

Delayed saccadic eye movements in glaucoma

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Purpose: To determine whether saccadic eye movements are altered in glaucoma patients.

Patients and methods: Sixteen patients with glaucoma and 21 control subjects were prospectively studied. Patients participated in a pro-saccade step task. Saccades were recorded using a noninvasive infrared oculometric device with head-mounted target projection. Medians of saccade reaction time, duration, amplitude, and peak velocity; frequency of express saccades; and percentage of trials with direction error were recorded. *t*-tests were used to compare the glaucoma and age-matched control groups. A correlation analysis of saccade parameters with visual field loss was also performed.

Results: Median saccade reaction times were significantly prolonged in glaucoma patients compared with controls (220.9 ± 49.02 ms vs 192.1 ± 31.24 ms; *t*-test: $P = 0.036$). Median duration, median amplitude, and median peak velocity of saccades did not show significant differences between glaucoma and control groups ($P > 0.05$). Frequency of express saccades was significantly decreased in glaucoma patients compared with controls (1.75 ± 2.32 vs 7.0 ± 6.99 ; *t*-test: $P = 0.007$). Saccade parameters in glaucoma patients showed no significant correlation with visual field loss.

Conclusion: Saccadic eye movements are significantly delayed in patients with early, moderate, or advanced glaucoma. Determination of median saccade reaction time may offer a novel functional test to quantify visual function in glaucoma patients. Further studies are needed to determine pathological processes implicated in delayed initiation of saccades, and to assess whether alteration of saccades affects daily activities in glaucoma patients.

Keywords: visual field, latency, visual dysfunction, brain, superior colliculus, quality of life

Introduction

Glaucomatous optic neuropathy is a leading cause of irreversible blindness worldwide.¹ Loss of sight in glaucoma is caused by death in retinal ganglion cells,² and involves visual functions such as form, motion, and color.³⁻⁵ Functional tests for the diagnosis of glaucoma and for the assessment of progression are processed by retinal ganglion cells that project to the lateral geniculate nucleus,⁶ a relay station to the primary visual cortex. In glaucoma, neurodegeneration in this major retino-geniculo-cortical pathway has been demonstrated.⁷⁻¹⁵

The effect of glaucoma on other visual functions such as eye movements that are controlled by alternative visual pathways is not well studied. Saccades are rapid eye movements that redirect the fovea to visual targets, such as a suddenly appearing visual stimulus.¹⁶ They are generated by a complex network of brain structures, including the retino-tectal pathway.¹⁷ Saccades can be measured precisely with reliable parameters such as saccade reaction time, saccade duration,¹⁸ amplitude,^{19,20} and peak velocity.^{21,22}

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Studies of these saccade parameters are used to assess the integrity of the saccade-generating neural network in various brain diseases.^{23–28} In addition, saccade parameters such as increased saccade reaction time are altered in various optic nerve pathologies affecting the nerve fibers that convey visual signals to the saccade-generating network.^{29,30} We hypothesize that eye movements may provide another functional marker of injury in glaucoma. The aim of this study was to determine whether saccadic eye movements are altered in glaucoma patients.

Material and methods

After study approval by St Michael's Hospital Research Ethics Board, informed consent was obtained from glaucoma and age-matched participants between the ages of 40 and 80 years. Patients with primary open-angle glaucoma and a history of uncontrolled intraocular pressure ($n = 16$) were prospectively recruited from the practice of a glaucoma specialist (NG). Glaucoma was defined by characteristic optic nerve head findings with corresponding visual field changes assessed by white on white automated perimetry. Vision loss was estimated by the sum of mean deviations of right and left visual fields. Exclusion criteria included other nonglaucomatous eye disease, monocularly, incisional eye surgery within a month, central acuity of less than 20/50 OU, history of neurological disease, and use of psychotropic medications known to affect saccade velocity.³¹ Control subjects ($n = 21$) were recruited from visitors or personnel working at the institution and from relatives of patients. All control subjects had normal eye examinations. Glaucoma and age-matched control subjects underwent full eye examinations. Age and visual acuity were not different between glaucoma and age-matched controls (Tables 1–3). Mean ages of glaucoma patients and controls were 63.2 ± 8.70 years and 60.9 ± 8.13 years, respectively ($P = 0.42$). Glaucoma patients showed minimal to advanced visual field loss (Table 3).

Table 1 Demographics^a

| | Control | Glaucoma | Significance |
|-------------------|---------------|---------------|--------------|
| Number | 21 | 16 | |
| Percentage female | 57% | 44% | |
| Age (years) | 60.9 (8.05) | 63.2 (8.70) | $P = 0.42$ |
| Acuity OD | 0.737 (0.213) | 0.700 (0.212) | $P = 0.61$ |
| Acuity OS | 0.693 (0.227) | 0.616 (0.254) | $P = 0.34$ |

Note: ^aVisual acuity measured as the decimal equivalent of the Snellen number. Values in parentheses are standard deviations. Significance P -values represent the outcome of an independent-samples t -test.

Abbreviations: OD, right eye; OS, left eye.

Table 2 Participant summary data for controls

| Age (years) | Gender |
|----------------|--------|
| Control | |
| 46 | Male |
| 50 | Female |
| 53 | Female |
| 56 | Male |
| 56 | Male |
| 56 | Female |
| 57 | Male |
| 57 | Male |
| 57 | Female |
| 58 | Female |
| 58 | Female |
| 61 | Female |
| 61 | Female |
| 62 | Female |
| 63 | Female |
| 65 | Male |
| 68 | Female |
| 70 | Male |
| 71 | Female |
| 74 | Male |
| 79 | Male |

Eye movement recordings

All glaucoma and control participants were tested under similar conditions under constant observation. Participants were seated 1.5 m away from an evenly lit wall with luminance measured at 500 cd/m² (Minolta Luminance Meter LS-100, Osaka, Japan). A noninvasive infrared oculometric device with a head-mounted system of low-power laser-target projections (saccadometer) (Ober Consulting, Poznan,

Table 3 Participant summary data for glaucoma

| Age (years) | Gender | Total mean deviation (dB) |
|-----------------|--------|---------------------------|
| Glaucoma | | |
| 72 | Male | 0.07 |
| 63 | Male | −1.01 |
| 77 | Male | −7.68 |
| 62 | Female | −9.01 |
| 57 | Female | −10.54 |
| 68 | Male | −11.19 |
| 61 | Female | −11.68 |
| 70 | Female | −11.89 |
| 71 | Female | −14.1 |
| 56 | Male | −18.62 |
| 59 | Male | −20.29 |
| 54 | Male | −21.64 |
| 60 | Female | −23.16 |
| 42 | Male | −26.56 |
| 69 | Female | −27.21 |
| 70 | Male | −36.82 |

Poland) projected three high-contrast (13 cd/m^2) discs subtending 0.1° in diameter, at 0° , 10° left, and 10° right, along the frontal plane at eye level. Viewing and recording were performed binocularly. Prior to proceeding with testing, all participants were required to report clearly seeing the red stimuli located at 0° , 10° left, and 10° right. Calibrations were made for both left and right stimuli under binocular viewing.

After a random foreperiod (500–1000 ms), the central fixation point was extinguished, and a randomly chosen 10° left or 10° right stimulus was projected. There were no gaps or overlaps, and the stimuli remained projected until either the participant performed a saccade or 2000 msec had elapsed. Each session consisted of 200 trials, measured over the course of 15 minutes. Saccade reaction time, duration, amplitude, peak velocity, and direction were recorded with a sampling rate of 1 kHz and a linear range within 7% for up to $\pm 30^\circ$ (Ober Consulting).²³ Blinks and head movements were automatically excluded by the Latency Meter Version 4.9 software (Ober Consulting), and analysis was performed on saccades made toward the stimulus. Trials with saccade reaction times between 50 ms and 600 ms were analyzed, removing anticipatory saccades (< 50 ms) and latencies due to inattention (> 600 ms).^{22,24–26} Trials with saccade reaction times between 50 ms and 100 ms were defined as express saccades,^{19,32–36} and their frequency was counted. Trials with direction error were analyzed separately.

Statistical analysis

Statistical analysis was performed using SPSS Version 14.0 (SPSS Inc, Chicago, IL) and SAS 9.2 (SAS Institute Inc, Cary, NC) with α level set at 0.05. Medians of saccade reaction time, duration, amplitude, and peak velocity, and frequency of express saccades were calculated. These variables in the glaucoma group were compared with age-matched controls using independent-samples *t*-tests. A *P*-value less than 0.05 was considered statistically significant. Bivariate correlations of the visual field loss (as measured by the sum of mean deviations of right and left visual fields) and various saccade variables were calculated using the Pearson correlation coefficient.

Results

Figure 1 shows a series of saccade recordings and histograms of saccade reaction times of representative glaucoma and control subjects. Saccade reaction times were prolonged in glaucoma patients compared with controls (Figure 2). Median saccade reaction time was significantly increased in glaucoma patients

compared with controls (220.9 ± 49.02 ms vs 192.1 ± 31.24 ms; $P = 0.036$) (Figure 3). Median duration, median amplitude, and median peak velocity were not statistically different between groups (54.7 ± 5.16 ms vs 52.8 ± 4.45 ms, $P = 0.25$; $10.4 \pm 1.88^\circ$ vs $9.5 \pm 1.69^\circ$, $P = 0.12$; $349.4 \pm 72.01^\circ/\text{s}$ vs $345.0 \pm 83.41^\circ/\text{s}$, $P = 0.87$) (Table 4).

There was a significant reduction in the number of express saccades in the glaucoma patients compared with controls (1.75 ± 2.32 vs 7.0 ± 6.99 ; $P = 0.007$). The percentage of direction errors between the glaucoma and control groups was not statistically different ($1.72 \pm 1.82\%$ vs $3.2 \pm 5.89\%$; $P = 0.34$) (Table 4), and neither were direction errors significantly correlated with the degree of visual field loss in the glaucoma group ($P = 0.54$).

Median saccade reaction time, median duration, median amplitude, and median peak velocity were not statistically correlated with the degree of visual field loss ($P = 0.64$, $P = 0.25$, $P = 0.14$, and $P = 0.38$, respectively).

Discussion

This is the first study to demonstrate that saccade latencies are affected in glaucoma. Glaucoma patients were slower to initiate the saccade compared with age-matched controls. Normal saccade reaction times in control subjects in our study are consistent with previous work.^{25,27,34}

The fact that other saccade parameters such as duration, amplitude, and peak velocity are not altered suggests that patients were able to detect the targets located at 10° to the right and to the left of the fixation point, and that once the saccades were initiated, the accuracy and the motor characteristics of the saccades were not significantly affected. Therefore, the glaucomatous pathological process seems to alter mainly the initiation of saccades that involve visual input as well as a complex saccade-generation network.

The neural network underlying saccade generation involves a multitude of structures, including superior colliculus, areas of the frontal lobe, and the basal ganglia.¹⁷ Visual input to the saccade-generating network is provided by a specific subpopulation of retinal ganglion cells that project directly to superior colliculus,^{6,37} and indirect visual input via the primary visual cortex also projects to the superior colliculus.³⁸ In view of the fact that delayed saccades have been described in various optic nerve diseases,^{29,30} the delayed saccades observed in patients with glaucomatous optic neuropathy are likely due to damage to retinal ganglion cells that provide direct retinal input to superior colliculus⁶ and/or that drive the visual information through the visual cortex.^{38,39} It is interesting to note that delayed saccades are found in patients

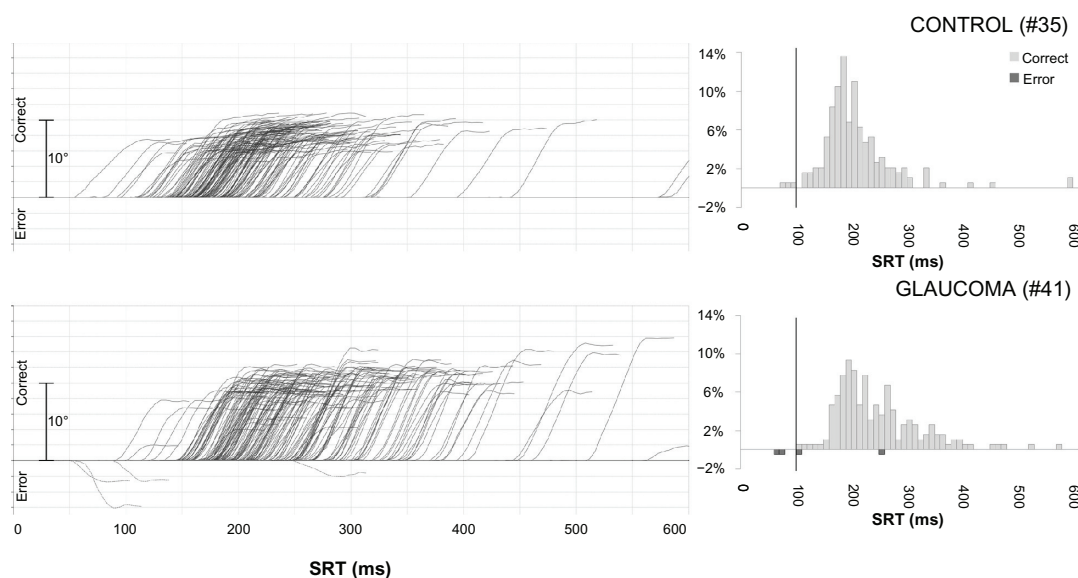


Figure 1 Traces of individual saccades for two subjects (left) and histograms of corresponding reaction times (right).^a

Notes: ^aThe left column shows eye position (in degrees) as a function of time (in ms) after the onset of the stimulus. Traces above the x-axis show saccades made in the correct direction for the stimulus, whereas those below show direction errors. Each curve represents a single saccade. The right column shows histograms of reaction times for the two subjects (percentage of total responses on the y-axis, saccade reaction times [SRT] in ms on the x-axis). Light bars above the x-axis represent saccades made in the correct direction, whereas dark bars below the x-axis represent direction error. Data points to the left of the bolded vertical line represent express saccades (saccade reaction times < 100 ms).

with mild visual field loss, as well as in advanced cases. It is not yet known whether the increased latency of nerve conduction in the retino-geniculate pathway^{40,41} and/or the decreased amplitude of retinal ganglion cell response⁴² reported in some glaucoma patients contribute to delayed saccades in glaucoma patients. Further studies are needed to determine whether the retinal ganglion cells conveying visual information to the saccade-generation network are affected in glaucoma.

The superior colliculus is critical to saccade generation, with a role in both visual and motor components.¹⁷ In addition to its sensory role as a visual information-recipient structure arranged in a retinotopic fashion, it plays an important role in

influencing saccade generation through its direct projection to the brainstem reticular formation,⁴³ which, in turn, projects to oculomotor neurons.⁴⁴ Ablation of superior colliculus in nonhuman primates leads to increased saccade reaction times and eliminates a subpopulation of express saccades.⁴⁵ Interestingly, in addition to prolonged saccade reaction time, we noted a reduced frequency of express saccades in glaucoma. Investigations in nonhuman primate experimental glaucoma may help to determine whether the retinal ganglion

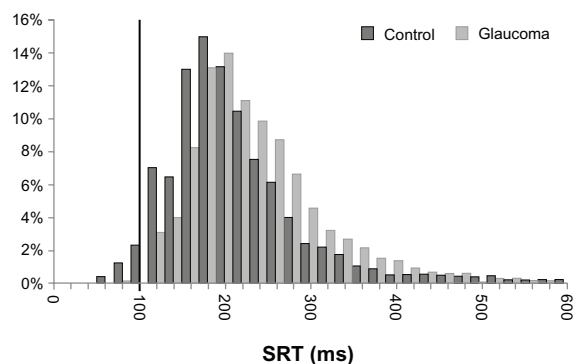


Figure 2 Saccade reaction times (SRT).^a

Notes: ^aHistogram shows the distribution of SRT for each group (percentage of total responses on the y-axis, and in ms on the x-axis). Dark bars represent data from control subjects; light bars represent data from glaucoma patients. Data points to the left of the bolded vertical line at 100 ms represent express saccades.

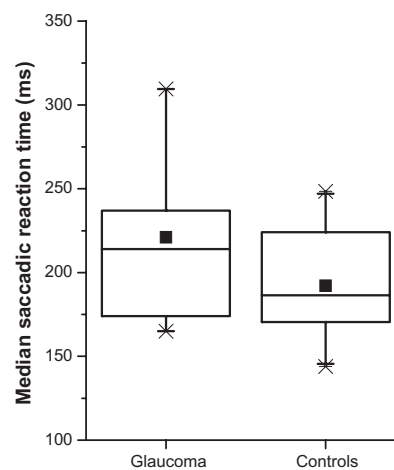


Figure 3 Box plots of median saccadic reaction times per group.^a

Notes: ^aThe horizontal bars across the boxes are the medians of the groups; small squares indicate group means. The boxes themselves delineate the 25th percentile to the 75th percentile of each group, the "whiskers" indicate the 5th and 95th percentiles, and the "X"s mark minima and maxima.

Table 4 Saccade parameters in glaucoma and controls

| Saccade parameter | Control | Glaucoma | P-value | t-value |
|---------------------------------|---------------|---------------|-------------|------------|
| Median reaction time (ms) | 192.1 (31.24) | 220.9 (49.02) | $P = 0.036$ | $t = 2.18$ |
| Median duration (ms) | 52.8 (4.45) | 54.7 (5.16) | $P = 0.25$ | $t = 1.17$ |
| Median amplitude (°) | 9.5 (1.69) | 10.4 (1.88) | $P = 0.12$ | $t = 1.57$ |
| Median peak velocity (°/s) | 345.0 (83.41) | 349.4 (72.01) | $P = 0.87$ | $t = 0.17$ |
| Express saccades (frequency) | 7.0 (6.99) | 1.75 (2.32) | $P = 0.007$ | $t = 2.88$ |
| Trials with direction error (%) | 3.2 (5.89) | 1.72 (1.82) | $P = 0.34$ | $t = 0.97$ |

cells and superior colliculus involved in the generation of saccades are, indeed, affected in glaucoma.

Few studies have looked at eye movements in glaucoma. Other types of gaze-shifting eye movements such as smooth pursuit have not yet been studied. Among the gaze-stabilizing eye movements, optokinetic nystagmus has been investigated and shown to exhibit characteristic differences in glaucoma patients as compared with controls, eg, in pursuit eye movement and optokinetic nystagmus elicitation tasks.^{46,47} Other studies have examined the eye movements of glaucoma patients as either pedestrians or drivers. Gaze behavior has been shown to differ in a group of glaucoma patients compared with controls when crossing a street,⁴⁸ whereas eye-tracking data have shown changes in the pattern of eye movements performed by glaucoma patients compared with controls while viewing a video of a driving scene.⁴⁹ Further studies are needed to determine whether delayed saccades in glaucoma may contribute to these altered eye movements.

Certain pharmacological agents are known to alter saccade parameters. Patients on psychotropic medications, including benzodiazepines, antipsychotics, and anticonvulsants, which are known to decrease saccade velocity,³¹ were excluded in this study. This study shows that saccade reaction time is increased in glaucoma patients, and though topical treatment effects cannot be ruled out, no statistically significant difference in saccade reaction times ($P = 0.42$) was noted between glaucoma patients on topical β -blockers ($n = 8$) compared with those who were not ($n = 8$).

Glaucoma patients are known to be at increased risk for falls and motor vehicle collisions.⁵⁰ These tasks are dependent on a person's ability to attend to and respond to visual stimuli. Further studies are needed to determine whether delayed saccades observed in glaucoma patients have functional

implications and contribute to an increased risk for falls and motor vehicle collisions.

Overall, this study provides the first insight into saccade alterations in glaucoma. Further studies are needed to investigate the possible locations of neural damage in pathways and centers involved in saccades, to determine whether saccade changes correlate with disease development and/or progression, and to evaluate their possible functional impact in patients with glaucoma.

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Disclosure

The authors report no conflicts of interest in this work.

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