Early impairment of magnocellular visual pathways mediated by isolated-check visual evoked potentials in primary open-angle glaucoma: a cross-sectional study

Qiaona Ye, Kezheng Xu, Zidong Chen, Zitian Liu, Yanmei Fan, Pingping Liu, Minbin Yu, Yangfan Yang

ABSTRACT

Objective To explore different performances in the magnocellular (MC) and parvocellular (PC) visual pathways in patients with primary open-angle glaucoma (POAG) and to objectively assess impairement in early stage of POAG.

Methods and analysis This is a cross-sectional study. MC and PC visual pathways were assessed using isolated-check visual evoked potential (ic-VEP). Visual acuity, intraocular pressure, fundus examination, optical coherence tomography and visual field were measured. Signal-to-noise ratios (SNRs), mediated by ic-VEP were recorded. The Spearman’s correlation analysis was used to estimate the relationships between visual functions and structures. Receiver-operating-characteristic (ROC) curves were used to estimate the accuracy in detection of early POAG.

Results 60 participants (30 early POAG eyes and 30 age-matched control subjects) were recruited. MC visual pathway showed a non-linear response function, while PC visual pathway was a linear response function as contrast increased. Early POAG eyes exhibited significantly weaker initial contrast gains and lower maximum responses in the MC visual pathway (p=0.001, p=0.004, respectively). The SNRs at 8% and 32% depths of modulation (DOM) were significantly correlated with temporal–fibre layer (RNFL) thickness in early POAG, which helped in understanding the mechanisms of visual impairment in the early stage of POAG.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several lines of evidence from experimental primates indicated the differential impairment of visual pathways in early glaucoma, but the objective and clinical evidence about glaucomatous visual impairment is few.

WHAT THIS STUDY ADDS

⇒ Our work provided electrophysiological evidence for differences in the processing of different contrast information in the early stage of primary open-angle glaucoma (POAG).

⇒ The magnocellular (MC) visual pathway was damaged in the early stage of POAG, which manifested as a decrease in contrast gain and maximum response mediated by isolated-check visual evoked potential.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The signal-to-noise ratios at 8% and 32% depths of modulation of MC-biased stimulation were significantly correlated with temporal–side retinal nerve fibre layer thickness in early POAG, which helped in understanding the mechanisms of visual impairment in the early stage of POAG.

INTRODUCTION

Glaucoma, a group of diseases characterised by optic nerve injury and progressive visual impairment, is regarded as one of the world’s leading causes of irreversible blindness. Standard automated perimetry (SAP) is the gold standard for glaucomatous functional assessment. However, it does not detect early functional damages until significant reductions of the retinal ganglion cells (RGCs). The ganglion cell layer plus inner plexiform layers (GCL+IPLs) analysis and retinal nerve fibre layers (RNFLs) thickness are also used to detect early glaucoma by assessing the structural changes of RGCs and the axions.

Several lines of evidence from experimental primates show that ganglion cells in the glaucomatous eye are less responsive to visual stimuli, both spatially and temporally, which indicated the differential impairment of visual pathways in early glaucoma. It is widely accepted that primate visual cortex...
is divided into two functionally distinct visual pathways. One is magnocellular (MC) pathway, originated from parasol RGCs, and the other is parvocellular (PC) pathway, derived from midget RGCs. The properties of the PC pathway are sensitive to high spatial acuity and red-green colour vision, while those of the MC pathway are important for achromatic visual sensitivity and motion vision. Recent works show that koniocellular (KC) pathway, a third visual pathway, is more complex.

Visual electrophysiology is a non-invasive and objective visual function examination, which can detect and study the functional integrity of the retina and visual cortex. Electroretinograms reflect the functions of photoreceptors and the partial ganglion cells, while visual evoked potentials (VEPs) can detect the electrical responses and interactions projecting from RGCs and their axons to visual cortex, which provide complementary information about early and later processing of information along the retino-geniculo-cortical pathway. Pattern electroretinograms and multifocal visual evoked potentials are able to detect glaucomatous damage but not clinically accepted as routine for glaucoma potentially because they are time-consuming and difficult to perform well.

The isolated-check visual evoked potential (ic-VEP) technique is designed and widely used in several diseases, such as retinitis, schizophrenia, amblyopia, etc., based on known physiological properties of visual neurons. It is flexible to adjust the parameters of the spatial frequency, temporal frequency and contrast, which tend to modulate M-biased or P-biased stimulation. Previous studies used the settled parameters of the machine as a tool for early POAG detection but did not modulate M-biased or P-biased stimulation. At present, early glaucomatous visual impairment is still controversial, and further clinical trials about objective evidence of early dysfunction in glaucoma are needed.

Therefore, our study is to explore and distinguish different performances in the MC and PC visual pathways mediated by ic-VEP in primary open-angle glaucoma (POAG) and assess potential impairment in early stage of POAG (early POAG). What is more, we also aim to investigate the relationships between central visual functions and retinal structures in patients with early POAG and evaluate the diagnostic accuracy of early POAG, which may help to improve the detection.

MATERIALS AND METHODS

Ethical approval

All participants in this study were recruited from the Glaucoma Clinic at Zhongshan Ophthalmic Center, Guangzhou, China. The study adhered to the tenets of Declaration of Helsinki. And informed consent was obtained from every patient.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or the dissemination plans.

Subjects

Sixty participants were enrolled and divided into two groups: healthy control and patients with early stage of POAG.

Ophthalmological examination including assessment of medical and family history, best-corrected visual acuity (BCVA) testing, slit-lamp biomicroscopy of anterior segment and fundus, gonioscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry (GAT) and fundus examination were recorded. VFs were assessed using a Humphrey field analyser (Carl Zeiss Meditec; Model 750; Humphrey Instruments) with a 30-2 Swedish Interactive Testing Algorithm standard program. The RNFL thickness and GCL+IPL thickness were analysed on optical coherence tomography (OCT, software V.6.0, Zeiss, Germany).

The inclusion criteria for all participants consisted of (1) ages between 18 and 80 years old, (2) BCVA of logMAR 0.5 or better, (3) a spherical equivalent refraction between −6.0 diopters (D) and +3.0D, and (4) open angles on gonioscopy. Exclusion criteria include (1) history of ophthalmic surgery (fundus or ocular surface surgery), (2) clinically significant cataract seriously affecting vision, (3) other optic neuropathy or neuropathy involving in the entire visual pathway, (4) secondary glaucoma: ocular trauma, uveitis, etc. (5) Other fundus diseases involving the macula or retina: age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy, etc, and (6) those with psychiatric disorders, pregnant women, the weak, etc.

Healthy controls were characterised by IOP ≤21 mm Hg, normal optic disc appearance and normal RNFL and VF results. Patients with POAG were defined as characteristic glaucomatous optic neuropathy (local narrowing, notching or absence of the neuroretinal rim) with associated RNFL defects on OCT and the corresponding VF defect on SAP. Only results with fixation loss less than 20% and both false-positive rates and false-negative rates less than 15% were included. Mean deviation (MD) ≥−6dB, defined as early stage of POAG on the basis of the modified Hodapp-Anderson Parrish criteria, were eligible for the study. If both eyes were qualified, one eye was chosen randomly. If both eyes demonstrated the same degree of glaucomatous damage, the eye with better visual acuity was evaluated for the study.

ic-VEP examination

Apparatus and stimuli

The two different visual pathways were evoked with Neucodia visual electrophysiological device (Neucodia, CN-V2.4, Huzhou Medconova Medical Technology, Huzhou, China). All stimuli were presented in the centre of a 17-inch organic light-emitting diode screen (PVM-A170; Sony, Tokyo, Japan) with a 1920×1080 resolution. The background luminance was 50 cd/m². Stimuli were isolated dark checks in 16×16 check arrays, subtending a total of 10×10 degrees of visual angle. A 1×1 degree red cross
was presented continuously in the centre of the stimulus for participants to maintain fixation. Luminance of the checks was sinusoidally modulated at 12.5 Hz, above and below the static check luminance (pedestal) in 6 depths of modulation (DOM, 1%, 2%, 4%, 8%, 16% and 32%). As described before, in magnocellular-biased (MC-biased) runs, the pedestal equalled the DOM and created appearing and disappearing stimuli, which preferentially activates the MC pathway. In parvocellular-biased (PC-biased) runs, the pedestal was fixed at 48% Weber contrast, so that stimuli never dropped below 16% contrast, which preferentially activates the parvocellular pathway.25

**Task procedure**

Participants conducted electrical signals through electrodes attached to the scalp, while their heads were on the chin-forehead rest to secure position and fixed at a distance of 55 cm in a relatively closed dark room to measured MC and PC visual functions. Ag-AgCl electrodes were placed at the scalp based on the international 10–20 system,26 the positive electrode was placed at Oz (occipital midline), the negative electrode was placed at Cz (central midline) and the ground electrode was placed at Fz (frontal midline).

**Data analysis**

Signal-to-noise ratios (SNRs), which were defined as the ratio between the averaged amplitude and the estimated noise, were recorded. The SNRs obtained from each eye were averaged for each condition and each DOM and were plotted as a function of DOM. The M-biased response curves, which are non-linear, were fitted using the non-linear Michaelis-Menten equation, whereas the linear P-biased response curves were fitted using a linear equation. Initial contrast gain, which was calculated as the SNR changes from 4% to 16% DOM divided by the DOM change (12%), and the maximal response, which was calculated as the average of SNR at 16% and 32% DOM were fitted using a linear equation. Whereas the linear P-biased response curves were fitted using a non-linear Michaelis-Menten equation, whereas the linear P-biased response curves were fitted using a linear equation.

**Statistical analysis**

Summary statistics of the demographic and clinical characteristics are presented for all eligible study eyes. Descriptive statistics are presented as means and SDs. The t-test or Wilcoxon rank-sum test was used for comparison of continuous data, and the χ² test was used for categoric data. P value ≤0.05 was considered statistically significant. The Spearman’s correlation analysis was used to estimate the relationships between central visual functions and retinal structures parameters. Receiver operating characteristic (ROC) curves were used to estimate the accuracy of diagnosis. Statistical analysis was carried out using a commercially available statistical software package (SPSS for Windows, V.25.0).

**RESULTS**

**Characteristics of the two groups**

Sixty participants (30 early POAG eyes and 30 age-matched control subjects) at Zhongshan Ophthalmic Center were recruited from January 2022 to September 2022. There were both 16 males in healthy control group and early glaucoma group. The mean ages in two groups were 40.3±9.4 and 44.5±15.8 (p=0.283). The MD, average RNFL thickness and average GCL+IPL thickness in patients with early POAG were significantly lower than that in healthy control group (table 1).

<table>
<thead>
<tr>
<th>Table 1 Characteristics of subjects</th>
<th>Control (n=30)</th>
<th>Early POAG (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>40.3 (9.4)</td>
<td>44.5 (15.8 )</td>
<td>0.283</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>16/14</td>
<td>16/14</td>
<td>–</td>
</tr>
<tr>
<td>LogMAR visual acuity (logMAR)</td>
<td>0.04 (0.08)</td>
<td>0.11 (0.14)</td>
<td>0.061</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>14.06 (2.40)</td>
<td>17.7 (4.04)</td>
<td>0.001**</td>
</tr>
<tr>
<td>C/D</td>
<td>0.39 (0.12)</td>
<td>0.66 (0.14)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>SAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD, dB</td>
<td>–0.33 (1.18)</td>
<td>–2.37 (1.80)</td>
<td>0.001**</td>
</tr>
<tr>
<td>PSD, dB</td>
<td>1.59 (0.45)</td>
<td>4.01 (2.63)</td>
<td>0.002**</td>
</tr>
<tr>
<td>VFI, %</td>
<td>99.3 (1.1)</td>
<td>95.6 (5.0)</td>
<td>0.004**</td>
</tr>
<tr>
<td>OCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVG RNFL, μm</td>
<td>99.5 (7.6)</td>
<td>80.9 (10.7)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Superior-RNFL, μm</td>
<td>125.3 (13.0)</td>
<td>96.1 (21.2)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Nasal-RNFL, μm</td>
<td>73.4 (7.2)</td>
<td>63.6 (12.9)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Inferior-RNFL, μm</td>
<td>128.7 (12.8)</td>
<td>96.2 (16.6)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Temporal-RNFL, μm</td>
<td>74.8 (8.0)</td>
<td>63.1 (16.6)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Min GCL+IPL, μm</td>
<td>82.8 (4.0)</td>
<td>68.3 (11.0)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>AVG GCL+IPL, μm</td>
<td>84.9 (4.0)</td>
<td>73.8 (7.9)</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

*p<0.01; p<0.05.

AVG GCL+IPL, average ganglion cell layer plus inner plexiform layers; AVG RNFL, average retinal nerve fibre layer; Inferior-RNFL, average inferior retinal nerve fibre layer; IOP, intraocular pressure; MD, mean deviation; Min GCI+IPL, minimum ganglion cell layer plus inner plexiform layers; Nasal-RNFL, average nasal-side retinal nerve fibre layer; OCT, optical coherence tomography; PSD, pattern standard deviation; SAP, standard automated perimetry; Superior-RNFL, average superior retinal nerve fibre layer; Temporal-RNFL, average temporal-side retinal nerve fibre layer; VFI, visual field index.
Characteristics of the MC and PC visual pathways in two groups

MC visual pathway-induced ic-VEP showed a non-linear response function with a steep initial slope as contrast increases through the low-contrast region and then reach a maximum response platform in both two groups. While PC visual pathway was a linear response function with increased contrast (figure 1A).

MC visual pathway impairment in early stage of POAG group

The SNRs at 8% DOM and 16% DOM were lower in early POAG eyes when compared with the healthy control group. There were significant differences between healthy control group and early POAG eyes at 8% and 16% DOM in MC-biased condition (p=0.025, p<0.001, respectively) (table 2, figure 1 B).

The initial contrast gains were 0.189±0.102 in the control group and 0.112±0.104 in early POAG eyes. And the maximum response were 3.060±1.086 in the control group and 2.216±1.025 in early POAG eyes. Similarly, early POAG eyes exhibited significantly weaker initial contrast gains and lower maximum responses in MC visual pathway compared with the healthy control group (p=0.001, p=0.004, respectively) (table 2, figure 1 C).

PC visual pathway in early stage of POAG group

The initial contrast gains of patients with early POAG showed lower responses in the PC-biased condition compared with the healthy control group, but there were no statistical differences (online supplemental table S1).

Structure-function relationships in early stage of POAG group

MC-biased condition

The correlations between the SNRs of ic-VEP and the parameters of OCT were shown in online supplemental table S2 in the MC-biased condition. There were significant correlations between the SNR at 8% DOM and temporal-side RNFL thickness (p=0.017) (online supplemental table S2) (figure 2 A). And significant correlations were shown between the SNR at 32% DOM and temporal-side RNFL thickness in early stage of the POAG group (p=0.020) (online supplemental table S2) (figure 2 B).

PC-biased condition

The correlations between the SNRs of ic-VEP and the parameters of OCT were not found in our statistics (online supplemental table S3).

Diagnostic accuracy of MC visual pathway parameters for early stage of POAG

ROC curve analysis was used to estimate the accuracy of group classification. Based on sensitivity and specificity, the optimal cut-off SNR at 16% DOM distinguishing early POAG patients from healthy control subjects was 2.07 (yielding a sensitivity of 80.0% and a specificity of 63.3%). And the areas under receiver-operating-characteristic curve (AUC) of 16% DOM was 0.780. The diagnostic accuracies of another two parameters of MC visual pathway, including initial contrast gain and maximum response, were slightly lower than 16% DOM. The AUCs of initial contrast gain and maximum response distinguishing patients with early POAG from healthy control subjects, respectively, were 0.750 (sensitivity 93.3%, specificity 46.7%) with the cut-off SNR of 0.08, 0.720 (sensitivity 80.0%, specificity 56.7%) with the cut-off SNR of 2.18 (figure 3).

DISCUSSION

Glaucoma is characterised by progressive loss of retinal ganglion cells and their axons. Any interruption of the transportation of the electrical pulses, which start from the ganglion cells to the cerebral cortex, can be monitored through the use of VEP. Our work provided electrophysiological evidence for differences in the processing of different contrast information in the early stage of POAG mediated by ic-VEP.

We can see M-biased stimulation showed a non-linear response function with a steep initial slope as contrast increases through the low-contrast region and then reach a maximum response platform. While P-biased stimulation was a linear response function with increase contrast. And this electrophysiological study implied the selective impairment of the visual pathway in early stage of POAG.

Unlike the other diseases, such as anisometropic amblyopia and schizophrenia, showed functional deficits both in MC-biased and PC-biased stimuli. Our work displayed that the contrast sensitivity and contrast gain signature of the inferred MC visual pathway were decreased in patients with early stage of POAG in agreement with previous studies. Patients with early stage of POAG exhibited weaker initial contrast gains in MC visual pathway, which means that electrical signal mediated by visual stimuli transmitted slowly in the MC visual pathways. What is more, the maximum response in glaucomatous eyes was reduced. In other words, the response thresholds of glaucomatous eyes were increased, which were consistent with a model of ganglion cell dysfunction due to reduced synaptic density. And the selective visual pathway damages in patients with early POAG were consistent with experimentally glaucomatous primates. Weber and Harman3 analysed the dendritic trees of MC ganglion cell and their response properties in glaucomatous retina and found that there was a reduction in the thickness and complexity of the dendritic arbour in glaucomatous retina compared with normal retina. Such changes may cause a reduction of effective retinal illuminance level, and thus affect contrast gain of ganglion cells, which provides support for the hypothesis that ganglion cell dysfunction can affect visual thresholds in patients with glaucoma.

The study further demonstrated the relationships between objective visual functions and structures in early stage of POAG. The SNRs at 8% DOM and 32% DOM were significantly correlated with temporal-side RNFL thickness in early POAG group in MC-biased stimulation, which exhibited the early structural impairment of early stage of POAG in some way. Several studies suggested

that the RGCs in the macular region were damaged in early-stage glaucoma, and involved defects that were deep and local as well as those that were shallow and widespread. The correlations between the SNRs of ic-VEP and the parameters of OCT were not found in our study in PC-biased stimulation. This suggested that the structural and functional correlation of the MC-biased stimulation was stronger than that of the PC-biased stimulation.

Figure 1  (A) The characteristics of the magnocellular and parvocellular visual pathways in the two groups. (B, C) The magnocellular visual pathway impairment in early primary open-angle glaucoma (POAG) group. **p<0.01; *p<0.05.
stimulation, which may lead to earlier detection of POAG damage. But further studies are needed.

Psychophysical methods and neuroimaging tests are also used to detect damage in glaucoma. Ouza et al.37 found that electrophysiological and psychophysical contrast sensitivity functions correlated more positively when temporal presentation was similar. And it suggests that the transient VEP is dominated by the MC pathway at low contrast levels. However, VaeganHollows38 showed psychophysics seems to tap different mechanisms, which explained the relatively lower specificity. The use of advanced MRI provides information about nerve fibres and estimates the integrity of nerve fibres indirectly,39 40 which demonstrate that glaucoma is a complex nervous system disease and affects the whole visual pathway.41 However, the selective visual pathway damage has not been reported with neuroimaging test.

Our work found that the SNR at 16% DOM in MC-biased condition was significantly lower in early POAG eyes compared with the healthy control group. Besides, the optimal cut-off SNR at 16% DOM distinguishing patients with early POAG from healthy control subjects was 2.07, yielding a sensitivity of 80.0% and a specificity of 63.3%. And the AUC of 16% DOM was 0.780. The accuracies of interictal VEP to differentiate patients with glaucoma from normal people differ according to the previous studies.14–16 The sensitivities differ by 70%
from 82% and the specificities are between 75% and 99%. In our opinion, besides the slight differences in the criteria for subject inclusion such as the stage of glaucoma and type of glaucoma, the different procedures for isolating the MC visual pathway could explain the various accuracies to some extent. The selection bias of the study populations may partly account for this result. Ageing also has an effect on the results of contrast sensitivity. McKendrick et al.\(^2\) found that normal ageing results in a reduction of contrast sensitivity for the low-spatial-frequency-sensitive components of both the MC and PC visual pathways. The mean age in our research was 41.9, which was younger than the reported literature, and thus the cut-off SNR at 16% DOM was higher in our study. It is said that MC visual pathway is almost saturated at 16% DOM. The low response platform at 16% DOM reflects the injury in axons of ganglion cells and thus damage in the MC visual pathway.\(^3\) The higher sensitivity and relatively lower specificity are apt for glaucoma screening. ic-VEP offers an objective, short time-consuming and convenient measurement in estimating visual functions, which may help the detection in patients with early glaucoma. Chen and Zhao\(^4\) found that the diagnostic standard based on single criterion used in the study tended to raise the misdiagnosis of early glaucoma. It is advised to combine multiple examination in early glaucoma detection.

As illustrated before,\(^2\) the two visual pathways are sensitive to different visual stimuli including colour, motion, contrast and so on. Isolated-check stimuli were used to identify responses origin from MC visual pathway and PC visual pathway in our study, and the characteristic contrast response functions were elicited by ic-VEP. However, we suggest that integrating multiple visual properties may be a good choice for selection of visual pathway because of the interaction in the visual cortex. Besides, this is a single-centre research with a small sample size. The pupil diameters of the subjects were not recorded. Işık and Şahin\(^5\) found that photopic pupil diameters were significantly correlated with the timing of VEP waveforms, and thus affected VEP results in eyes with early glaucoma to some extent. What is more, we did not emphasise that the inclusion criteria for the early glaucoma group must be newly diagnosed patients. Therefore, the types and numbers of medications of IOP-lowering were not recorded.

To summarise, the MC visual pathway was found damaged in early stage of POAG, which manifested as a decrease in contrast gain and maximum response mediated by iC-VEP, but not in the PC visual pathway. The SNRs at 8% and 32% DOM of MC-biased stimulation were significantly correlated with temporal-side RNFL thickness in early POAG, which helped in understanding the mechanisms of visual impairment in the early stage of POAG. MC-biased stimulation mediated by ic-VEP showed a moderate diagnostic accuracy, which may help in early POAG detection in screening and diagnosis.

**Contributors** QY, ZC, YY and MY conceived and designed the study. QY, ZC and ZL performed the study. QY, YF and PL collected the data. QY, KX and MY analysed and interpreted the data. QY wrote the initial draft. QY, YY and MY revised the manuscript. YY and MY are the guarantors of the study.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The study adhered to the tenets of Declaration of Helsinki. The study was approved by the ethical committee of Zhongshan Ophthalmic Center, Sun Yat-sen University (No. 2020KYPJZ202).

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**Data availability statement** Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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