Spatial Contrast Sensitivity for the Diagnosis of Glaucoma

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Purpose: To investigate spatial-contrast sensitivity (SCS) assessment as a tool for the diagnosis of glaucoma.

Methods: Glaucoma (64 eyes), glaucoma suspect (62 eyes) and controls (80 eyes) aged 30-76 years were randomly enrolled. Three groups were evaluated with Full-Threshold 30-2 program of the Humphrey Field Analyzer and monocular and binocular SCS using the Functional Acuity Contrast Test chart. The correlation between monocular SCS and the visual field indexes (MD, PSD) were analyzed in patients with glaucoma and glaucoma suspect. The diagnostic power of SCS was assessed at each spatial frequency.

Results: Patients with glaucoma and glaucoma suspect showed significantly decreased SCS ($p < 0.001$ at 1.5, 3, 12, 18 c/d and $p = 0.021$ at 6 c/d) compared to controls. The correlation between MD and monocular SCS ($R = 0.533$, $p < 0.001$ at 1.5 c/d, $R = 0.548$, $p < 0.001$ at 3 c/d, $R = 0.517$, $p < 0.001$ at 6 c/d, $R = 0.663$, $p < 0.001$ at 12 c/d, $R = 0.530$, $p < 0.001$ at 18 c/d), and PSD and monocular SCS ($R = -0.579$, $p < 0.001$ at 1.5 c/d, $R = -0.559$, $p < 0.001$ at 3 c/d, $R = -0.575$, $p < 0.001$ at 6 c/d, $R = -0.624$, $p < 0.001$ at 12 c/d, $R = -0.610$ at 18 c/d, $p < 0.001$) was significant in glaucoma. The correlation between PSD and monocular CSF was significant at 12 c/d and 18 c/d in glaucoma suspect ($R = -0.584$, $p < 0.001$ at 12 c/d, $R = -0.605$ at 18 c/d, $p < 0.001$). Largest AROC was obtained at 18 c/d spatial frequency for differentiating controls versus glaucoma and controls versus glaucoma suspect (AROC, 0.781, 0.751, respectively).

Conclusions: The impairment of SCS may be a useful psychophysical indicator for the diagnosis of glaucoma.

Key words: Glaucoma, Preperimetric glaucoma, Contrast sensitivity, Visual field index

Introduction

Glaucoma is associated with the pathological progressive loss of retinal ganglion cells (RGC) and functional visual field defects.¹ Both the diagnosis and monitoring of glaucoma are often based on the testing to identify and quantify the pattern of visual field defects and/or the thinning of the retinal nerve fiber layer as well as changes in the optic nerve head. Compared to morphological evaluation, the functional testing such as the visual field test actually measures visual sensitivity, and therefore is particularly important in following and assessing the effect of glaucoma treatment. The functional deficit observed in the visual field test manifests as decreased contrast sensitivity.

The decreased contrast sensitivity observed in glaucoma has been associated with RGC death.² Anatomical and functional studies have shown that, in primates with induced glaucoma, magnocellular (MC) ganglion cells can have reduced synaptic density and responsiveness before cell death.³ Such changes in the MC ganglion cell cause reduction in the effective retinal illuminance, resulting in decreased contrast sensitivity.⁴ Originally, MC ganglion cells were thought to be preferentially susceptible to glaucoma, however, recent evidence suggests that parvocellular (PC) ganglion cells can be damaged in glaucoma.⁵⁻⁸ Moreover, significant loss of neurons in both the MC and PC layer of the lateral geniculate nucleus have been observed in an experimental monkey model of glaucoma.⁹⁻¹¹ Therefore, there are diverse anatomical changes, from retinal ganglion cells to the central visual system, in glaucoma. Based on these knowledges, this study was conducted to determine the change of monocular and binocular spatial-contrast sensitivity (SCS) and whether SCS, as a central visual function, was related to the mean deviation (MD) or pattern standard deviation (PSD) of the visual field in patients with glaucoma

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and glaucoma suspect.

Materials and Methods

This study was conducted at Chonnam National University Hospital between March 2010 and July 2010. Informed consent was obtained from all subjects in accordance with the tenets of the Declaration of Helsinki and institutional approval was obtained from the research ethics board, Chonnam National University Hospital. Prospective evaluation of three groups was performed including glaucoma patients (64 eyes of 41 patients), glaucoma suspects (62 eyes of 40 patients), and controls (80 eyes of 40 patients) (Table 1). The patients included in the study were examined by a glaucoma specialist (S.W.P). All patients were required to be no history of intraocular surgery and neurological disease, orthotropic by near and far cover uncover tests, with a minimum best corrected Snellen visual acuity of 0.5 in each eye, differing by no greater than one Snellen acuity line, reliable measurements of the visual field (<20% fixation losses, <33% false-positive and false negative responses) performed on the Full-Threshold 30-2 program of the Humphrey Field Analyzer (Carl Zeiss Meditec Inc, Dublin, CA, USA). Glaucoma was defined by the characteristic glaucomatous optic nerve head findings (e.g., generalized or localized thinning of the neuroretinal rim), untreated intraocular pressure (IOP) at least >24 mmHg and required the presence of corresponding visual field deficits in one or both eyes. Glaucoma suspects were required to have a normal Humphrey 30-2 visual field, untreated intraocular pressure (IOP) at least >24 mmHg and optic nerve head findings suspicious for glaucoma (e.g., localized thinning of the neuroretinal rim). Control subjects were recruited from hospital personnel or accompanying relatives of patients, and had normal eye examinations.

For each subject the contrast sensitivity function was determined using the Functional acuity contrast test (FACTTM, Stereo Optical company, Chicago, IL, USA). The chart is viewed at a distance of 3.05 m and at a luminance level of 85 cd/m². The spatial frequencies tested were ranging between 1.5 and 18c/d (cycle per degree). The lighting conditions were standardized with a light meter (Stereo Optical) to insure the test accuracy. The light meter was held 5 cm from the center of the chart and a luminance of 85 cd/m² was measured. The patients were wearing their best distance correction. Each eye was tested separately, then binocularly to determine the monocular and binocular contrast sensitivity function. The contrast of the correctly identified target in each row is scored as the contrast threshold for that spatial frequency.

Statistical analysis was performed using a commercially available statistical package (SPSS version 12.0 for Windows; SPSS Sciences, Chicago, IL, USA). All data were submitted for a one-way analysis of variance (ANOVA) to compare the performance of the three groups (glaucoma, glaucoma suspect, and controls) across all measures. A post hoc Tukey test was performed to determine individual group differences. The correlations between MD and contrast sensitivity tests, and PSD and contrast sensitivity tests were analyzed using the Pearson correlation test. Areas under the receiver operator characteristic curves (AROC) were generated for each spatial frequency in controls versus glaucoma and controls versus glaucoma suspect. In addition, the X² test was used to analyze gender. In all statistical analyses, a $p < 0.05$ was considered significant.

Results

The results of this study showed clear overall differences of SCS among glaucoma, glaucoma suspect and controls. The

Table 1. Demographic and clinical data for glaucoma, glaucoma suspect and controls

Demographic data	Glaucoma	Glaucoma Suspect	Control	<i>p</i> -value
Number of patients	41	40	40	-
Eyes with glaucoma	64	62	80	-
Mean age, years (range)	59.0 (30 - 76)	58.4 (36 - 74)	58.5 (32 -75)	0.957
Gender (female/male)	21/20	20/20	20/20	0.851
Snellen visual acuity	0.83 ± 0.28	0.81 ± 0.27	0.82 ± 0.23	0.865
Pupil size (mm)	3.24 ± 1.21	3.31 ± 1.03	3.39 ± 1.25	0.921

Table 2. Clinical data for glaucoma, glaucoma suspect and controls

Clinical data	Glaucoma	Glaucoma Suspect	Control	p-value	Tukey Post Hoc test
MD of visual field	-9.10 ± 8.32	-0.35 ± 1.53	-0.21 ± 2.18	<0.001	G-GS, $p < 0.001$; G-C, $p < 0.001$
PSD of visual field	7.27 ± 4.61	1.90 ± 1.20	0.64 ± 0.21	<0.001	G-GS, $p < 0.001$; G-C, $p < 0.001$
Contrast sensitivity test (monocular)					
1.5 c/d	24.9 ± 15.1	25.4 ± 6.0	33.9 ± 13.1	<0.001	G-C, $p < 0.001$; GS-C, $p < 0.001$
3 c/d	28.3 ± 18.1	30.9 ± 14.1	44.5 ± 19.9	<0.001	G-C, $p < 0.001$; GS-C, $p < 0.001$
6 c/d	26.2 ± 18.0	31.0 ± 14.6	45.8 ± 23.1	0.021	G-C, $p = 0.021$; GS-C, $p = 0.029$
12 c/d	19.3 ± 11.5	19.1 ± 16.3	24.1 ± 12.6	<0.001	G-C, $p < 0.001$; GS-C, $p = 0.038$
18 c/d	6.1 ± 5.6	6.3 ± 4.4	10.1 ± 5.1	<0.001	G-C, $p = 0.013$; GS-C, $p = 0.026$
Contrast sensitivity test (binocular)					
1.5 c/d	30.9 ± 13.3	30.8 ± 10.4	36.9 ± 14.4	0.023	G-C, $p = 0.041$; GS-C, $p = 0.039$
3 c/d	40.1 ± 23.7	41.1 ± 14.2	53.4 ± 17.5	0.001	G-C, $p = 0.021$; GS-C, $p = 0.019$
6 c/d	33.4 ± 19.1	33.9 ± 15.0	54.5 ± 21.0	<0.001	G-C, $p < 0.001$; GS-C, $p < 0.001$
12 c/d	17.6 ± 13.7	21.1 ± 18.0	26.8 ± 9.7	0.002	G-C, $p = 0.027$; GS-C, $p = 0.031$
18 c/d	8.0 ± 8.6	9.2 ± 9.6	12.0 ± 5.6	0.034	G-C, $p = 0.034$; GS-C, $p = 0.041$

MD = mean deviation; PSD = pattern standard deviation; G = glaucoma; GS = glaucoma suspect; C = control.

Table 3. Areas under receiver operating characteristic curves (AROCs) for each spatial frequency in glaucoma and glaucoma suspect

FACT contrast sensitivity	Control vs. Glaucoma			Control vs. Glaucoma suspect		
	AROC	95% confidence intervals	p-value	AROC	95% confidence intervals	p-value
1.5 c/d	0.752	0.679-0.824	<0.001	0.687	0.608-0.767	<0.001
3 c/d	0.775	0.715-0.852	<0.001	0.730	0.648-0.813	<0.001
6 c/d	0.743	0.670-0.815	<0.001	0.684	0.604-0.765	<0.001
12 c/d	0.727	0.652-0.802	<0.001	0.657	0.565-0.750	0.001
18 c/d	0.781	0.712-0.851	<0.001	0.751	0.670-0.831	<0.001

FACT = functional acuity contrast test; AROC = areas under the receiver operator characteristic curve.

subject characteristics are summarized in Table 1. Each of groups did not differ in terms of the mean age (ANOVA, $p = 0.957$), gender (X^2 test, $p = 0.851$), Snellen visual acuity (ANOVA, $p = 0.865$) and pupil size (ANOVA, $p = 0.921$). The MD and PSD (Humphrey 30-2 protocol) of the glaucoma patients (-9.10 ± 8.32 , 7.27 ± 4.61) differed from the glaucoma suspect (-0.35 ± 1.53 , 1.90 ± 1.20) and controls (-0.21 ± 2.18 , 0.64 ± 0.21) (ANOVA, $p < 0.001$), respectively, (Table 2). The values of contrast sensitivity function (CSF) of the three groups are summarized in Table 2. The monocular CSF of the glaucoma (64 eyes) and the glaucoma suspect (62 eyes) were significantly low at all spatial frequencies compared to the controls ($p < 0.001$ at 1.5 c/d, $p < 0.001$ at 3 c/d, $p = 0.021$ at 6 c/d, $p < 0.001$ at 12 c/d, $p < 0.001$ at 18 c/d). The binocular CSF of glaucoma (41 patients) and glaucoma suspect (40 patients) were also significantly low at all spatial frequencies compared to the controls ($p = 0.023$ at

1.5 c/d, $p = 0.001$ at 3 c/d, $p < 0.001$ at 6 c/d, $p = 0.002$ at 12 c/d, $p = 0.034$ at 18 c/d). The correlation between MD and monocular CSF was evaluated in the glaucoma group and the results showed significant correlations ($R = 0.533$, $p < 0.001$ at 1.5 c/d, $R = 0.548$, $p < 0.001$ at 3 c/d, $R = 0.517$, $p < 0.001$ at 6 c/d, $R = 0.663$, $p < 0.001$ at 12 c/d, $R = 0.530$, $p < 0.001$ at 18 c/d). The correlations between PSD and monocular CSF showed significant correlations across all spatial frequencies in the glaucoma group ($R = -0.579$, $p < 0.001$ at 1.5 c/d, $R = -0.559$, $p < 0.001$ at 3 c/d, $R = -0.575$, $p < 0.001$ at 6 c/d, $R = -0.624$, $p < 0.001$ at 12 c/d, $R = -0.610$ at 18 c/d, $p < 0.001$; Fig. 1).

The correlation between MD and monocular CSF was evaluated in the glaucoma suspect group and the results showed no significant correlations ($R = 0.238$, $p = 0.062$ at 1.5 c/d, $R = 0.165$, $p = 0.200$ at 3 c/d, $R = 0.163$, $p = 0.205$ at 6 c/d, $R = -0.099$, $p = 0.443$ at 12 c/d, $R = 0.014$, $p = 0.915$ at 18 c/d). The

Table 4. Sensitivity and specificity values using FACT contrast sensitivity scores as detectors of glaucoma and glaucoma suspect

Abnormal classification of FACT contrast sensitivity scores	Control vs. Glaucoma		Control vs. Glaucoma suspect	
	Sensitivity	Specificity	Sensitivity	Specificity
1.5 c/d < 30.5	51.9%	87.5%	50.6%	82.3%
3 c/d < 34.5	65.6%	78.1%	66.8%	72.6%
6 c/d < 39.0	52.9%	90.6%	61.4%	69.4%
12 c/d < 26.0	40.2%	98.4%	45.2%	80.6%
18 c/d < 7.0	79.6%	86.9%	74.6%	85.8%

FACT = functional acuity contrast test.

Figure 1. Correlation between mean deviation of the visual field and contrast sensitivity test and correlation between pattern standard deviation of the visual field and contrast sensitivity in glaucoma patients. **Figure 2.** Correlation between mean deviation of the visual field and contrast sensitivity test and correlation between pattern standard deviation of the visual field and contrast sensitivity in glaucoma suspect patients.

correlations between PSD and monocular CSF were significant at 12 c/d and 18 c/d in the glaucoma suspect group ($R = -0.003$, $p = 0.984$ at 1.5 c/d, $R = -0.116$, $p = 0.368$ at 3 c/d, $R = -0.002$, $p = 0.990$ at 6 c/d, $R = -0.584$, $p < 0.001$ at 12 c/d, $R = -0.605$ at 18 c/d, $p < 0.001$; Fig. 2).

Table 3 shows the AROC with 95% confidence intervals (CIs)

for each spatial frequency measured by use of the FACT contrast sensitivity chart in controls versus glaucoma and control versus glaucoma suspect. Contrast sensitivity measurements at 1.5 c/d (AROC, 0.752, 0.687), 3 c/d (AROC, 0.775, 0.730), 6 c/d (AROC, 0.743, 0.684), 12 c/d (AROC, 0.727, 0.657), 18 c/d (AROC, 0.781, 0.751) in the controls versus glaucoma and the

controls versus glaucoma suspect, respectively. Largest AROC was obtained when the measurement of SCS was tested at 18 c/d spatial frequency for differentiating controls versus glaucoma and control versus glaucoma suspect. Table 4 includes sensitivity and specificity for classification criteria involving all spatial frequencies. Cutoff values for each spatial frequency are also shown in Table 4. The cutoff value obtained here were highest diagnostic value for sensitivity and specificity. Sensitivity values ranged between 40.2 to 79.6% in the controls versus glaucoma and 45.2 to 74.6% in the controls versus glaucoma suspect. Specificity values ranged between 78.1 to 98.4% in the controls versus glaucoma and 69.4 to 85.8% in the controls versus glaucoma suspect. FACT contrast sensitivity scores of less than 7 at 18 c/d spatial frequency showed sensitivity and specificity of 79.6%, 86.9% and 74.6%, 85.8% in the controls versus glaucoma and the control versus glaucoma suspect, respectively.

Discussion

Glaucoma usually affects mid-peripheral and paracentral vision before a reduction of macular function can be detected. On standard automated perimetry (SAP), which is usually performed in the clinical setting, the pattern of glaucomatous visual field defects progresses from a mid-peripheral visual field defect such as a nasal step or arcuate scotoma to a central visual field defect, such as paracentral or central scotoma. The SAP evaluates mid peripheral visual function rather than central visual function within 30 degrees of the posterior pole. This visual field defect is usually accompanied by RNFL loss resulting in RGC death. Compared to the optic disc evaluation, the SAP measures visual function, and therefore is particularly important in following and assessing the effect of glaucoma treatment. The SAP has become an integral tool in the management of glaucoma. However, the value of the SAP depends on the reliability of the patient's responses. In addition, it has been shown that 30-50% of retinal ganglion cells may be lost before an abnormality appears on SAP.^{12,13} Therefore, the SAP provides little or no information about the impairment of visual function for patients with glaucoma suspect with no visual field defect.

The central visual function like contrast sensitivity can be

used as an indirect evaluation of glaucomatous damage based on the fact that more than 50% of the RNFL originates from the macula.¹⁴⁻¹⁶ Spatial contrast sensitivity testing measures the contrast thresholds at different spatial frequencies. Therefore, contrast testing seeks to objectively assess the equivalent of the patient's visual function in daily life. Reduced contrast sensitivity occurs when visual acuity is reduced for any reason, such as with an uncorrected refractive error and anterior segment abnormality such as a cataract and keratoconus and a posterior segment abnormality such as macular degeneration, diabetic retinopathy or glaucoma. The MC system and the PC system are the main neural systems in the retino-geniculo-cortical pathway. The MC pathway originates with the MC ganglion cells. These MC ganglion cells have large soma with large dendritic fields and large axons. These cells are rare in the foveal area and increase in number toward the near periphery. The MC pathway transmits the information for motion detection, contrast sensitivity at low spatial frequency and low grade stereopsis.¹⁷⁻¹⁹ The PC pathway originates with the PC ganglion cells, which have small soma and small dendritic fields. These cells are of relatively high density in the fovea and decrease in number toward the near periphery. The PC pathway transmits the information for color perception and fine stereopsis.¹⁷⁻¹⁹ The MC ganglion cells are sensitive to high temporal and low spatial frequency stimuli, and PC ganglion cells are sensitive to low temporal and high spatial frequency.^{20,21} Many studies suggest neuronal damage in the MC and PC pathways from the RGC to the lateral geniculate nucleus relay of neurons terminating in the primary visual cortex in the experimental glaucoma model.⁵⁻¹¹ A variety of functional tests such as motion-automated perimetry and frequency-doubling perimetry have shown deficits in the MC pathway in patients with glaucoma.^{22,23} The color pattern electroretinogram and psychophysical testing for red green sensitivity show deficits in the PC pathway in patients with glaucoma.^{24,25} Although several studies have revealed preferential damage to the MC pathway, a discussion about the selective loss of retinal ganglion cells in the MC and PC pathway for glaucomatous RGC death falls outside the scope of the present study. Because of the difference of RGC density, according to retinal eccentricity, it would be expected that perimetric defects would occur in the peripheral visual field before

the central field.^{16,26} Conversely, vision in the central field is preserved until late stages because the initial RGC density is high. Zeimer et al.²⁷ initially reported reduced macular thickness in glaucoma. Recently, the studies with spectral-domain optical coherence tomography showed that the thickness of macular ganglion cell complexes was reduced in glaucoma and glaucoma suspect patients.^{28,29} Therefore, central visual function could be impaired during the process of glaucomatous damage.

Previous studies have concentrated on evaluating whether psychophysical studies would be possible to diagnosis glaucoma in patients prior to visual field damage using various contrast sensitivity tests and reported that the monocular and binocular CSF were significantly reduced across the spatial frequency range from low to high or contrast sensitivity loss at higher spatial frequencies precedes loss at lower spatial frequencies or loss at higher spatial frequencies occurs before loss of sensitivity on the SAP.³⁰⁻³⁵

Among the commercially available printed contrast sensitivity tests, the FACT contrast sensitivity chart enables assessment of spatial contrast sensitivity function easily in the clinical setting with minimal equipment requirement. It can be used to assess a broad range of contrast sensitivity functions with low to high spatial frequencies.

In accordance with previously published studies,^{30,31} the current study confirmed that the binocular and monocular spatial CSF of patients with glaucoma were significantly reduced at all spatial frequencies compared to control subjects. In addition, the binocular and monocular spatial CSF of glaucoma suspect patients were significantly reduced at all spatial frequencies compared to control subjects and testing of SCS at high spatial frequency like 18 c/d had similar and largest AROC for differentiating the controls versus glaucoma and the controls versus glaucoma suspect, (AROC, 0.781, 0.751), respectively. This result showed that early loss of higher SCS occurred in the glaucoma suspect patients before glaucomatous visual field defects appear on the SAP.

These findings explain why many glaucoma patients with normal central visual field and good Snellen visual acuity report poor quality of vision. In this study, loss of spatial CSF across all ranges of spatial frequency was significantly correlated with worsening of MD and PSD in patients with glaucoma

and loss of the spatial CSF at 12 c/d and 18 c/d was significantly correlated with worsening of PSD in patients with glaucoma suspect.

The ideal visual function test should be useful both before clinical signs of glaucoma are manifested, and in following the patient over the full range of optic disc damage after glaucomatous damage is observed.³⁶ In addition, patient acceptability and a short test duration are needed to be practical in the clinical setting. Although the basic mechanism for measurement of the sensitivity of the SAP and FACT is different, we found the correlation between the MD and PSD of the SAP and the SCS in patients with glaucoma and glaucoma suspect.

Although the sample size was small in our study and the diagnostic ability of the SCS was moderate, considering the easy performance of spatial CS testing using FACT, in the clinical setting, SCS measurement may be a good complementary tool to visual field testing for the diagnosis of glaucoma and glaucoma suspect.

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