMAR = logarithm of the minimum angle of resolution, MD = mean deviation, NEI VFQ = National Eye Institute Visual Function Questionnaire, POCG = primary open-angle glaucoma, PVEPs = pattern visual evoked potentials, SD = standard deviation, SPSS = Statistical Package for the Social Sciences, VRQOL = vision-related quality of life, WE = worse eye.

Keywords: glaucoma, multivariable model, pattern visual evoked potentials, Rasch analysis, vision-related quality of life, visual field

1. Introduction

Glaucoma is the second leading cause of blindness, and the disease progression has been widely studied.[1] The disease progression has been reported to be reversible to some extent when diagnosed at the early stage.[2,3] An increasing number of studies have suggested that bilateral asymmetry (eg, interocular

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difference) might be well recognized as an early diagnostic sign and risk factor of glaucomatous damage.[4–6] To precisely assess asymmetric glaucomatous lesions, many studies have reported the use of a series of clinical markers in functional[7–11] and structural assessments.[4] A high frequency of asymmetric visual field defects at the early stage of glaucoma has been revealed in previous studies.[7,8] Furthermore, a large population-based survey found a correlation between higher structural asymmetry and glaucoma prevalence.[12] Recently, bilateral asymmetry in retinal anatomic features detected at the early stage of glaucoma has attracted attention.[4] However, visual field damage may not be detected until a large number of retinal ganglion cells have been lost,[13] and the retinal structural changes, to a large extent, have been reported to be permanently irreversible.[14]

Previous studies suggested that electrophysiology technology can detect glaucomatous disorders in subclinical stages.[15,16] Electrophysiology disorders have been reported to occur approximately 4 years before the initial loss of visual field[17] and 8 years before the initial changes of retinal anatomic features.[14] The pattern visual evoked potential (PVEP) technique, an objective and noninvasive method, offers an opportunity to quantitatively measure neurophysiological damage to the entire visual pathway.[18] Few studies have evaluated the potential presence of bilateral asymmetry in PVEPs. We hypothesized that bilateral asymmetry can be detected in PVEPs in patients with glaucoma and that larger bilateral asymmetries may affect vision-related ability of these patients.

Thus, in the present study, we sought to:

(1) investigate bilateral asymmetry in PVEPs and conventional clinical markers in a cohort of glaucoma patients and

(2) assess the association between clinical measurement parameters (especially bilateral asymmetry parameters) and the vision-related quality of life (VRQOL) in this cohort.

2. Methods

This study was a cross-sectional cohort study. The study was approved by the Ethics Committee of Tianjin Eye Hospital (Registration Number TJYYLL-2016-20). All procedures in this study were performed in accordance with the ethical standards of the Helsinki Declaration. Written informed consent was obtained from all the enrolled participants after the motivation and possible consequences of the study were explained.

This study recruited primary open-angle glaucoma (POAG) and chronic angle-closure glaucoma (CACG) patients from clinics in the Tianjin Eye Hospital, a large university-associated teaching hospital that serves patients from a large area. Details of the study design and data collection process have been described previously.[19] Subjects underwent comprehensive ophthalmic examinations, including slit-lamp biomicroscopy, intraocular pressure testing using Goldmann applanation tonometry, fundoscopy testing using a handheld direct ophthalmoscope, best-corrected visual acuity testing, best-corrected contrast sensitivity (CS) testing, visual field testing and PVEP testing. A series of clinical information, including age, sex, history of ocular conditions, and medical history were obtained from participants and analyzed as potentially confounding factors in this article. The inclusion criteria were as follows: subjects with intraocular pressure of ≤18 mm Hg and subjects with spherical refraction of ≤±5.0 diopter and cylinder correction of <2.0 diopter. The exclusion criteria were as follows: subjects with a nonglaucomatous condition that might influence visual function, such as visually-significant cataracts (Lens Opacities Classification System III[20] greater than Grade 2); patients with a non-glaucomatous neuro-ophthalmic condition that affects quality of life and/or PVEP results; and patients who received incisional eye surgery within the last 6 months or laser therapy in 1 month.

Control group subjects were enrolled from health checkup person who came to our hospital and the subjects had a best-corrected visual acuity of 0.10 (logarithm of the minimum angle of resolution [logMAR] VA) or better. Control subjects underwent slit-lamp biomicroscopy, intraocular pressure, fundoscopy examination, best-corrected visual acuity, and PVEP testing. The inclusion criteria were as follows: subjects with intraocular pressure of ≤21 mm Hg and subjects with spherical refraction of ≤±5.0 diopter and cylinder correction of <2.0 diopter. The exclusion criteria were as follows: subjects with any glaucomatous or a nonglaucomatous condition that might influence visual function; subjects with a neuro-ophthalmic condition that affects quality of life and/or PVEPs results; and patients who received incisional eye surgery within the last 6 months or laser therapy in 1 month.

2.1. Subjective clinical measurement

Monocular best-corrected visual acuity was measured using a logMAR early treatment diabetic retinopathy chart in a quiet, dim room (mean luminance of $85 \, cd/m^2$) at a distance of 4 m. CS was tested in the same room using CSV-1000E charts (Vector Vision, Haag-Streit, Harlow, UK) at a distance of 4 m. A single quantity, the area under the log CS function, was calculated to characterize the overall CS function.[21] Visual field defects were

tested using the Humphrey 24-2 Swedish Interactive Threshold Algorithm standard perimeter (Carl Zeiss Meditec, Dublin, CA). The definitions of better eye (BE) and worse eye (WE) have been described (see Table, Supplemental Digital Content 1 [Table 1, http://links.lww.com/MD/D344], which illustrates the definition of the BE and the WE).

The severity of glaucoma in the study cohort was classified on the basis of mean deviation (MD) in the WE visual field as mild (−2.00 to −10.00 dB), moderate (−10.01 to −20.00 dB), or severe (<−20.00 dB).[22]

2.2. PVEP measurement

PVEPs were recorded using the Roland-Consult Electrophysiological Test Unit-portable system (Wiesbaden, Germany) based on the International Society for Clinical Electrophysiology of Vision standards.[23] The procedure has been described previously.[19] Gold cup skin electrodes were fixed in the following positions: the active electrode was placed approximately 3 cm above the mid-point of the occipital protuberance, the ground electrode was clipped onto the left earlobe, and the reference electrode was attached to the forehead. The amplitude and latency parameters of P100 were analyzed.

For the patients (n = 17) from whom a measurable response in the PVEPs test could not be obtained, a latency of 150 (ms) and an amplitude of 0 (μV) were assigned so that the results could be computed. Examples of PVEPs reports are shown in Figure 1.

2.3. Bilateral asymmetry index

The bilateral asymmetries of clinical variables were quantitatively evaluated by the bilateral asymmetry index (BAI). To assess relative bilateral asymmetry in the PVEP parameters, the absolute value was used. We calculated the BAI in PVEP parameters for each individual using the following equation:

$$BAI = |(\text{Better eye} - \text{Worse eye})/(\text{Better eye} + \text{Worse eye})|$$

The BAIs in visual acuity, CS and visual field MD, and pattern standard deviation were calculated as the absolute value of the difference between the values of the BE and WE. The formula for BAI is as follows:

$$BAI = |\text{Better eye} - \text{Worse eye}|$$

For an individual with completely symmetrical eyes, the value of BAI is 0. As asymmetry in the parameters between the BE and the WE increases, the BAI increases. The BAI was treated as a continuous variable.

2.4. Rasch analysis of VRQOL

VRQOL were evaluated using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) (see Table, Supplemental Digital Content 2 [Table 2, http://links.lww.com/MD/D345], which demonstrates the item content of the NEI VFQ -25). We recorded the responses of NEI VFQ-25 scored from 1 (worst visual ability) to 5 (best visual ability), with a score of 0 responding to missing data, and some category responses were reversed for Rasch analysis so that all items would be of the same polarity.

Rasch analysis was performed using Winsteps software (Version 3.72.3, J.M. Linacre, Chicago, IL, available at www.winsteps.com) to check the validity and the psychometric
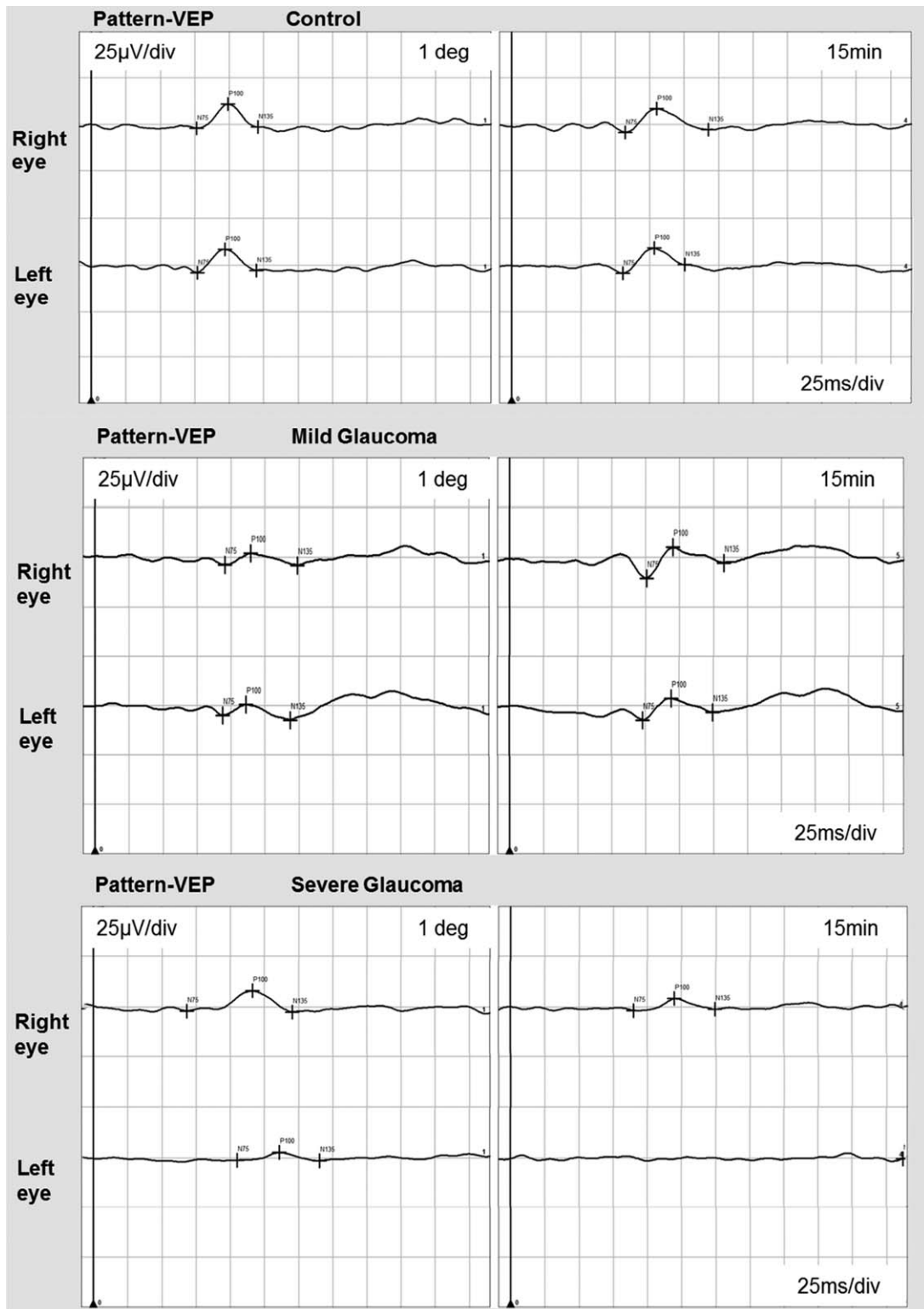
Figure 1. Results of PVEPs from a control participant, a mild glaucoma patient, and a severe glaucoma patient. PVEPs recordings from 3 participants (a control participant [top row], a mild glaucoma patient [middle row] and a severe glaucoma patient [bottom row]). PVEPs = pattern visual evoked potentials, VEP = visual evoked potentials.

properties of the questionnaire and to calculate person measures of each participant (see Text, Supplemental Digital Content 3, http://links.lww.com/MD/D346, which demonstrates the processes of Rasch analysis). The unit of this measure is defined as a logit (log-odds scale), and it enables us to place participants on a linear interval scale according to their visual ability.

2.5. Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 17, Chicago, IL). The characteristics were examined using proportions, means, medians, and standard deviations (SDs). The criterion validity of the Rasch-calibrated VEI VFQ-25 questionnaire was assessed by evaluating person measure scores to distinguish between the 3 subgroups of individuals with different severities. Student t test was used to compare the means in the normally distributed data of continuous variables in both the glaucoma group and the control group. Mann–Whitney U test was conducted to compare the means in the non-normally distributed data of the continuous variables in both the glaucoma group and the control group. Mean measurements of the 2 eyes were compared using Student t test for paired samples. Kruskal–Wallis H test was performed for the comparison of age in the 3 severity subgroups. A Chi-squared test was used to compare sex and glaucoma type in the 3 severity subgroups. After normalizing all the data, we used univariate linear regression models of clinical variables to assess the possible correlations with VRQOL, and then variables with P-values less than .05 were entered in a multivariate analysis. β regression coefficients and 95% confidence intervals (CIs) unadjusted and adjusted for age, sex, duration of glaucoma, and glaucoma type were calculated. All statistical tests were 2-tailed. The statistical significance level was set to be $P < .05$.

3. Results

The cohort consisted of 60 glaucoma patients (120 eyes) and 65 age and sex-matched control group participants (130 eyes). The sociodemographic and clinical characteristics of the participants are shown in Table 1. In the glaucoma group, the mean (SD) age was 61.47 (12.04) years, the median age was 64 years, the mean (SD) duration of glaucoma was 3.23 (1.65) years, and 41.67% of the subjects (25/60) were male. In the control group, the mean (SD) age was 60.54 (10.51) years, and 53.8% (35/65) of the subjects were male.

The Rasch-calibrated NEI VFQ-25 scores displayed good ordered thresholds, infit and outfit statistics (see Table, Supplemental Digital Content 4 [Table 3, http://links.lww.com/MD/D347], which demonstrates the infit and outfit errors of the Rasch-calibrated NEI VFQ), person separation indices; additionally, the scores did not display multidimensionality (see Table, Supplemental Digital Content 5 [Table 4, http://links.lww.com/MD/D348], which demonstrates the dimensionality analysis of NEI VFQ) and differential item functioning. However, targeting was not satisfied. In the meantime, the Rasch-calibrated NEI VFQ-25 scores distinguished between the 3 subgroups of individuals with different severities ($P = .002$) (see Table, Supplemental Digital Content 6 [Table 5, http://links.lww.com/MD/D349], which demonstrates the participant demographics and clinical characteristics in different glaucoma severity). These results indicated that the Rasch-calibrated NEI VFQ-25 showed good criterion validity and psychometric properties. For the control group, we did not perform Rasch analysis due to a high floor effect for all items, and a composite score of the original NEI VFQ-25 questionnaire was calculated to characterize the overall VRQOL (see Text, Supplemental Digital Content 3, http://links.lww.com/MD/D346, which demonstrates the calculation of the NEI VFQ-25 scores).

For the glaucoma group, univariate analysis revealed that worse Rasch-calibrated NEI VFQ-25 person measure scores were significantly associated with the BAI of clinical markers (Table 2). Increases in the BAI of PVEPs latency ($\beta = -0.661$, 95% CI, -0.859 to -0.464, $P < .001$) (see Table 2 and Fig. 2) and amplitude ($\beta = -0.655$, 95% CI, -0.873 to -0.455, $P < .001$) (Table 2) in 15 minutes check size had the highest β coefficient with deterioration in the Rasch-calibrated NEI VFQ-25 scores. Decreases in the Rasch-calibrated NEI VFQ-25 scores also correlated with some of the clinical markers in the worse eye, but the β coefficient was low. Subsequently, variables with P values less than .05 in the univariate analysis were included in a multivariate analysis. As shown in Table 3, larger BAI of PVEPs latency in 15 minutes check size ($\beta = -0.549$, 95% CI, -0.758 to -0.353, $P < .001$) and BAI of MD ($\beta = 0.331$, 95% CI, -0.532 to -0.131, $P = .002$) were linearly associated with decreasing Rasch-calibrated NEI VFQ-25 person measure scores ($F = 30.215$, $P < .001$). After adjusting for age, sex, duration of glaucoma, glaucoma severity, and glaucoma type, the Rasch-calibrated NEI VFQ-25 person measure scores were significantly associated with the BAI of PVEPs latency in 15 minutes check size ($\beta = -0.478$, 95% CI, -0.708 to -0.248, $P < .001$) and the BAI of MD ($\beta = -0.249$, 95% CI, -0.454 to -0.044, $P = .018$). These 2 variables explained 66.6% of the VRQOL person measure scores ($F = 10.927$, $P < .001$). In the meantime, the BAI of PVEPs did not show any correlation with NEI VFQ-25 scores in the control group (see Fig. 3 and Table, Supplemental Digital Content 7 [Table 6, http://links.lww.com/MD/D350], which demonstrates the univariate analysis of clinical variables and NEI VFQ-25 composite score in the control group).

4. Discussion

In this study, we evaluated bilateral asymmetry in a cohort of patients with glaucoma, and its potential ability to detect glaucomatous impairment. Bilateral asymmetry in PVEPs was quantitatively investigated for the first time. The present data suggests that bilateral asymmetry in PVEPs and visual field tests might be valid markers for explanations of VRQOL impairment in glaucoma patients.

It has been suggested that asymmetric structural and functional impairment is recognized as one of the main characteristics of glaucoma in patients[4–6,24] and mouse models.[25] Lee et al[24] documented retinal anatomic asymmetry in glaucoma diagnosis. In 2018, Hou et al[4] found significant interocular asymmetry in the retinal nerve fiber layer in patients with early-stage glaucomatous visual field damage. However, retinal structural changes may be permanent and irreversible,[14] and a large number of retinal ganglion cells have been shown to be lost before detectable visual field damage occurs.[13] It is crucial to detect glaucomatous damage in subclinical stages. Previous studies suggested that electrophysiology disorders can be detected years before the initial loss of visual field[17] and retinal nerve fiber layer thickness.[14] Marcella et al[26] noted that PVEPs tests are sensitive for the early detection of patients at risk of developing glaucoma. If proper screening and/or treatment can be provided at this stage, neurophysiological function can be saved after glaucomatous damage occurs.[2,3] In our study, significant bilateral asymmetry in the PVEPs was shown in the glaucoma group, and most subjects in this group had mild to moderate glaucomatous visual field damage. This result suggests that bilateral asymmetry in the PVEPs can potentially be used to diagnose glaucoma at a relatively early stage.

Table 1

Sociodemographic and clinical characteristics of participants.

Variables	Patients Mean (SD)	Range	Control Mean (SD)	Range	*P*-value
Number of participants	60	–	65	–	–
Age, yr	61.47 (12.04)	27 to 79	60.54 (10.51)	34 to 82	.231[†]
Sex*					.175[†]
Male	25	42%	35	54%	
Female	35	58%	30	46%	
Duration of glaucoma, yr	3.23 (1.65)	2 to 10	–	–	–
Type of glaucoma*					
CACG	42	70%	–	–	–
POCG	18	30%	–	–	–
Visual field					
Better eye MD, dB	−4.47 (5.40)	−28.41 to 1.02	–	–	–
Worse eye MD, dB	−12.63 (9.84)	−30.06 to −2.01	–	–	–
BAI of MD	8.28 (8.62)	0.08 to 25.80			
Better eye PSD, dB	3.10 (2.60)	1.24 to 12.90	–	–	–
Worse eye PSD, dB	5.82 (3.67)	1.27 to 12.46	–	–	–
BAI of PSD	0.34 (0.26)	0.01 to 0.80			
Contrast sensitivity					
Better eye	1.02 (0.28)	0.33 to 1.56	–	–	–
Worse eye	0.85 (0.30)	0.33 to 1.43	–	–	–
BAI	0.30 (0.27)	0.00 to 0.91	–	–	–
Visual acuity (logMAR)	Better eye		Right eye		
	0.16 (0.22)	−0.10 to 0.86	0.03 (0.05)	−0.1 to 0.10	–
	Worse eye		Left eye		
	0.35 (0.32)	−0.10 to 1.50	0.03 (0.05)	−0.1 to 0.10	–
	BAI		BAI		
	0.27 to 0.30	0.00 to 1.40	0.04 (0.05)	0.00 to 0.20	<.001[‡]
PVEP	Better eye		Right eye		
Latency in 1 deg size, ms	108.72 (10.81)	90.4 to 150	102.36 (5.10)	84.5 to 115.70	–
Amplitude in 1 deg size, μV	11.08 (5.04)	0 to 31.90	12.19 (3.90)	5.26 to 25.8	–
Latency in 15 min size, ms	123.07 (13.69)	99.2 to 150	111.56 (5.69)	101 to 126.8	–
Amplitude in 15 min size, μV	13.94 (8.79)	0 to 34.70	15.31 (5.66)	5.88 to 31.6	–
	Worse eye		Left eye		
Latency in 1 deg size, ms	115.6 (16.02)	90.4 to 150	102.84 (5.58)	82.2 to 114.5	–
Amplitude in 1 deg size, μV	8.16 (5.15)	0 to 30	12.27 (4.29)	4.97 to 25.6	–
Latency in 15 min size, ms	130.52 (15.66)	100.4 to 150	112.02 (5.91)	101 to 125.6	–
Amplitude in 15 min size, μV	8.17 (6.82)	0 to 32.60	15.52 (6.11)	4.37 to 35.9	–
	BAI		BAI		
Latency in 1 deg size	0.04 (0.05)	0 to.21	0.01 (0.01)	0 to 0.03	<.001[‡]
Amplitude in 1 deg size	0.25 (0.26)	0.01 to 1.00	0.08 (0.05)	0 to 0.24	<.001[‡]
Latency in 15 min size	0.05 (0.05)	0 to 0.18	0.01 (0.01)	0 to 0.03	<.001[‡]
Amplitude in 15 min size	0.42 (0.37)	0.02 to 1.00	0.10 (0.07)	0 to 0.32	<.001[‡]

Data are mean (standard deviation) unless otherwise indicated.

BAI = bilateral asymmetry index, CACG = chronic angle-closed glaucoma, logMAR = logarithm of the minimum angle of resolution, MD = mean deviation, POCG = primary open-angle glaucoma, PSD = pattern standard deviation, PVEP = pattern visual evoked potentials, SD = standard deviation.

* Date are presented as No. (%).

[†] *P*-value was based on Mann–Whitney *U* test.

[‡] *P*-value was based on Student *t* test.

Moreover, there has been an increasing concern that certain degrees of interocular asymmetry of structure exist in healthy individuals across a wide age range.[10–12,27–32] However, the normal tolerance limits for the amount of asymmetry have not yet been precisely determined. Nevertheless, in the present study, there was no significant bilateral asymmetry in the PVEPs in the control group ($P < .001$), which suggests that bilateral asymmetry in the PVEPs can potentially be used for distinguishing individuals with glaucomatous damage from normal individuals.

In this study, the multivariable analysis revealed that bilateral asymmetry in the PVEPs and visual field tests can be used for detecting glaucomatous visual function loss. A potential explanation for these results might be that a large between-eyes gap can decrease neural summation and result in binocular inhibition. Binocular inhibition is likely related to interocular suppressive mechanisms in cortical layer VI.[33] Thus, these data illustrated that bilateral asymmetry in visual function loss may be risk factors of glaucomatous impairment.

Although POAG and CACG may not share the same pathological progression, our data did not show any difference in the BAI of PVEPs between the POAG and CACG subgroups ($Z = −1.331$, $P = .183$). Huang et al[34] declared that CACG patients had greater interocular asymmetry of visual field defects than did POAG patients. The conflicting results might be due to the relatively small sample size in the POAG group (N = 18); additional studies with a larger POAG sample size are needed. In

Table 2

Univariate analysis of clinical variables and the Rasch-calibrated National Eye Institute Visual Function Questionnaire −25 in the glaucoma group (N = 60).

Variables	Rasch-calibrated NEI VFQ-25		
	β	95% CI	P
BE logMAR VA	−0.233	−0.489 to 0.023	.073
WE logMAR VA	−0.438	−0.675 to −0.202	**<.001**
BAI of logMAR VA	−0.475	−0.706 to −0.244	**<.001**
BE CS	0.074	−0.188 to 0.377	.572
WE CS	0.429	0.192 to 0.667	**.001**
BAI of CS	−0.542	−0.763 to −0.321	**<.001**
BE MD in VF, dB	0.019	−0.244 to 0.282	.884
WE MD in VF, dB	0.448	0.213 to 0.683	**<.001**
BAI of MD	−0.488	−0.717 to −0.258	**<.001**
BE PSD in VF, dB	−0.04	−0.302 to 0.223	.764
WE PSD in VF, dB	−0.409	−0.649 to −0.170	**.001**
BAI of PSD	−0.475	−0.706 to −0.244	**<.001**
BE PVEP L in 1 deg size, ms	0.066	−0.208 to 0.348	.618
BE PVEP A in 1 deg size, μV	0.026	−0.251 to 0.306	.845
BE PVEP L in 15 min size, ms	0.013	−0.265 to 0.292	.923
BE PVEP A in 15 min size, μV	0.046	−0.229 to 0.327	.724
WE PVEP L in 1 deg size, ms	−0.266	−0.550 to −0.013	**.040**
WE PVEP A in 1 deg size, μV	0.244	−0.012 to 0.528	.061
WE PVEP L in 15 min size, ms	−0.439	−0.715 to −0.215	**<.001**
WE PVEP A in 15 min size, μV	0.455	0.223 to 0.721	**<.001**
BAI of PVEP L in 1 deg size	−0.465	−0.698 to −0.233	**<.001**
BAI of PVEP A in 1 deg size	−0.468	−0.707 to −0.235	**<.001**
BAI of PVEP L in 15 min size	−0.661	−0.859 to −0.464	**<.001**
BAI of PVEP A in 15 min size	−0.655	−0.873 to −0.455	**<.001**

Bold items were significant to $P < .05$. Non-bold items were not significant factors on modeling. β (95% CI) statistics were based on normalized data. P-value was based on t test.

A = amplitude, BAI = bilateral asymmetry index, BE = better eye, CS = contrast sensitivity, L = latency, logMAR = logarithm of the minimum angle of resolution, MD = mean deviation, N = number of participants included, NEI VFQ = National Eye Institute Visual Function Questionnaire, PSD = pattern standard deviation, PVEP = pattern visual evoked potentials, VA = visual acuity, VF = visual field, WE = worse eye.
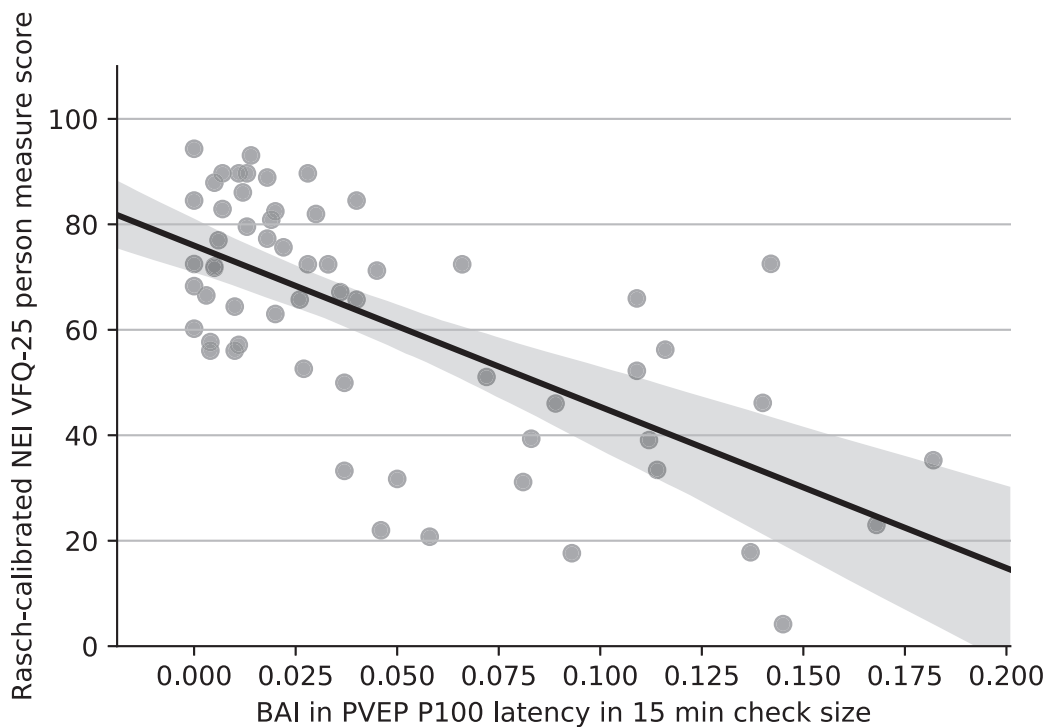

Figure 2. Relationship between Rasch-calibrated NEI VFQ-25 scores and the BAI in PVEPs in patients with glaucoma. Scatter plot of the Rasch-calibrated NEI VFQ-25 person measure scores versus the BAI of PVEPs P100 latency in 15-min check size. The black solid line indicates the linear regression between them ($\beta = -0.661$, 95% confidence interval [CI], −0.859 to −0.464, $P < .001$). The gray shade represents the 95% CI for the slope of linear regression. BAI = bilateral asymmetry index, NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25, PVEPs = pattern visual evoked potentials.

Table 3

Multivariable linear analysis of clinical variables and the Rasch-calibrated National Eye Institute Visual Function Questionnaire-25 in the glaucoma group (N=60).

Variables	Rasch-calibrated NEI VFQ-25				
	β	95% CI	P	F	P
Unadjusted				30.215	**<.001**
BAI PVEP L in 15 min size	−0.549	−0.758 to −0.353	**<.001**		
BAI of MD	−0.331	−0.532 to −0.131	**.002**		
Adjusted*				10.927	**<.001**
BAI PVEP L in 15 min size	−0.478	−0.708 to −0.248	**<.001**		
BAI of MD	−0.249	−0.454 to −0.044	**.018**		

Bold items were significant to $P<.05$. Non-bold items were not significant factors on modeling. F statistics based on normalized data.

A=amplitude, BAI=bilateral asymmetry index, L=latency, MD=mean deviation, N=number of participants included, NEI VFQ=National Eye Institute Visual Function Questionnaire, PVEP=pattern visual evoked potentials.

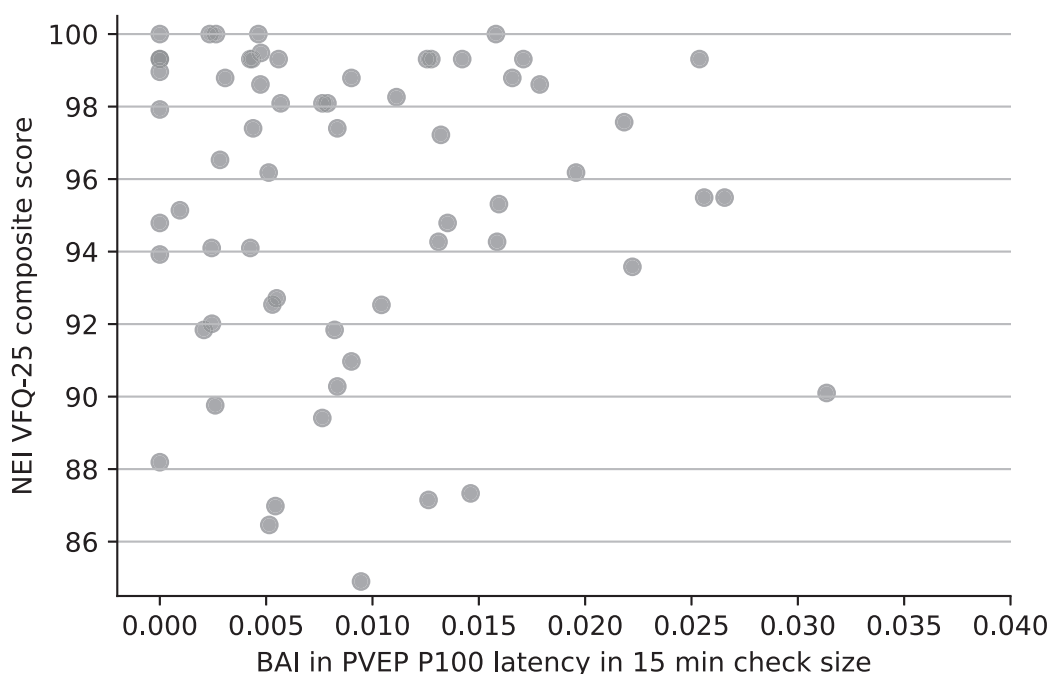* Adjusted for age, gender, duration of glaucoma, and glaucoma type.

Figure 3. Relationship between NEI VFQ-25 composite scores and the BAI in PVEPs in the control group. Scatter plot of the NEI VFQ-25 composite scores versus the BAI in PVEPs P100 latency in 15 min check size in the control group (N=65). The scatter plot shows no significant correlation between them ($\beta = -0.063$, 95% confidence interval, −0.315 to 0.188, $P=.616$). BAI = bilateral asymmetry index, NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25, PVEPs = pattern visual evoked potentials.

addition, since histopathological changes in individuals with glaucoma have always been the focus of researchers,[35] further studies concerning whether interocular asymmetric biological processes occur should be conducted.

There are several limitations of our study. First, we recruited participants from our single-center and this procedure may cause bias in the results. Additional multicenter studies with individuals of multiple ethnicities should be conducted. Second, we did not include a sufficient number of individuals to perform subgroup analysis for different severities of glaucoma, and future studies with a larger sample size are needed. Furthermore, the Rasch-calibrated VRQOL questionnaire did not have satisfactory targeting. However, to maintain the original structure of the Rasch-calibrated questionnaires, we did not change the remaining items. Finally, we need a longitudinal study to further

investigate bilateral asymmetry changes over time in clinical variables.

In this study, bilateral asymmetry in PVEPs was investigated for the first time. The research data suggests that bilateral asymmetry in PVEPs and visual field tests might be valid markers of and explain VRQOL impairment. Bilateral asymmetry in clinical variables can provide both quantitative and qualitative information for glaucoma monitoring. This study may help bridge the gap in understanding between patients and clinicians and increase awareness of how glaucomatous neuropathic progression may interfere with patients' daily life.

Author contributions

Data curation: Li Yang.

Formal analysis: Li Yang.
Funding acquisition: Xin Tang.
Investigation: Li Yang.
Methodology: Li Yang.
Project administration: Xin Tang.
Writing – original draft: Li Yang.
Writing – review and editing: Xin Tang.

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