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Fast Visual Field Progression is Associated with Depressive Symptoms in Patients with Glaucoma

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Abstract

Purpose—To evaluate the association between rates of progressive visual field loss and the occurrence of depressive symptoms in patients with glaucoma followed over time.

Design—Prospective observational cohort study.

Participants—The study included 204 eyes of 102 patients with glaucomatous visual field defects on standard automated perimetry (SAP).

Methods—All patients had Geriatric Depression Scale (GDS) questionnaires and visual field tests obtained over a mean follow-up time of 2.2 ± 0.6 years. Change in depressive symptoms was assessed by calculating the difference between GDS scores at the last follow-up visit from those at baseline. Rates of visual field loss were assessed by SAP. An integrated binocular visual field was estimated from the monocular SAP tests and rates of change in mean sensitivity (MS) over time were obtained from linear mixed models. Regression models were used to investigate the

association between progressive visual field loss and changes in depressive symptoms, adjusting for potentially confounding clinical and socioeconomic variables.

Main Outcome Measures—The association between rates of change in binocular SAP MS and change in GDS questionnaire scores.

Results—There was a significant correlation between change in the GDS scores during follow-up and change in binocular SAP sensitivity. Each 1 dB/year change in binocular SAP MS was associated with a change of 2.0 units in the GDS scores during the follow-up period ($P = 0.025$). In a multivariable model adjusting for baseline disease severity, change in visual acuity, age, gender, race, Montreal Cognitive Assessment score, education, income, and comorbidity index, each 1 dB/year change in binocular SAP MS was associated with a change of 3.0 units in the GDS score ($P = 0.019$).

Conclusions—Faster visual field progression was associated with the occurrence of depressive symptoms in patients with glaucoma.

INTRODUCTION

Glaucoma is a progressive optic neuropathy and one of the leading causes of visual impairment and decrease in vision-related quality of life.[1–3] Due to its chronic nature, potential for causing irreversible blindness, and inherent side effects of the treatment, glaucoma can often impose a psychological burden to patients.[3–6] The prevalence of depressive symptoms among glaucoma patients varies from 6 to 16% in different studies and has been reported to be higher than in patients without the disease.[7–12]

Several previous studies have shown a relationship between severity of visual field loss and the occurrence of depressive symptoms in patients with glaucoma.[7–16] These studies have employed a cross-sectional design and suggested that worse disease severity was associated with higher prevalence of depressive symptoms.[11, 12, 14–17] However, the cross-sectional design may impose limitations to the study of this association, as it does not allow an assessment of how visual field changes over time would impact patients' well-being and how they might be associated with depressive symptoms. In previous studies, we have shown that the rate of visual field loss was associated with decline in self-reported quality of life as measured by the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25).[18–21] The NEI VFQ-25 measures several aspects of quality of life, including the ability to perform everyday tasks such as reading and driving.[22] It is likely that a patient with a fast rate of visual field loss experiences greater difficulty with activities of daily living, potentially leading to depressive symptoms, as compared to a subject whose disease has been progressing slowly. In fact, a study by Kiely et al[23] suggests that functional impairment in physical and/or social domains explains much of the longitudinal association between sensory loss and depressive symptoms.

In the present study, we investigated the relationship between the rate of visual field loss and the occurrence of depressive symptoms in a cohort of patients with glaucoma followed over time.

METHODS

Participants from this study were included in a prospective longitudinal study designed to evaluate functional impairment in glaucoma conducted at the Laboratory of Performance and Visual Function of the University of California San Diego. The institutional review board at the University of California San Diego approved the methods, and written informed consent was obtained from all participants. The study adhered to the laws of the Health Insurance Portability and Accountability Act, and all study methods complied with the Declaration of Helsinki guidelines for human subject research.

All participants underwent a comprehensive ophthalmologic examination including review of medical history, visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann applanation tonometry, corneal pachymetry, gonioscopy, dilated fundoscopy examination using a 78-diopter lens, stereoscopic optic disc photography, and standard automated perimetry (SAP) using the 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard of the Humphrey Field Analyzer II, model 750 (Carl Zeiss Meditec, Inc., Dublin, CA, USA). Only subjects with open angles on gonioscopy were included. Patients with coexisting retinal disease, uveitis, or nonglaucomatous optic disc neuropathy were excluded from the study.

Glaucoma was defined by the presence of two or more consecutive abnormal SAP tests at baseline, defined as a pattern standard deviation with $P < 0.05$ and/or glaucoma hemifield test results outside normal limits, and evidence of glaucomatous optic neuropathy based on masked assessment of stereophotographs. A subject was considered to have glaucoma if damage was present in at least one eye.

The presence of depressive symptoms was evaluated with the Geriatric Depression Scale (GDS) questionnaire. For inclusion in the study, subjects were required to have completed a baseline and a follow-up GDS questionnaire over a minimum period of one year. In addition, they were required to have had at least three visual fields during the corresponding period. Data for this study were obtained during the period extending from March 2011 to April 2015. During follow-up, each patient was treated at the discretion of the attending ophthalmologist.

Monocular and Binocular Visual Fields

Monocular SAP was performed using the 24-2 SITA Standard test at all visits during the follow-up period. Only reliable tests (33% fixation losses and 15% false positives) were included. In addition, visual fields were reviewed and excluded in the presence of artifacts, such as eyelid or rim artifacts, fatigue effects, inattention, or inappropriate fixation. Visual fields were also reviewed for the presence of abnormalities that could indicate diseases other than glaucoma, such as homonymous hemianopia. To evaluate binocular visual field (BVF) loss, sensitivities of the monocular SAP threshold sensitivities of the right and left eyes were used to calculate an integrated BVF. The sensitivity for each point of the BVF was estimated using the binocular summation model described by Nelson-Quigg et al.[24] Evaluation of rates of visual field change was performed using the mean sensitivity (MS) of the BVF. The MS was calculated as the average of the BVF threshold sensitivities for the integrated field.

Geriatric Depression Scale

The GDS questionnaire is a self-reported tool that has been validated for screening depression in the elderly and is used commonly used as part of a geriatric assessment.[25] The 15-item GDS consists of 15 dichotomous (yes/no) questions about depressive symptoms in the past week (Fig 1, available at www.aaojournal.org). One point is assigned to each answer and the cumulative score is rated on a scoring grid, so possible scores range from 0 to 15. Scores above 5 are suggestive of depression and scores equal to or greater than 10 are almost always indicative of depression. A more detailed scoring can also be used to stage depression: from 5 to 8 is indicative of mild depression, from 9 to 11 of moderate depression, and from 12 to 15 of severe depression. We obtained an estimate of the change in the occurrence of depressive symptoms by subtracting the final GDS score from the baseline GDS score. Therefore, an increase in the scores indicated increased incidence of depressive symptoms during follow-up.

Demographic, Clinical, and Socioeconomic Variables

Socioeconomic and clinical questionnaires were also administered to patients at the time of the baseline GDS. These questionnaires contained a survey about demographics, history of ocular and medical conditions, degree of education, and income level. Because depressive symptoms can have multiple causes and several factors might contribute to it, these factors were included as potential confounding factors in the analysis of the relationship between change in GDS scores and progressive field loss. Variables were categorized for inclusion in the multivariable models as degree of education (at least graduate school degree [yes/no]), income (less than $25 000/year [yes/no]), use of antidepressants (yes/no), and use of topical non-selective beta-blockers (yes/no). For comorbidities, we investigated the presence or history of the following conditions: diabetes mellitus, arthritis, auto-immune diseases, high blood pressure, heart disease, asthma, stroke, and cancers. A simple summation score was used to create a comorbidity index.[19] All subjects also completed the Montreal Cognitive Assessment (MoCA) test. The MoCA test is a 30-point cognitive screening tool developed to detect mild cognitive impairment. Change in visual acuity during follow-up was calculated as the difference between the logarithm of the minimum angle of resolution (logMAR) visual acuity at the last follow-up visit and baseline visit for each eye. The eye with better visual acuity at baseline was considered as the better eye for the purpose of analysis of change in visual acuity.

Statistical Analysis

Rates of visual field loss from SAP were obtained by linear mixed models.[26–28] A univariable linear regression model was then initially used to evaluate the relationship between change in GDS scores and rates of visual field loss. Subsequently, the relationship was studied after adjustment for potentially confounding factors such as visual acuity, age, gender, race, disease severity, use of antidepressants, use of topical non-selective beta-blockers, presence of comorbidities, degree of cognitive impairment, and socioeconomic variables.

All statistical analyses were performed using commercially available software Stata, version 13 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05.

RESULTS

The study included 204 eyes of 102 subjects with glaucomatous visual field loss. Table 1 shows the clinical and demographic characteristics of the included subjects. Mean age at baseline was 67.4 ± 12.2 years. There were 55 males (53.9%) and 47 females (46.1%). At baseline, average mean deviation (MD) of the worse and better eyes of glaucoma patients were -4.6 ± 6.2 dB and -1.8 ± 4.0 dB, respectively. However, there was a wide range of MD values of visual fields included in the study, ranging from -26.4 to 2.6 dB. The average binocular MS at baseline was 29.2 ± 3.7 dB. Baseline GDS score was 2.3 ± 2.6 units, ranging from 0 to 8 units.

Subjects were followed for an average of 2.2 ± 0.6 years (range, 1.0 to 3.9 years), from the date of the first visual field to the date of the last visual field closest to the GDS questionnaire. The median number of available SAP visual field tests during follow-up was 7 (interquartile range, 4 to 10). Mean rate of change in binocular MS was -0.3 ± 0.3 dB/year (range, -1.5 to 0.1 dB/year). Mean change in GDS scores was -1.2 ± 2.5 units (range, -8 to 5 units). Table 2 shows results of univariable models investigating factors associated with change in GDS scores over time. There was a significant relationship between change in the GDS scores during follow-up and rates of change in binocular SAP sensitivity. Each 1 dB/year faster decline in binocular SAP MS was associated with an increase of 2.0 units in the GDS scores during the follow-up period [95% confidence interval (CI): 0.3 to 3.7; $P = 0.025$; $R^2 = 5.0\%$]. When rates of visual field change were assessed by the SAP MD values of the better eye, as defined by the eye with higher SAP MD (less field defect) at baseline, the relationship was similar. Each 1 dB/year faster rate of progression in SAP MD of the better eye was associated with a 1.8 units increase in GDS scores over time (95% CI: 0.3 to 3.3; $P = 0.017$; $R^2 = 5.5\%$). No statistically significant association was seen between change in SAP MD of the worse eye and change in GDS scores ($P = 0.281$).

Baseline disease severity and change in visual acuity were not significantly associated with change in GDS scores during follow-up. Age, gender, and race were also not significantly associated with change in GDS scores over time in the univariable models. There was also no relationship between change in GDS scores and the variables education, income, use of antidepressants, use of topical non-selective beta-blockers, MoCA score, and the comorbidity index.

In the multivariable model adjusting for potentially confounding variables, the rate of change in binocular MS was still significantly associated with change in the GDS scores (Table 2). Each 1 dB/year faster decline in binocular SAP MS was associated with an increase of 3.0 units in the GDS scores (95% CI: 0.5 to 5.5; $P = 0.019$) (Fig 2). In the multivariable model using the rate of change in SAP MD values of the better eye, each 1 dB/year faster decline in SAP MD values of the better eye was associated with an increase of 2.8 units in the GDS scores (95% CI: 0.5 to 5.0; $P = 0.015$).

DISCUSSION

In the current study, we showed that rates of visual field change as assessed by SAP were significantly associated with depressive symptoms in patients with glaucoma followed over time. Patients with rapidly progressing disease showed an increase in the incidence of depressive symptoms, as assessed by changes in a previously validated depression scale. To the best of our knowledge, such association has not been previously demonstrated in the literature. Our findings indicate that assessment of rates of visual field progression in glaucoma may be important for indicating patients at risk for developing depressive symptoms over time.

Patients with rapid visual field progression had greater change in GDS scores compared to those with slower field changes over time. In the univariable model, each 1 dB per year faster loss in binocular SAP MS was associated with a change of 2.0 units in the GDS scores during follow-up. This finding indicates that faster visual field loss can increase the occurrence of depressive symptoms in patients with glaucoma. It is possible that increased difficulties with activities of daily living or impaired social engagement could explain this association.[23] In fact, in previous studies we demonstrated that faster rates of visual field loss were associated with longitudinal decline in self-reported quality of life.[18–21] Patients with relatively slower visual field progression may have more time to adapt to their limited functional status by developing compensatory strategies that might decrease the impact of the disease and, therefore, would have lower chance of developing or reporting depressive symptoms.

It should be noted that despite its statistically significant association with change in GDS scores, rates of visual field change explained only a relatively small proportion of the change seen in the responses to GDS questionnaires over time. This is probably explained by the multifactorial etiology of this condition. Nevertheless, rates of visual field loss were still significantly associated with depressive symptoms after adjustment for confounding factors. Each 1 dB loss in binocular SAP MS per year was associated with a change of 3.0 units in the GDS score in the multivariable model.

Depression is one of the leading causes of disability and most studies have reported a higher prevalence of depression in patients with glaucoma compared to controls.[7, 9–12] Glaucoma was a significant predictor of depression after adjustment for demographic factors and comorbidities in a nationally representative population sample, but not after adjustment for self-reported general health condition.[12] The same study showed that among participants with glaucoma, self-reported measures of vision were significant risk factors for depression, whereas objective measures of vision were not.[12] Jampel et al reported that symptoms of depression were related to worse self-reported visual function in newly diagnosed glaucoma patients from the Collaborative Initial Glaucoma Treatment Study.[14] However, the same study failed to correlate monocular objective measures of visual function with most of the symptoms of depression.[14] Although these results may seem to contrast to the positive relationship between rates of visual field change and depressive symptoms found in our study, the differences might be explained, at least in part, by the different study designs. Previous investigations have used cross-sectional data, which may be affected by the wide

inter-individual variability in subjective perceptions about the impact of disease on well-being.[11, 12, 14–17] In addition, the impact of disease severity on a patient's quality of life may be affected by the possible development of compensatory mechanisms, as described above. By employing a longitudinal design, the present study may be able to provide a better evaluation of how functional loss in glaucoma would impact quality of life and patient well-being. In fact, we demonstrated that rates of visual field loss were more important in predicting change in depressive symptoms than disease severity as assessed in a single point in time.

The present study has limitations. The average follow-up time was relatively short, considering the long-term duration of a disease such as glaucoma. Despite that, we found statistically significant and relevant associations between longitudinal changes in SAP and GDS scores, but longer term follow-up may provide us with improved estimates of this relationship. Another limitation of our study is that we included only baseline values for a number of potentially confounding clinical and socioeconomic variables, such as comorbidities. It would probably have been better to assess whether change occurred in these variables over the duration of follow-up. However, investigating change in the impact of comorbidities over time would be an extremely difficult if not impossible task to conduct due to the many variables that could affect it, such as change in the severity of many conditions, impact of a variety of treatments and their side effects. Although we evaluated the impact of baseline MoCA scores on GDS changes over time, longitudinal changes in cognitive status could also be a potential confounding factor affecting the report of depressive symptoms. However, repeated MoCA evaluations were available during follow-up for 80 (78.4%) of the 102 subjects and there was no significant relationship between change in MoCA scores and change in GDS scores (P = 0.199). When the multivariable model also included change in MoCA scores in this restricted sample, rates of visual field progression were still significantly associated with change in GDS scores (P = 0.013). Another limitation of our study is that we did not perform longitudinal systematic lens opacity grading to evaluate a possible effect of worsening cataracts in explaining the occurrence of depressive symptoms. However, there was no significant relationship between change in visual acuity and change in GDS scores in our population. Therefore, we believe that cataract most likely did not have a significant impact in explaining the relationships found in our study.

It could be argued that the change in depressive symptoms for some patients in our study may have occurred simply from the fact that they may have been informed by the attending physician of the progression or stability of their visual fields. However, it is likely that our study replicated what usually happens in clinical practice and the reported associations are likely to be of clinical relevance. It should be noted, however, that the report of depressive symptoms by patients might also have been affected by the timing of application of the GDS questionnaires. For example, if in a discussion with the physician a patient was told about visual field progression and the GDS questionnaire happened to be applied shortly thereafter, this patient might have reported a higher prevalence of depressive symptoms at that point than he or she would report if questioned at a later point in time. Unfortunately, we were not able to control the timing of questionnaire application in relation to patient-physician interactions. Future studies should attempt to clarify this issue.

In conclusion, fast visual field loss was significantly associated with the incidence of depressive symptoms in patients with glaucoma. Our findings suggest that rates of change may be indicative of the risk for developing depressive symptoms in patients with glaucoma and they emphasize the need for an accurate and precise assessment of rates of change in monitoring this disease.

Abbreviations

NEI VFQ-25	25-item National Eye Institute Visual Function Questionnaire
SAP	standard automated perimetry
GDS	Geriatric Depression Scale
BVF	binocular visual field
MS	mean sensitivity
MoCA	Montreal Cognitive Assessment
MD	mean deviation

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Geriatric Depression Scale Questionnaire *(Participant Fills Out)*

Visit Code: _____ Participant ID: _____ DOB: _____/_____/_____ Date: _____/_____/_____

Instructions: Circle the answer that best describes how you felt over the <u>past week</u>.

1. Are you basically satisfied with your life?		Yes	No
2. Have you dropped many of your activities and interests?		Yes	No
3. Do you feel that your life is empty?		Yes	No
4. Do you often get bored?		Yes	No
5. Are you in good spirits most of the time?		Yes	No
6. Are you afraid that something bad is going to happen to you?		Yes	No
7. Do you feel happy most of the time?		Yes	No
8. Do you often feel helpless?		Yes	No
9. Do you prefer to stay at home, rather than going out and doing things?		Yes	No
10. Do you feel that you have more problems with memory than most?		Yes	No
11. Do you think it is wonderful to be alive now?		Yes	No
12. Do you feel worthless the way you are now?		Yes	No
13. Do you feel full of energy?		Yes	No
14. Do you feel that your situation is helpless?		Yes	No
15. Do you think that most people are better off than you are?		Yes	No

Figure 1.

The 15-item Geriatric Depression Scale (GDS) questionnaire consists of 15 dichotomous (yes/no) questions about depressive symptoms in the past week. Of the 15 items, 10 indicated the presence of depressive symptoms when answered positively, while questions 1, 5, 7, 11, and 13 indicated the presence of depressive symptoms when answered negatively.
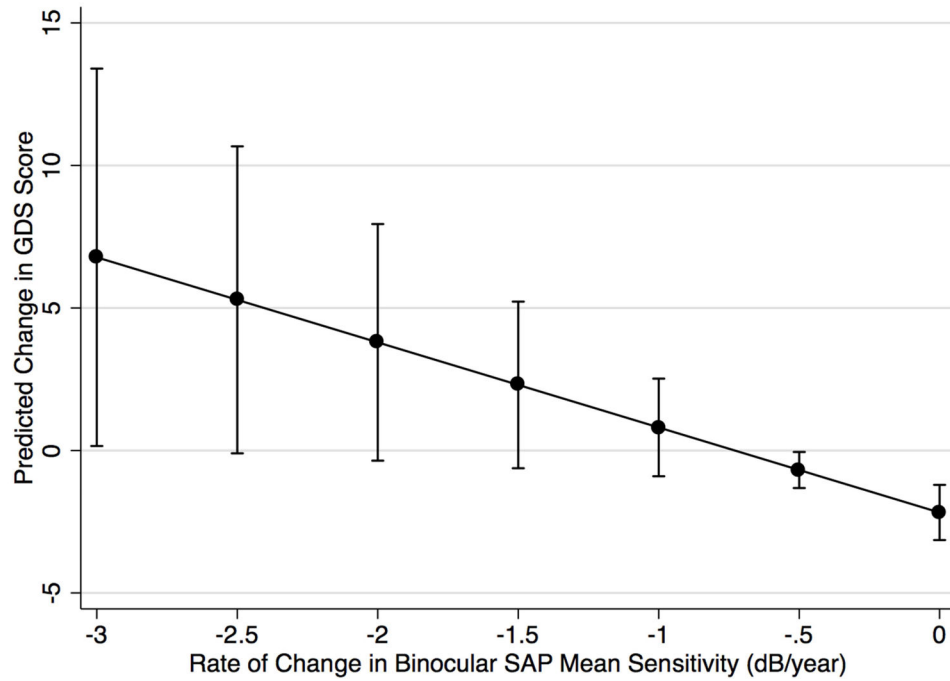
Figure 2.
Predicted changes with 95% confidence interval in the Geriatric Depression Scale (GDS) score for different values of rate of change in binocular standard automated perimetry (SAP) mean sensitivity (dB/year).

Table 1

Baseline demographic and clinical characteristics of subjects included in the study (n = 102)

Characteristic	Value
Age, years	67.4 ± 12.2
Gender, n (%) female	47 (46.1)
Race, n (%)	
Caucasian	54 (52.9)
African American	34 (33.3)
Asian	9 (8.8)
MD SAP 24-2 (worse eye), dB	−4.6 ± 6.2
MD SAP 24-2 (better eye), dB	−1.8 ± 4.0
Binocular MS SAP 24-2, dB	29.2 ± 3.7
Visual acuity (worse eye), logMAR	0.01 ± 0.12
Visual acuity (better eye), logMAR	−0.05 ± 0.10
Geriatric Depression Scale score	2.3 ± 2.6
Educational level (at least college school degree), n (%)	88 (86.3)
Income (less than $25,000), n (%)	13 (12.8)
Use of antidepressants, n (%)	11 (10.8)
Use of topical non-selective beta-blockers, n (%)	29 (28.4)
Montreal Cognitive Assessment score	27.8 ± 2.2
Comorbidity index	1.5 ± 1.3

MD = mean deviation; SAP = standard automated perimetry; dB = decibels; MS = mean sensitivity; logMAR = logarithm of the minimum angle of resolution.

Values are presented as mean ± standard deviation, unless otherwise noted.

Table 2

Results of the univariable and multivariable regression models for explaining change in Geriatric Depression Scale score in glaucoma patients

Characteristic	Univariable Model		Multivariable Model	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Rate of change in binocular MS, per 1 dB/year faster loss	2.0 (0.3 to 3.7)	0.025	3.0 (0.5 to 5.5)	0.019
Baseline binocular MS, per 1 dB lower	0.1 (0.0 to 0.2)	0.191	0.0 (−0.2 to 0.2)	0.878
Change in visual acuity of better eye, per 0.1 logMAR higher	0.0 (−0.6 to 0.5)	0.954	−0.1 (−0.7 to 0.4)	0.671
Age, per 1 decade older	−0.1 (−0.5 to 0.3)	0.541	−0.4 (−0.9 to 0.1)	0.093
Gender, female	0.4 (−0.6 to 1.4)	0.446	0.3 (−0.7 to 1.3)	0.556
Race, Caucasian	0.5 (−0.6 to 1.6)	0.352	0.3 (−1.1 to 1.7)	0.707
Educational level, at least college school degree	−0.4 (−1.9 to 1.0)	0.549	−0.4 (−2.1 to 1.2)	0.599
Income, less than $25,000	−0.6 (−2.1 to 0.9)	0.428	−1.0 (−2.5 to 0.6)	0.214
Use of antidepressants, yes	1.3 (−0.3 to 2.9)	0.108	1.6 (−0.1 to 3.4)	0.072
Use of topical non-selective beta-blockers, yes	0.6 (−0.5 to 1.7)	0.270	0.4 (−0.8 to 1.6)	0.506
Montreal Cognitive Assesment score, per 1 unit lower	−0.1 (−0.3 to 0.2)	0.550	−0.1 (−0.4 to 0.2)	0.412
Comorbidity index, per 1 unit higher	−0.1 (−0.5 to 0.3)	0.789	−0.1 (−0.6 to 0.4)	0.826

CI = confidence interval; MS = mean sensitivity; dB = decibel; logMAR = logarithm of the minimum angle of resolution.