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Myasthenia Gravis: Dynamic Changes in Saccadic Waveform, Gain, and Velocity

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The effects of refixation fatigue, maintained gaze fatigue, and intravenous edrophonium on saccadic waveform, gain, and velocity were studied in 10 patients with ocular myasthenia gravis. Refixation fatigue was minimal. Gaze maintenance had four separate but differing effects on waveform and gain; normalized peak velocities did not decrease. Edrophonium caused hypermetria and increased gain but normalized peak velocities were either unchanged or decreased. These effects represent, in part, selective impairment of the tonic, as distinct from phasic, fibers in the extraocular muscles and compensatory increase in central saccadic gain induced by the muscle weakness.

INTRODUCTION

In the previous paper (14) we presented and analyzed the complex waveforms of saccadic eye movements in patients with ocular myasthenia. We herein report our studies of the fatigue effects of both repetitive

Abbreviations: n—normal; s—slow; o—overshoot with glissadic return; u—undershoot with glissadic return; do—dynamic overshoot; m—multiple, closely spaced saccades; dd—discrete deceleration; O—orthometric; HR—hypermetric; HO—hypometric; SEM—slow eye movement; SP—saccadic pulse; DSP—double saccadic pulse; SWJ—square wave jerk; MSWJ—macro square wave jerk; MSO—macro saccadic oscillation; r—ramp drift; p—pendular drift; t—triangular drift; e—exponential runaway; c—central; P—peripheral; T—target position; pos—eye position; vel—eye velocity.

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refixation and maintained gaze, and the effects of the administration of edrophonium on myasthenic saccades. Changes in saccades reflecting peripheral and secondary central mechanisms were demonstrated and analyzed in an attempt to elucidate the roles in saccadic control of the various measures of system performance (i.e., vision, efference copy, and proprioception).

METHODS

This study was an extension of that previously described (14) using the same instrumentation and patients. Following the repetitive refixations between eccentric targets described in the previous study, the subjects maintained fixation on a target 20° (or for those with limited excursions, an angle well within the upper limits of amplitude ability) to the right for 3 min. At the conclusion of this gaze-holding segment they again alternated fixations between the three targets (eccentric left, center, and eccentric right) for an additional 3 min. This was followed by 3 min of maintained leftward gaze and an equal amount of refixations. Edrophonium (7 to 10 mg) was then administered intravenously as the patient continued the refixations for several additional minutes.

RESULTS

Refixations. There was no significant change in the saccadic metrics or trajectory during any of the three refixation tasks for each patient. There was considerable intrasubject gain (saccadic amplitude ÷ target amplitude) variation throughout the refixation time interval. Comparison of initial gains with those at the end of the interval revealed either no change or only a slight decrease. Velocities, normalized for actual rather than intended amplitudes, did not change.

Fixation Stability during Maintained Gaze. Six of the ten patients developed nystagmus during the 3 min of maintained eccentric deviation (patients 2, 4, 5, 7, 8, 10). The slopes of the slow phases of the nystagmus ranged from linear to a decreasing-velocity exponential. The fast phases showed dynamic overshoots (do).[2] Double saccadic pulses occurred in patients 2, 4, and 8.

The instability during gaze holding of patient 8 is illustrated in Fig. 1. During right gaze, a direction-reversing nystagmus with dynamic overshoots occurred for a period of about 20 s. Later, a high-frequency nystagmus of low amplitude appeared. During maintained gaze to the left

[2] See accompanying paper (14) for a complete explanation of the symbols used to describe waveform metrics, trajectories, and intrusions.

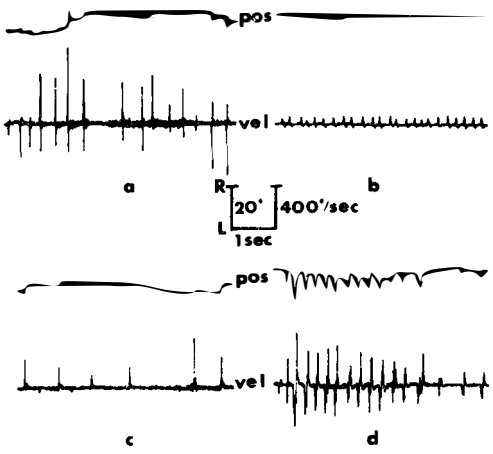

FIG. 1. Eye position (pos) and velocity (vel) record of patient 8. During maintained right gaze: a—direction-reversing nystagmus and b—high-frequency, low-amplitude nystagmus. During maintained left gaze: c—right-beating, low-frequency nystagmus and d—double saccadic pulses. All Figures show the fixing eye.

(20°), a right-beating nystagmus with a long slow phase occurred followed by a series of double saccadic pulses.

Waveform Changes after maintained Gaze and Edrophonium. Three

TABLE 1
Waveform Changes[a]

					After maintained								
		Initial			Right gaze			Left gaze			After edrophonium		
Patient	Saccadic direction	HO	O	HR	HO	O	HR	HO	O	HR	HO	O	HR
1													
(2–4)	O→R	100	—	—	100	—	—	100	—	—	100	—	—
	L→O	100	—	—	100	—	—	100	—	—	100	—	—
	O←R	100	—	—	100	—	—	100	—	—	100	—	—
	L←O	100	—	—	100	—	—	100	—	—	100	—	—
6													
(5, 8, 9)	O→R	100	—	—	100	—	—	—	—	100	—	—	100
	L→O	100	—	—	21.3	—	78.7	100	—	—	—	—	100
	O←R	55.6	—	44.4	80	—	20	—	—	100	—	—	100
	L←O	100	—	—	—	—	100	66.7	—	33.3	—	—	100
7													
(10)	O→R	58.8	41.2	—	83.3	—	16.7	100	—	—	66.7	22.2	11.1
	L→O	94.1	—	5.9	86.6	6.7	6.7	90.5	—	9.5	71.4	—	28.6
	O←R	50	25	25	53	23.5	23.5	56.5	17.4	26.1	—	33.3	66.7
	L←O	100	—	—	82.4	17.6	—	90.9	—	9.1	16.7	83.3	—

[a] Values are percentages of occurrence of the waveform. HO—hypometria. O—orthometria. HR—hypermetria. Patients 1, 6, and 7 are typical of their subgroups.

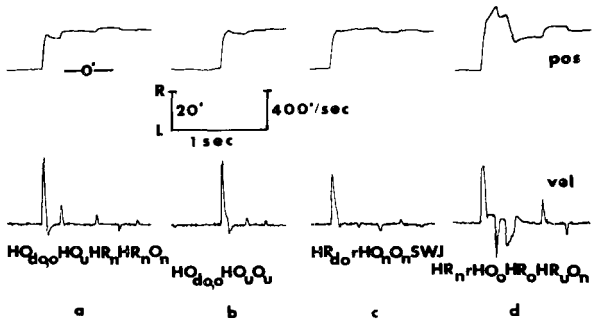

FIG. 2. Eye position (pos) and velocity (vel) records of patient 9 showing the changes of saccadic waveform. a—initial, b—after maintained right gaze, c—after maintained left gaze, and d—after edrophonium administration. For waveform abbreviations see (14).

different kinds of waveform changes occurred and are described in Table 1 which details the percentrages in three patients, each typifying a subgroup.

(i) The initial hypometria (HO) of saccadic eye movements remained essentially unchanged after maintained gaze and after the administration of edrophonium (patients 1 through 4); patients 3 and 4 did make several hypermetric movements after edrophonium, however.

(ii) This group showed clearly identifiable effects of gaze holding. One effect, after maintained gaze to the left, was hypermetric (HR) saccades to the right; right gaze holding caused hypermetric saccades to the left. The hypermetria occurred predominantly in movements from primary position (0°) in the direction opposite the previous gazeholding and was not the dominant pattern for similarly directed movements toward the primary position. In this subgroup, edrophonium caused hypermetric saccades in all directions of gaze. An example of the changing metrics and dynamics of the movements of patient 9 are shown in Fig. 2.

(iii) There were two additional patients (7 and 10) in whom only a small percentage of change occurred after maintained gaze and edrophonium.

Gain Changes after Maintained Gaze and Edrophonium. Gain changes after maintained gaze were not uniform (Table 2). Patient 2 is somewhat representative of the four patients who remained hypometric in Table I. The other four patients in Table 2 were from the group that showed identifiable gaze-holding effects. In patient 2, saccades in the direction of the previous gaze holding usually showed a decrease in gain. The other patients manifested four distinct changes which will be described in the Discussion. In these four patients, the gains increased after edrophonium. Figure 3a shows the variation in gain of patient 6, including the postedrophonium increase.

A question could be raised about the diagnosis of ocular myasthenia in

TABLE 2

Gain Changes[a]

Patient	Saccadic direction	Initial	After maintained		After edrophonium
			Right gaze	Left gaze	
2	O → R	0.63	0.54	0.64	Not calculated
	L → O	0.87	0.76	0.99	
	O ← R	0.87	0.86	0.78	
	L ← O	0.76	0.84	0.76	
5	O → R	0.75	0.65	0.82	1.14
	L → O	0.93	1.04	1.08	1.30
	O ← R	0.97	1.21	0.95	1.55
	L ← O	0.85	0.94	0.99	1.45
6	O → R	0.75	0.74	1.31	1.13
	L → O	0.71	1.02	0.77	1.28
	O ← R	0.97	0.81	1.28	1.15
	L ← O	0.82	1.36	1.04	1.20
8	O → R	1.01	1.03	0.97	1.18
	L → O	1.05	1.10	1.09	1.19
	O ← R	0.91	1.03	0.91	1.17
	L ← O	0.92	0.96	1.01	1.25
9	O → R	0.94	0.91	0.93	1.14
	O ← R	0.24	0.47	0.30	0.48

[a] Saccadic amplitude ÷ target amplitude.

those patients who did not show a change after edrophonium. Each of these patients had a demonstrably positive edrophonium test witnessed by at least one of the investigators prior to being included in the study. In some, the positive response was limited to an eyelid.

Velocity–Amplitude Relationship. The normalized velocity–amplitude relationships during the initial refixations, refixations after maintained gaze, and after the administration of edrophonium are shown in Table 3 for five patients. Normalization is for actual rather than intended amplitude. The numbers in Table 3 are the ratios of the patients' peak velocities to those of normals (13) for equivalent amplitude movements. Patient 2 is representative of the first subgroup of Table 1; patients 5, 6, and 8 are from the second subgroup; and patient 10 is from the third subgroup. There was no drug effect on gain or waveform in the first subgroup, and in the third subgroup the effects were variable and unpredictable (see Table 1).

Most patients had "super normal" values (i.e., greater than 1.00) during the initial refixations; this was independent of subgroup. Those values less

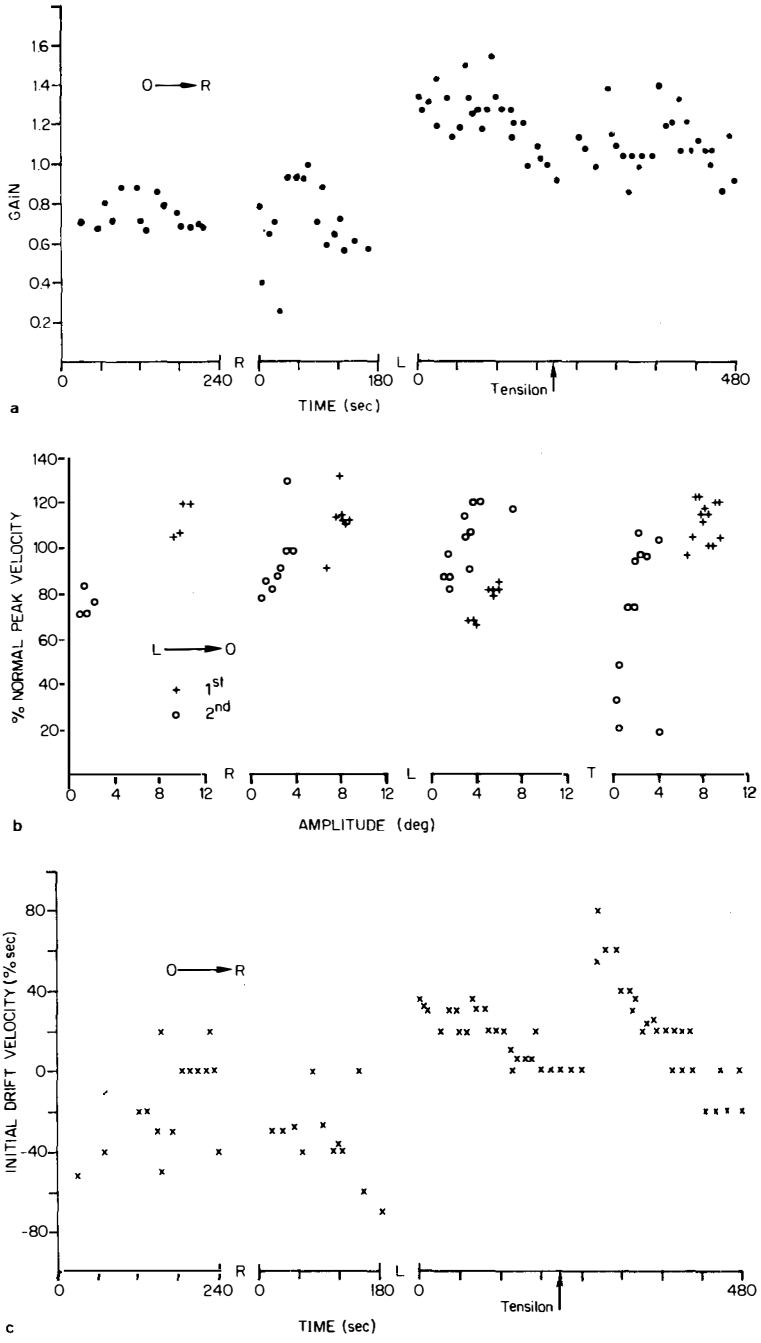

FIG. 3. Changes in a—gain, b—velocity–amplitude, and c—initial drift velocity of patient 6. Movement directions are shown.

TABLE 3

Velocity–Amplitude Relationship[a]

Patient	Saccadic direction	Initial	After maintained		After edrophonium
			Right gaze	Left gaze	
2	O → R	1.45	1.25	1.22	
	L → O	1.64	1.88	1.60	
	O ← R	1.82	1.60	1.62	
	L ← O	1.78	1.48	1.21	
5	O → R	1.10	1.13	1.19	0.77
	L → O	1.11	1.10	1.17	0.80
	O ← R	1.72	1.71	1.70	1.24
	L ← O	1.34	1.39	1.28	1.0
6	O → R	1.16	1.30	1.21	0.98
	L → O	1.13	1.11	0.76	1.12
	O ← R	0.99	0.81	1.20	1.01
	L ← O	1.28	1.15	1.15	0.98
8	O → R	0.66	0.60	0.69	0.62
	L → O	0.96	0.83	0.99	0.91
	O ← R	0.83	0.74	0.72	0.85
	L ← O	0.71	0.67	0.63	0.70
10	O → R	1.38	1.23	1.21	
	L → O	1.38	1.29	1.18	
	O ← R	1.30	1.25	1.39	
	L ← O	1.33	1.14	1.22	

[a] Normalized.

than 1.00 reflected trajectory peculiarities, such as discrete decelerations, which prevented development of high-peak velocities. Gaze-maintenance fatigue did not result in any systematic variation of normalized peak velocities either within a subgroup or in relation to gain changes. In these patients in subgroup ii who had initially increased velocities, edrophonium produced a decreased velocity normalized for the increased amplitude (i.e., higher gain—Table 2). For those whose velocities were initially normal or below, edrophonium did not produce any significant velocity change (Fig. 3b).

In patients 3 and 9, not shown in the table, there was an increase in the velocity–amplitude relationship in particular directions after giving edrophonium although the eye movements remained hypometric. Thus, the only instances of edrophonium causing an increased normalized peak velocity were for those where a small increase in gain resulted which did not overcome the initial hypometria.

TABLE 4

Initial Drift Velocity[a]

Patient	Saccadic direction	Initial	After maintained		After edrophonium
			Right gaze	Left gaze	
6	O → R	−16.2	−33.8	+18.4	+31.6
	L → O	−54.9	−30.6	+11.4	+54
	O ← R	−30	+8.4	−27.2	+47
	L ← O	−48.8	+2.0	−24.4	+44.6
9	O → R	−38.4	−22.8	−16.4	+75.2
	R → O	+75.1	−12	+57.6	+66

[a] In degrees per second. The direction of drift relative to the accompanying saccade is indicated by a plus (same) or a minus (opposite) sign.

Initial Drift Velocity. In trajectories which overshoot or undershoot (indicating a pulse–step mismatch) the rapid portion of eye movement is followed by a slow drifting movement (glissade). The initial portion of the drift velocity is a measure of the tonic muscular force relative to the phasic force. Table 4 shows the initial drift velocities of patients 6 and 9 in degrees per second with a sign dependent on the direction of drift relative to the accompanying saccade (i.e., plus indicates an undershoot trajectory with drift in the direction of the saccade). A measure of the relative effects of the drug on tonic and phasic fibers is obtained by comparing the sign and magnitude of the initial drift velocity after edrophonium with the initial value. The postedrophonium changes of the initial drift velocity (Table 4) were most distinct in these patients of subgroup ii from Table 1.

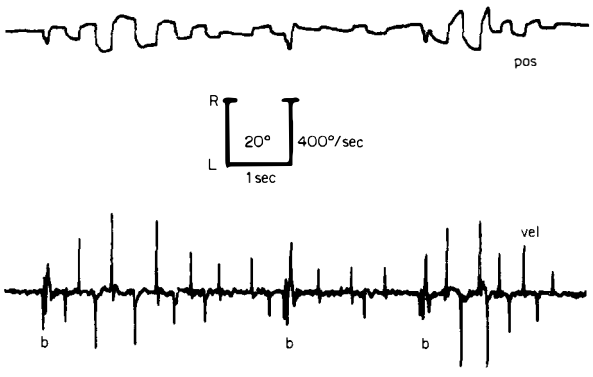

FIG. 4. Eye position (pos) and velocity (vel) record of patient 6 after edrophonium administration showing macro saccadic oscillations.

Pronounced changes of the initial drift velocity occurred in patient 6 after administration of edrophonium (with a drift to the contralateral side for a few seconds followed by a steep increase in ipsilateral drift velocity) (Fig. 3c). The effects of maintained-gaze fatigue, even in these two patients chosen for the pronounced effect of edrophonium, was highly variable in both magnitude and direction as was normalized peak velocity (Table 3).

Additional Effects of Edrophonium. The following waveforms occurred after edrophonium: macro saccadic oscillations (MSO) in patients 6 (Fig. 4) and 9; nystagmus in patient 3; hypermetria (HR) in patients 5 through 9; saccadic pulses (SP) in patient 2; and glissades and square wave jerks (SWJ) in patients 6 and 9.

DISCUSSION

Saccadic Velocities. The "supernormal" saccadic velocities in ocular myasthenia gravis confirm the findings of Yee *et al.* (18) and support their conclusion that phasic muscle fibers may be relatively spared in this disease.

Initial Refixation Fatique. The lack of fatique effect (consistent change in waveform, gain, or normalized peak velocity) during 3 min of refixation is in agreement with some (12, 18) but not all previous studies. In one such report (4), the investigators used a computer program to extract variables of interest from the data. Whereas this is reliable with simple waveforms such as orthometric saccades or vestibular nystagmus, we doubt that any computer program working with low-pass filtered signals (35 Hz) could identify accurately the components of the extremely complex waveforms in myasthenia gravis (14) and obtain true gain and velocity values. It is possible that the lower amplitudes of refixations might account for the discrepancy performed by our patients or that refixation fatigue does occur, as shown for a single patient (17), but uncommonly.

Maintained Gaze Fatigue. This occurred in 6 of the 10 patients who developed nystagmus with slow phases ranging from linear [similar to physiological end-point nystagmus (2)] to a decreasing-velocity exponential [muscle–paretic nystagmus similar to gaze–paretic nystagmus (7)]. Linear slow phase nystagmus at small lateral gaze angles might be equivalent to the physiological end-point nystagmus which appears in normal subjects at greater gaze angles. To overcome the peripheral deficit in myasthenia gravis, the innervation required to maintain a small eccentric gaze position is greater than normal and may equal the innervation which, in a normal, would be associated with the larger gaze angles at which one finds end-point nystagmus. A small (long time constant) "leak" in the neural integrators or the plant would produce small-amplitude nystagmus with linear-appearing slow phases. A larger leak in the plant would result in a

faster decay of muscle force and muscle–paretic nystagmus with a decreasing-velocity slow phase.

The dynamic overshoots and double saccadic pulses during maintained lateral gaze might be secondary to proprioceptive feedback sensing fatigue and stimulating the pulse generators in an attempt to overcome the effects of fatigue. The direction-reversing nystagmus that occurred in one patient during maintained gaze is not satisfactorily explained.

Refixations after Maintained Gaze. The four patients (Table 1) who demonstrated little or no response in the saccadic eye movement waveforms after maintained gaze, or later after edrophonium administration, all had long-standing ocular myasthenia. In those remaining six patients, four distinct categories of changes could be identified after maintained lateral gaze: (i) Muscle fatigue—hypometria in the direction of gaze holding. (ii) "Rest-effect"—hypermetria in the direction opposite of gaze holding. (iii) Increased saccadic gain—hypermetria in the direction of gaze holding. (iv) "Paradoxical response"—hypometria in the direction opposite of gaze holding.

Muscle fatigue induced in the agonists during maintained gaze explains the hypometria of saccades in the direction of the previous gaze holding (Table 1, patient 6, O → R, after maintained right gaze).

Both the agonist and antagonist muscles must be considered in the metrics of the "rest effect" (Table 1, patient 6, L ← O, after right gaze and O → R after left gaze). Because the agonist is completely inhibited during the saccade, rest of the agonist alone can affect the saccadic trajectory. However, when the pulse of innervation is over, both agonist and antagonist muscles receive tonic innervation and the resulting metrics depend on the "rest effect" of the agonist relative to the fatigue of the antagonist. These factors are additive; both a rested agonist and a fatigued antagonist could cause increased hypermetria in a saccade made in the direction opposite that of previous gaze holding. Reversal of initial drift velocity after gaze holding (Fig. 3c) is also explained by the "rest effect."

Short-term increased saccadic gain manifested by greater hypermetria in the direction of previous gaze holding (Table 1, patient 6, L → O, after right gaze and O ← R and L ← O, after left gaze) might, like dynamic overshoots and double saccadic pulses, be a response to proprioceptive information from a fatiguing agonist during maintained gaze. Centrally mediated gain changes require several days to develop (1).

Explanation for the "paradoxical response" of increased hypometria in a direction opposite to that of maintained gaze (Table 1, patient 6, O ← R, after right gaze and L → O, after left gaze) is more difficult. During maintained gaze, both rest of the soon-to-be agonist muscle and fatigue of the soon-to-be antagonist muscle should lead to hypermetria and the observed hypometria was unexpected. It is possible that the previously

explained increased gain in the direction of gaze holding may be linked to an effective decreased gain in the opposite direction. The fact that the "paradoxical response" occurred only in movements which returned the eyes to center (O ← R after right-gaze and L → O, after left gaze for patient 6, Table 1) and was associated with increased gain in the same centering movements (L → O, after right gaze and O ← R, after left gaze for patient 6, Table 1) supports that hypothesis.

In no instances did the maintained gaze reduce the normalized peak velocities of the subsequent refixations.

Edrophonium Effect. The four patients (Table 1) who did not respond to edrophonium all had long-standing myasthenia. As shown in Tables 1 and 2, the main effects of edrophonium administration were hypermetria and increased saccadic gain (Fig. 2d, Fig. 3a). The gain increase establishes the contribution of central nervous system plasticity in myasthenia gravis, as noted previously by others (16, 17). Central gain increases in response to the weak myasthenic extraocular muscles and this gain increase is manifested when the muscle defect is transiently alleviated by edrophonium. The fact that most patients exhibited hypometric saccades prior to edrophonium reflected the inability of saccadic plasticity to overcome totally the often variable peripheral deficit. The variability of the edrophonium effects is probably a function of both varying muscle responsivity and also intersubject differences in gain plasticity. When the gain was sufficiently increased, as in patient 6 (Fig. 4), edrophonium administration resulted in a high-gain instability of the saccadic system. This produced macro saccadic oscillations in addition to hypermetria (3).

Despite increased gain, we found either a decrease or no change in normalized peak velocity following edrophonium (Table 3). The only exception to this was in particular directions for two patients. The constancy of peak velocity again reflects a more pronounced effect of myasthenia gravis on tonic fibers (18) and a similar preferential edrophonium responsivity of these fibers. A dramatic indicator of the effects of edrophonium, in some patients, was an increase in the initial drift velocity (Table 4 and Fig. 3c), another reflection of tonic activity. For patient 6 and the O → R movement of patient 9, edrophonium had a more dramatic effect on the tonic than the phasic fibers since overshooting trajectories became undershooting. Morphological studies in ocular myasthenia gravis have failed, to date, to yield distinct differences between phasic and tonic fibers in eye muscles (10, 11). If receptors of both phasic and tonic muscles were equally involved in ocular myasthenia gravis, the normally greater safety factor of the phasic fibers (6) could account for preferential clinical dysfunction of the tonic fibers. Except for a single case presentation (17), none of the previous studies reporting an increase in saccadic velocity after administration of edrophonium was normalized for

increased saccadic size (4, 9, 16). In one, closely spaced saccades were not analyzed individually (9). In another (4), the one velocity–amplitude curve indicating an increased velocity cannot be properly evaluated without waveform information which is lost in the computer algorithm used to analyze the data. This may have prevented the plotting of the true amplitudes of the individual saccades.

Proprioception. We have proposed proprioceptive feedback to explain saccadic intrusions during maintained gaze fatigue and increased saccadic gain after maintained gaze. In the previous paper (14) we concluded that proprioceptive feedback was the most viable explanation for some of the saccadic waveforms. The literature on extraocular muscle proprioception is extensive and contradictory (8). There is no doubt, however, that extraretinal position sense from the eyes reaches consciousness in humans (15) but the physiologic role of this feedback on the control of eye movements has been uncertain (5). In a system so dependent on visual feedback, the role of proprioception has been masked resulting in this lack of agreement. Myasthenia gravis has, however, provided a situation where intrasaccadic failure at the ocular motor plant and the increased central gain secondary to the plant deficit eliminate vision and efference copy as possible measures of this failure. Central generation of multiple, closely spaced saccades to overcome the hypometric muscle response is most probably due to information fed back from the muscle via fast proprioceptive pathways. Vision is suppressed during the saccade and the efferent signal is higher than normally required (as evidenced by the edrophonium response). We hypothesized that under these unique conditions the normally tertiary proprioceptive information assumes a dominant role in the saccadic response.

In summary, our study confirms the previous report of "supernormal" saccadic velocities (18) in ocular myasthenia gravis which indicates a relative sparing of phasic muscle fibers. No significant fatigue resulted from repetitive refixations. Maintained eccentric gaze, however, caused fatigue manifested by nystagmus and saccadic intrusions. After gaze maintenance, the saccadic waveforms and gains, but not normalized peak velocities, were often changed. The changes reflect a variable admixture of rest and fatigue on the agonist and antagonist muscles. The major effect of edrophonium was hypermetria, an unmasking of increased central gain consequent to the myasthenic deficit. This provides another example of central adaptation in addition to the examples presented in the preceding paper (14), which were deemed responsible for the complex waveform changes.

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