‘Saccadic Jitter’ Is a Quantitative Ocular Sign in Myasthenia Gravis

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Purpose. To examine the variability of saccadic peak-velocity amplitude relationships in myasthenic and nonmyasthenic ocular palsies.

Methods. The authors measured centrifugal saccades in nine patients with myasthenia gravis, nine patients with proven nonmyasthenic ocular palsies, and three normal subjects. Patients made repetitive saccades for 8 minutes. Saccades were analyzed at the start of the task, after 3 minutes of the task (fatigue), and at 1 minute after edrophonium. The authors fitted an exponential function to individual data and averages for amplitude bins and calculated the root mean square error of the curves. They then subtracted the root mean square error of curves fitted to bin averages from that of curves fitted to individual saccades: The result was an index of the variability of saccadic peak velocity, which they called saccadic jitter.

Results. Compared to those without myasthenia, the saccades of patients with myasthenia showed more variability in the initial and the fatigue periods. The change induced by edrophonium did not distinguish between the groups.

Conclusions. Signal detection analysis indicated that saccadic jitter has little value as a screening tool but is a useful diagnostic sign in 42% of myasthenic saccadic analyses.

Variability is a characteristic feature of the symptoms and signs of myasthenia gravis. Fluctuation in motor function occurs over long periods and shorter intervals, sometimes even hours or minutes.1 Some of this variability is caused by muscle fatigability. This reflects the normal decline of acetylcholine quanta released with repetitive nerve stimulation: in myasthenia gravis, because acetylcholine is less effective from reduced numbers of functioning postsynaptic receptors, the number of quanta eventually falls below a critical threshold for activation of muscle fibers, and weakness ensues.2 This reduced “safety factor” for neuromuscular transmission can be detected as a fall in the amplitude of the compound muscle action potential with repetitive nerve stimulation, which is now a standard diagnostic test for this disease.3 Ocular signs of fatigability include Cogan’s lid twitch,4 intrasaccadic fatigue,5 muscle paretic nystagmus,6-8 and saccadic fatigue with repetitive refixation.8-11

Another neurophysiologic test for myasthenia is single fiber electromyography.1213 This test assesses the transmission safety factor by measuring the variability in the timing between the responses of two muscle fibers belonging to the same motor unit when they have been activated by the patient or by nerve stimulation. In myasthenia and other disorders of the neuromuscular junction, there is an increase in the asynchrony of the two responses as well as more response failures. This moment-to-moment variability is termed jitter. A quantifiable behavioral parallel of this variability has not been described in ocular or other muscles.

Saccadic peak velocity can be related to saccadic amplitude by an exponential function in normals14 and in patients with myasthenic and nonmyasthenic palsies.1516 The “goodness of fit” of this function, as for any regression line, can be assessed by the root mean square error,14 which is an index of the difference between the observed peak velocities for given amplitudes and the peak velocities predicted for those amplitudes from the exponential function. Moment-
to-moment variability in the peak-velocity amplitude relationship of saccades will be reflected in this term. In this article, we examine whether the root mean square error of the saccadic peak-velocity amplitude relationship distinguishes between myasthenic and nonmyasthenic eye movements.

METHODS

Subjects

We studied three groups of subjects: nine myasthenic patients with ocular involvement, nine patients with proven nonmyasthenic palsies, and three normal controls. Patients with ocular or generalized myasthenia had both a compatible clinical syndrome and abnormal jitter on single-fiber electromyography, defined as mean jitter greater than 50 μsec in 20 fibers or more than 20 fibers having jitter greater than 45 μsec.13 Patients taking acetylcholinesterase inhibitors were tested after a period off medication. In ocular myasthenia medication was withheld for at least 24 hours before testing; patients with generalized myasthenia were tested in the morning before their first daily dose. The mean age of this group was 51.2 years (range, 19 to 76 years) with a mean duration of symptoms of 22 months (range, 0.75 to 81 months).

We tested patients with ocular motor palsies of known etiology (Table 1). These patients had either an imaged lesion or a syndrome incompatible with myasthenia (e.g., third nerve with pupillary involvement, idiopathic polyneuropathy). Graves’ disease was excluded because of its known association with myasthenia gravis. This group without myasthenia had a mean age of 51.6 years (range, 31 to 70 years) with a mean duration of symptoms of 5 months (range, 0.25 to 16 months). Three normal controls whose mean age was 33.6 years also were tested. Tenets of the Declaration of Helsinki were followed, informed consent was obtained from all subjects, and the aims and methods of this study were approved by the medical ethics committee of The Toronto Hospital.

TABLE 1. Features of Nine Patients Without Myasthenia

<table>
<thead>
<tr>
<th>Ocular Motor Defect</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Left VI palsy</td>
<td>Carcinomatous meningitis</td>
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<tr>
<td>Left VI palsy</td>
<td>Progressive multifocal</td>
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<tr>
<td>Right VI palsy</td>
<td>Multiple sclerosis</td>
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<tr>
<td>Left III palsy</td>
<td>Diabetes, pupil involving</td>
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<tr>
<td>Right III palsy</td>
<td>Intracavernous aneurysm</td>
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<tr>
<td>Right III palsy</td>
<td>Intracavernous aneurysm</td>
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<tr>
<td>Left III and VI palsy</td>
<td>Cavernous sinus fistula</td>
</tr>
<tr>
<td>All movements</td>
<td>Miller Fisher syndrome</td>
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<tr>
<td>All movements</td>
<td>Mitochondrial myopathy</td>
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We recorded eye movements with magnetic search coil oculography (CNC Engineering, Seattle WA). Recordings were made on a rectilinear inkjet polygraph, stored on magnetic tape, and digitized on-line at 200 Hz for analysis by interactive programs using a PDP 11/73 computer (Digital Equipment, Maynard, MA). Most subjects had binocular recordings. Subjects sat with their heads against a stationary backrest. An intravenous line with a slow infusion of normal saline was inserted into the antecubital vein before recording. Subjects watched a 0.25° helium-neon laser spot back-projected onto a semitranslucent screen 1 m away, either with the nonparetic eye occluded in patients with strabismus or viewing binocularly if both eyes were affected equally. The target stepped at predictable 1-second intervals between 20° left, primary, and 20° right over 8.5 minutes. With patients in whom vertical limitations of movement were the most prominent, 20° up and 20° down were used instead of left or right. At 4 minutes, 0.2 mg of edrophonium was injected, followed 30 seconds later by 0.8 mg when the initial dose was tolerated.

Analysis

The computer identified eye movements with velocities greater than 46.9° per second as saccades. Saccade onset was defined as the time when eye velocity exceeded 51.3° per second, and the end was defined as the time when velocity fell below this value. We analyzed saccades from three periods of 1-minute duration: at the onset of recording (initial period), after 3 minutes (fatigue period), and 1 minute after the final injection of edrophonium (edrophonium period). We studied only saccades away from the primary position (that is, centrifugal saccades) to isolate active muscle function because passive elastic restoring forces of orbital muscles and ligaments contribute to centripetal saccades.

Amplitudes were plotted against peak velocities in both directions for all saccades from a given period: a saccadic analysis refers to an analysis performed on all saccades of one eye in one direction. A curve was fitted to the data with a computerized nonlinear regression analysis,14 using the formula PV = Vmax (1 – e^−A/C) [PV = peak velocity, Vmax = asymptotic velocity, A = amplitude, C = constant].14 Root mean square error (RMSE) was calculated by averaging the square of the difference between the observed peak velocity for the amplitude of each saccade and the predicted peak velocity for that amplitude, as calculated by the equation.

We also performed a bin analysis by dividing a subject’s saccades into amplitude bins of 5° width (except for the first bin, which contained saccades of 2.5°
or less). We calculated the mean peak velocity for saccades within each bin and fitted exponential functions to these bin averages, and RMSE were derived for these bin averages (RMSE_{bin}). Bin averaging reduces the variability introduced by individual saccadic fluctuations and has been used to verify that the underlying relation of myasthenic saccades is still well described by an exponential function, despite the increased scatter of individual saccades. RMSE_{bin} indicates the normal variability in fitting the theoretical function to observed data. If an increased RMSE is not caused by individual saccadic fluctuations but to an inappropriately chosen theoretical function, then RMSE_{bin} also will be significantly elevated. The difference between the RMSE derived from individual points in the raw data and the RMSE_{bin} from bin averages can be considered to represent the contribution of variability of individual saccades (saccadic jitter [SJ]) to the overall RMSE. In other words, RMSE = RMSE_{bin} + SJ.

We used analysis of variance to determine whether there was a significant difference between the three groups (myasthenia gravis, nonmyasthenic palsies, and normal subjects) in any variable (RMSE, RMSE_{bin}, and SJ) in any time period (initial, fatigue, or edrophonium). Analysis of variance also was used to examine the change in SJ with edrophonium, as measured by subtracting the SJ from either the initial or the fatigue periods from the SJ of the edrophonium period.

We also constructed receiver-operating characteristics from empiric data as well as normal distributions derived from the means and standard deviations of the data. From these curves, we calculated d_{a}, a sensitivity index that measures the ability of a test to discriminate between two populations, and s, the slope of the curve in normalized space. This technique allows determination of sensitivities and specificities for a continual range of criteria, and construction of criteria with predetermined sensitivities or specificities. We measured the discriminative ability of our test at 95% sensitivity, 95% specificity, and determined the value at which sensitivity equalled specificity.

RESULTS

Figure 1 plots peak-velocity amplitude relationships for abducting saccades of the right eyes of (A) a patient with myasthenia and (B) another patient with a right VI nerve palsy. Raw data and bin averages are shown along with the exponential function fitted to the raw data. The myasthenic trace shows significant scatter of individual saccades around the curve, reflected in the large RMSE of 33.4, greater than the RMSE of 10 in the patient with the VI nerve palsy. However, the average peak velocities of amplitude bins in the myasthenic patient conform as well to the exponential function as do the average values for the patient with the VI nerve palsy. RMSE_{bin} of the myasthenic patient is 12.7, approximately the same as that of the patient with the VI nerve palsy (11.7).

The RMSE of the three groups are displayed in Figure 2, and the group means and standard deviations of RMSE from the initial, fatigue, and edrophonium periods are given in Table 2. The RMSE of the initial and edrophonium periods were significantly larger in the group with myasthenia compared with the normal group and the group without myasthenia. In contrast, the RMSE_{bin} did not differ between any group in any period (Table 2), confirming that the exponential function fit equally well to the average bin data from all three groups. We previously concluded from this that the underlying relation between saccadic amplitude and peak velocity could be adequately characterized by this exponential function for both myasthenic and nonmyasthenic palsies, in addition to normal subjects.

Saccadic jitter, defined as the amount of variability in RMSE remaining after subtraction of RMSE_{bin}, is displayed in Figure 3. It was significantly increased in initial and fatigue periods in patients with myasthenia compared to normals and patients without myasthenia.

The change in saccadic jitter after edrophonium can be represented by subtracting either the SJ from...
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FIGURE 2. Root mean square error (RMSE) of the exponential function fitted for data of individual saccades of a given patient, as in Figure 1, plotted for the three subject groups for the three different analysis periods. Each line connects the RMSE from initial (I), fatigue (F), and edrophonium (E) periods for saccades in one direction for one eye of one patient.

The initial period or the SJ from the fatigue period from the SJ of the edrophonium period: No significant difference was found.

We plotted receiver-operator curves for SJ from the initial and the fatigue periods. Figure 4 shows the points calculated from the raw data and the curves derived from normal distributions fitted to the patient data. The sensitivity indices ($d_+$) and the slopes of the curves in normalized receiver-operating characteristic space ($s$) are given in Table 2. The curves for SJ confirm the impression in Figure 3 that, at lower values of SJ, there is significant overlap between patients with and without myasthenia. As $z$ (true positives) approaches 1.65 (that is, 95% sensitivity), both curves approach the diagonal line, which indicates no discriminative ability. Where these tests have a sensitivity of 95%, the specificity is 5% or less. In other words, there is an equal chance for patients with or without myasthenia to meet the criterion. Thus, SJ from neither the initial nor the fatigue period is a useful screening sign for myasthenia.

On the other hand, when $z$ (false positives) is $-1.65$ (that is, 95% specificity), testing for SJ in the initial period will still have a sensitivity of 42%. Thus, almost half the myasthenic eye movements have a specific increase in SJ. The value of SJ corresponding to this criterion is 12.70. When this criterion is applied to the data illustrated in Figure 3, five of the nine patients with myasthenia had at least one SJ value above 12.70, whereas none of the three normal subjects and only one of the nine patients with nonmyasthenic palsies had an SJ value above this. Fatigue SJ has a lower sensitivity of 28% when specificity is set at 95%, corresponding to SJ of 16.67. Compromise criteria for which specificity equals sensitivity also can be chosen. For SJ from the initial period, sensitivity equaled specificity when both were 68%, corresponding to SJ of 5.39; for SJ from the fatigue period, sensitivity equaled specificity when both were 63%, corresponding to SJ of 6.99.

DISCUSSION

We found that the variability of the peak-velocity amplitude relationship of saccades (RMSE) was increased in patients with proven myasthenia gravis, in comparison with patients with proven nonmyasthenic palsies. Because the variability in the fit of the curve to the average peak velocities of saccadic amplitude bins (RMSE$_{bin}$) did not differ between the two patient groups and the normal subject group, we concluded that the neural process relating saccadic amplitude to peak velocity conformed to an exponential function in all three groups. Thus, the increase in RMSE in myasthenia was not caused by the use of an erroneous function to characterize the relationship. Rather, increased variability was caused by increased scatter of the data around the mean position of the curve. We characterized this scatter by subtracting RMSE$_{bin}$ from RMSE. This value we called saccadic jitter, which represents the moment-to-moment variability in the saccadic peak-velocity amplitude relationship. It differs from electromyographic jitter (the asynchrony in muscle fiber action potentials of a motor unit on single fiber electromyography) in that SJ reflects variability in the group action of many muscle fibers and motor units, whereas electromyographic jitter represents variability of muscle fibers within one motor unit. Nevertheless, both increased saccadic jitter and increased electromyographic jitter reflect the tenuous nature of neuromuscular transmission in myasthenia gravis.

This variability might be easier to detect in saccadic eye movements than in other muscles for a number of reasons. First, current technology allows saccades to be quantified more accurately than movements of any other muscle. Second, 70% or more of ocular motor neurons are active even when the eye is at rest in primary position; abducens motor neurons, for example, have firing rates of 30 to 230 spikes/second in this position. Moreover, during saccades, firing rates can reach 800 spikes/sec, tending to saturate for saccadic amplitudes of more than $10^°$. In other muscles, firing rates as low as 5 to 20 spikes/second lead to depression of quantal release of acetylcholine, a depression that leads to weakness in myasthenia because of the reduced safety factor for neurotransmission. The high firing rates in ocular motor
neurons at rest and during activity suggest that extraocular muscles are especially prone to neurotransmission failure in myasthenia.

Saccadic jitter in myasthenia was significantly different from that of patients with nonmyasthenic ocular palsies at the beginning of testing and also after 3 minutes of repetitive saccades. However, at lower values of SJ, there was considerable overlap of data from patients with and without myasthenia. This overlap, coupled with the difference in standard deviations of the two groups, meant that there was no criterion that was highly sensitive for myasthenia without an unacceptably high false-positive rate. However, it was possible to choose a criterion that was highly specific for myasthenia and still detected almost half of myasthenic saccadic analyses and more than half the patients tested. Therefore, testing for saccadic jitter is not a useful screening procedure for myasthenia gravis, but a high SJ value is a good diagnostic sign for this disease.

![Graphs showing saccadic jitter (SJ) for initial and fatigue periods](image_url)

**FIGURE 3.** Saccadic jitter (SJ), as defined in Figure 1 and Table 2, for the three subject groups. (A) SJ from the initial period. Dotted line indicates the criterion required for 95% specificity (SJ = 12.70; see Results). Note that a third of myasthenic saccadic analyses lie above this line. (B) SJ from the fatigue period. Diamonds are individual points. Bars indicate group mean ± 1 SD.
Intersaccadic variability in peak velocity profiles in myasthenia were found by Sollberger et al.\(^2\), however, they did not describe a quantifiable abnormality, and they did not study control patients. Variability in saccadic peak-velocity amplitude relationships has also been described in normal subjects.\(^2\)\(^3\)\(^4\)\(^6\)\(^7\)\(^8\) In part, this derives from the system’s ability to vary velocity inversely with duration to achieve saccades of the same amplitude\(^2\)\(^9\): \(PV(D) = kA\), where \(PV\) is peak velocity, \(D\) is duration, \(A\) is amplitude, and \(k\) is a constant \((k \approx 1.65)\).\(^5\) Therefore, it is imperative that studies of abnormalities in myasthenic eye movements be accompanied by appropriate control patients, in particular those with conditions likely to be part of the differential diagnosis of ocular myasthenia. Also, the criteria for defining myasthenia and nonmyasthenia must be strict given the diagnostic uncertainty in myasthenia gravis, especially with purely ocular forms of the disease. Our study demonstrates that patients with myasthenia have an increased variability in the saccadic peak-velocity amplitude relationship that can be quantified and used as a specific diagnostic sign of disease.

**Key Words**

myasthenia gravis, ocular motor palsy, saccades, variability

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**References**


**FIGURE 4.** Receiver-operating curves for saccadic jitter from the initial period (solid line, solid diamonds) and from the fatigue period (dashed line, empty diamonds). Coordinates are plotted in \(Z\) (normalized) space, where 0 indicates the mean \((P = 0.5)\), and 1 indicates 1 SD away from the mean \((P = 0.64)\). The dotted diagonal line indicates equal probability of true and false positives (no discriminative power). Note that both curves approach the diagonal for high probabilities of true positives, indicating that these tests would not be good screening tools.