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Myasthenia Gravis: Saccadic Eye Movement Waveforms

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The study of the refixational saccadic eye movements of 10 patients with myasthenia gravis revealed large intra-and intersubject variability and a diversity of waveforms necessitating the development of a recursive classification scheme which separated the dynamics of the eye's trajectory and the metrics of the completed movement. The waveforms reflected the admixture of the primary peripheral myasthenic deficit and compensatory central adaptation to it. Whenever possible, the peripheral and central factors were identified for each waveform component. The prevalence of multiple, closely spaced saccades and dynamic overshoots in this population coupled with their absence in other peripheral disorders, suggests a possible role for proprioception in ocular motor control.

INTRODUCTION

Intracellular recordings from abducens and oculomotor motoneurons in alert monkeys (13, 18, 19) indicated that a pulse increase in neuronal firing frequency produced saccadic eye movements and a step change (above the

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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steady-state baseline firing frequency of the primary position) was responsible for stopping and maintaining the eyes at a new eye position. Thus, the pulse–step is the innervational sequence underlying saccadic eye movements. Recently, Sindermann *et al.* (24) showed that braking is helped by a pulse in the antagonist nerve at the termination of the saccade. The nature of the pulse–step motoneuronal firing patterns may be inferred from careful study of the saccadic waveform. Such analyses were made in normal subjects [3, 6] who often make dysmetric saccades (26, 27), as well as in patients with central (8, 10, 14, 15, 25) or peripheral nervous system disease involving extraocular movements (1, 16). Although great care must be taken in the latter cases, some inferences are possible.

Of the many published eye movement studies designed to assist in the diagnosis of myasthenia gravis, few have included waveform analysis. Schmidt (20, 21) described selected eye movement patterns explained on the basis of muscle fiber fatigue. Most saccades were found to be hypometric (which he attributed to insufficient phasic innervation). Yee *et al.* (28) compared saccades of 10 myasthenic patients and 8 patients with other causes of ophthalmoparesis. All the myasthenic patients studied were capable of making at least a 20° horizontal excursion. Their major finding in the myasthenic patients was a faster than normal initial saccadic segment which could not be sustained. The 20° eye movements often were hypermetric (overshot) whereas 40° movements began rapidly but terminated with a slow "glissadic"[2] segment. Those authors interpreted their findings as follows: to compensate for myasthenic extraocular muscles the brain stem saccadic mechanisms generated pulses with excessive firing frequencies. This accounted for the hypermetria of small saccades in addition to the high velocity of both small saccades and the initial portions of larger saccades. With larger saccades, the myasthenic muscles could not sustain their maximum firing rate and the saccadic velocity rapidly decreased, creating the terminal glissadic portion.

We herein report the investigation of saccadic eye movements in 10 ocular myasthenic patients. Our analysis of saccadic waveform, considerably more detailed than previously undertaken, should allow more accurate insight into the central strategies used by the saccadic system in response to myasthenic muscular malfunction. In the accompanying papers we report on the dynamic changes in saccadic waveform, gain, and velocity induced by maintained gaze and edrophonium chloride adminis-

[2] The term glissade was introduced to describe a slow terminal portion of disconjugately dysmetric saccades in normal subjects (27). It has since been explained on the basis of pulse and step mismatches (6). We will be using the term descriptively to designate the slow terminal portion of the saccade without necessarily implying a mechanism of central firing frequency mismatch or ocular muscle fatigue.

tration (22), and modeled the saccadic eye movement system with provisions for extraocular muscle deficits (2).

SUBJECTS

Twelve consecutive patients with ocular myasthenia gravis were studied but 2 were eliminated because of technical recording problems. The clinical features of the 10 patients are in Table 1. The duration of the disease varied from several weeks (patient 7) to 50 years (patient 3). No patient had thymectomy or steroid therapy. Five patients were either not taking anticholinesterase medication or had not had any medication on the day of the study. Five patients had their last mestinon dose from 2 to 7 h prior to the recording. The limitations of eye movement excursions varied from minimal (patient 7) to severe (patient 1).

METHODS

Horizontal eye movement recordings were made by using infrared oculography, with a system bandwidth (position and velocity) of DC to 100 Hz (Biometric Model 200 and a rectilinear Beckman Type R Dynograph). The patients were seated in a modified dental chair with head brace and chin rest. Targets were red light-emitting diodes mounted on an arc 1.14 m from the patient. Recordings were carried out in subdued light. The amplitude of the calibration refixations were dependent on the amount of

TABLE 1

Myasthenia Gravis Patient Data

Patient	Sex	Age (years)	Disease duration (years)	Last dose (h)	Motility (Abd./Add.)	
					Right eye	Left eye
1	F	13	5	4	3°/2°	3°/8–10°
2	M	79	10–12	2	45°/50°	50°/55°
3	M	72	50	3	20°/15°	5°/3°
4	M	46	20	5	40°/35°	40°/30°
5	M	57	20	>12	Ptosis	15–20°/10–15°
6	M	17	1/2	>12	Ptosis	10–15°/10°
7	F	15	<1/12	None	Full	Slight lateral rectus paresis
8	M	64	1/2	>12	35°/50°	40°/55°
9	F	19	1	>12	Ptosis	50°/10°
10	M	60	10	7	Slight medial rectus paresis	Full

the patient's eye muscle pareses (±20° or less). Patients made refixations from center to eccentric targets in both directions for approximately 3 min at a rate of approximately one movement per 2 s. In four patients a monocular recording was necessary because of uniocular ptosis of the contralateral eye; in the other six, simultaneous binocular recordings were made. In case 10, problems with recording the paretic right eye forced us to record the nonparetic left eye with the right eye fixating the targets; the waveform of the right eye was inferred from that of the left (binocular recordings in the other patients established waveform equivalence in the two eyes within their useful range). We analyzed the waveform and velocity of all saccades made by the subjects. In the accompanying paper (22) the effects of fatigue and recovery during and after gaze holding, and the effects of edrophonium chloride on the waveforms are presented.

RESULTS

The saccadic waveforms in our myasthenic patients were so numerous and complex that the creation of a new saccadic metrics and trajectory nomenclature was necessary if we were to achieve meaningful functional descriptions. Our classification scheme attempts to preserve existing concepts and nomenclature while making new additions only as required for specificity in delineating pathological patterns.

Saccadic Metrics and Trajectory Classification. Based upon pulse–step variability, the most extensive classification of the possible configuration of saccades in response to target displacement listed 13 distinct possibilities, 11 of which were found in a study of normal subjects (3, 6). Their classification did not include the numerous patterns exhibited by myasthenic patients which necessitated separation of the metrics [accuracy of the initial saccade, i.e., orthometric, hypermetric (overshoot) or hypometric (undershoot)] from the description of its trajectory. The corrective movements following hyper- or hypometric initial saccades are also variable and their patterns require the same description of metrics and trajectory.

The various trajectory types are listed and explained below: Normal (n) implies normal velocity–amplitude and duration–amplitude relationships for the *actual* magnitude of the saccade independent of its *desired* magnitude. Slow (s) implies a pathologically slow (lengthy) saccade for its magnitude (again, the metrics of the saccades are irrelevant in these descriptions). Overshoot with glissadic return (o) implies a pulse–step mismatch (neuronal and/or muscular), pulse greater than step. Undershoot with glissadic tail (u) implies a pulse–step mismatch (neuronal and/or muscular), pulse less than step. Dynamic overshoot[3] (do) implies an

[3] A dynamic overshoot is an overshooting saccade corrected immediately (without latency) by a return saccade to the target (4).

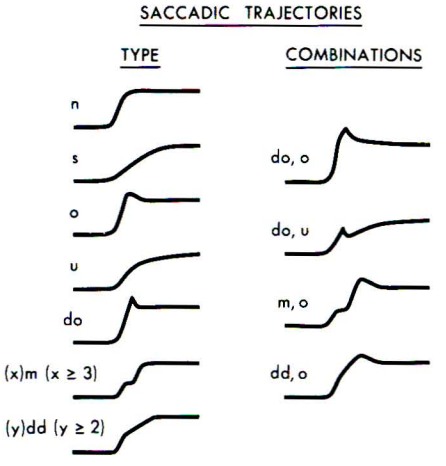

FIG. 1. Illustration of the seven trajectory types and several combinations. n—normal, s—slow and/or long, o—overshoot with glissade, u—undershoot with glissade, do—dynamic overshoot, (x)m ($x \geq 3$)—x multiple closely spaced, (y)dd ($y \geq 2$)—y discrete decelerations. The combinations are: do, o—dynamic overshoot with overshoot glissade; do,u—dynamic overshoot with undershoot glissade; m,o—double saccade with overshoot glissade; dd,o—single discrete deceleration with overshoot glissade.

immediate saccade in the opposite direction. Multiple closely spaced saccades (m) implies additional saccade(s) (occurring within 70 ms) in the same direction. Discrete deceleration (or decelerations) (dd) implies discrete changes in the slope of the saccadic trajectory. The seven waveform types as well as common combinations are illustrated in Fig. 1. Readers are referred to Bahill *et al.* (3, 6) for further explanation of these trajectories based on relative matching of brain stem innervational patterns of the pulse and step firing frequencies. Similar explanations based on the relative matching of the pulse and step of force or tension developed by the extraocular muscles in response to the neuronal pulse–step (7, 17) can also be advanced.

TABLE 2

Recursive Waveform Classification

Initial movement			
Metrics		Trajectory[a]	Correction
O	Orthometric	n, s, o, u, do, m, dd	None
HR	Hypermetric	n, s, o, u, do, m, dd	O, HR, HO
HO	Hypometric	n, s, o, u, do, m, dd	O, HR, HO

[a] The trajectory types are depicted in Fig. 1.

It must be realized that, unlike normal subjects, patients with myasthenia gravis may exhibit any of these seven types, or combinations of the same, and still not be on target (orthometric) at their termination. We define orthometric, hypermetric, and hypometric responses as follows: Orthometric (O)—an accurate *final eye position* which results from a single package of brain stem firing frequency changes (i.e., saccades occurring with intersaccadic intervals less than 100 ms). Hypermetric (HR)—the *final eye position* resulting from the initial package of neural activity overshoots the target; this requires correction in the opposite direction. Hypometric (HO)—the *final eye position* resulting from an insufficient initial package of neural activity and/or muscular failure undershoots the target; this requires correction in the same direction.

Each of the above three metric responses may consist of a movement of any of the seven trajectory types described and, if not orthometric, at least one other corrective movement type will follow after an appropriate (125 ms) latency.

The descriptions of trajectory types and metric responses results in the recursive classification scheme which contains all possible saccadic responses to target repositioning (or voluntary refixations). Table 2 illustrates the possible combinations and the recursive nature of the classification scheme. Several examples of pathological responses and their classification are shown in Fig. 2. Although this nomenclature may at

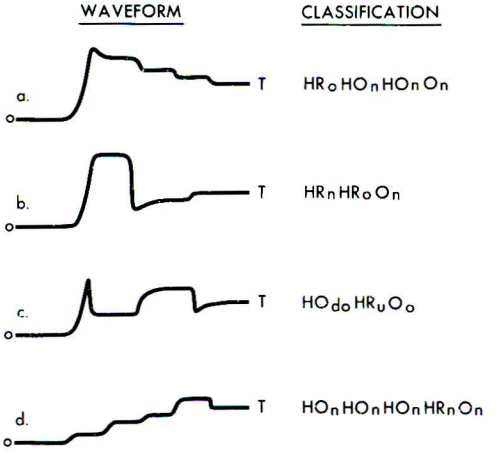

FIG. 2. Examples of several waveforms and their recursive classification. a—hypermetric with overshoot glissade, hypometric–normal, hypometric–normal, orthometric–normal. b—hypermetric–normal, hypometric with overshoot glissade, orthometric–normal. c—hypometric with dynamic overshoot, hypermetric with undershoot glissade, orthometric with overshoot glissade. d—hypometric–normal, hypometric–normal, hypometric–normal, hypermetric–normal, orthometric–normal. T—target position.

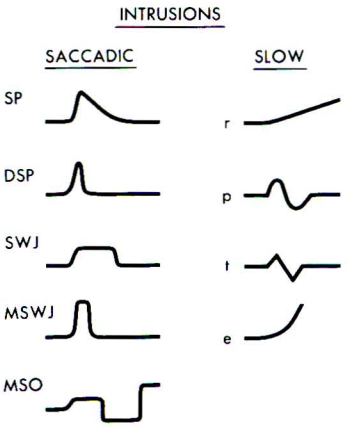

FIG. 3. Illustration of saccadic and slow eye movement intrusions. SP—saccadic pulse (stepless saccade). DSP—double saccadic pulse. SWJ—square wave jerk. MSWJ—macro square wave jerk. MSO—macro saccadic oscillation. r—ramp, p—pendular, t—triangular, e—exponential runaway.

first seem cumbersome, it is easily learned (abbreviations were chosen from the descriptive words themselves) and is the only way accurate differentiations can be made among the complex waveforms exhibited in this and other disorders.

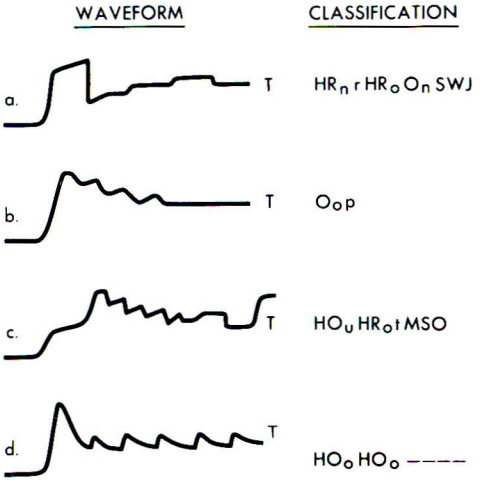

FIG. 4. Examples of waveforms with intrusions. a—hypermetric–normal, ramp, hypermetric with overshoot glissade, orthometric–normal, square wave jerk. b—orthometric with overshoot glissade, pendular. c—hypometric with undershoot glissade, hypermetric with overshoot glissade, triangular, macro saccadic oscillation. d—hypometric with overshoot glissade, hypermetric with overshoot glissade, etc. (nystagmus). T—target position.

TABLE 3

Hypometria[a]

Waveforms	Patients															
							7						10			
	1	2	3	4	5	6	O→R	L→O	O←R	L←O	8	9	O→R	L→O	O←R	L←O
$HO_{do,o}HO_{do,o}$---O_{do} or $HO_{do,o}O_{do}$	100	89.2				8.5						3.4				
HO_nO_u or $HO_nHO_uHO_nO_n$			100		30.3							22				
$HO_{do,o}HO_n$---O_n or $HO_{do,o}O_n$				4.2	26.3	43.6				5.3		29.2				
$HO_{dd}HO_n$---O_n				16.9							6.8					
HO_nHO_n---O_n				11.3	17.1	4.2	29.4	94.1	50		2.3	13.6	66.7	36	4	
$HO_{do,o}HR_nO_n$ or $HO_{dd,do,o}HR_nO_n$				18.3		7					25	5.1				
HO_mHO_n---O_n				4.2	5.3		29.4									
HO_uHO_u---O_n						19.7										
HO_nHO_o---or $HO_{dd,do}HO_o$---										94.7	5.7					
$HO_{dd,do,o}HO_n$---O_n or $HO_{dd,do,o}O_n$											31.8					
$HO_nHO_nHR_nO_n$					6.6	4.2								24	4	
$HO_{m,dd}HO_n$---O_n				45												
$HO_{dd}HO_uHO_nO_n$					9.1											
Totals	100	89.2	100	100	94.7	87.2		82.7			71.6	73.3		33.3		

[a] See Results for waveform classifications and percentage values.

During refixation as well as steady fixation, both saccadic and slow eye movement (SEM) intrusions were observed; they are illustrated in Fig. 3. Saccadic intrusions are types SP through MSO and SEM intrusions r, p, t, and e. Type SP is a saccadic pulse (stepless saccade) with an exponential decay back to the baseline; type DSP is a double saccadic pulse; type SWJ is a square wave jerk; type MSWJ is a macro square wave jerk (9); and type MSO is a macro saccadic oscillation (23). Type r is a ramp drift; type p is a pendular drift; type t is a triangular drift; type e is an exponential runaway (included for completeness in describing other pathological eye movements). Thus, intrusions of both fast and slow categories may be observed in the midst of, or following, a saccadic response. Figure 4 illustrates some possible waveforms and their classifications.

Saccadic metrics for each movement will be indicated by upper case letters (O, HR, HO) with the particular trajectories shown by lower case subscripts (n, s, o, u, do, m, dd). Intrusions will be upper case for saccadic (SP, DSP, SWJ, MSWJ, MSO) and lower case for slow (r, p, t, e) movements. All waveforms in this paper will be so labeled to facilitate comparisons and remove the ambiguity present in simple descriptive terminology.

Waveforms. Tables 3 through 5 provide the metric and trajectory analysis of the waveforms demonstrated in the 10 myasthenic patients. The responses of patients 7 and 10 are separated in these tables for each of the required refixations because they both had a slight paresis of one muscle (Table 1). Their percentages are referenced to the total number of movements of the type shown in the column headings. Percentages in the Total rows of these tables and those for all other patients are referenced to

TABLE 4

Orthometria[a]

	Patients										
		7						10			
Wave-forms	2	O→R	L→O	O←R	L←O	8	9	O→R	L→O	O←R	L←O
O_u							23.7				
O_n				25		1.1	3	29.1		4	20
$O_{m,u}$		41.2									
O_{sdd}[b]						6.8					
$O_{do,o}$	10.8										
Totals	10.8		10.1			7.9	26.7		13.1		

[a] See Results for classifications and percentage values.
[b] y = 2, 3, etc.

TABLE 5

Hypermetria[a]

	Patients											
			7						10			
Waveforms	5	6	O→R	L→O	O←R	L←O	8	9	O→R	L→O	O←R	L←O
HR_nO_n	5.3				25		1.1		4.2	16	24	28
$HR_{do,o}HR_oO_n$		12.7										
$HR_nHO_nHO_n$---O_n							2.3	3		16	4	24
$HR_{dd}O_n$							10.2					24
$HR_{dd}HO_nO_n$							6.8					4
$HR_{dd}HR_nO_n$											28	
HR_mO_n				5.9						8	32	
Totals	5.3	12.7			7.3		20.4	3			54.4	

[a] See Results for classifications and percentage values.

the total number of movements of all types. Nine patients had predominantly hypometric saccades (Table 3), 4 showed orthometric movements which ranged from approximately 8 to 27% in frequency (Table 4), and only patient 10 manifested a preponderance of hypermetria (Table 5).

Patients 1, 3, and 4 made only hypometric saccades, with 1 and 3 restricted to only single-type trajectories (Table 3). Patient 1 had hypometric jerks with dynamic overshoot ($HO_{do,o}$---O_{do}); patient 2 showed this type of hypometria 89% of the time. In both patients (1 and 2) these short saccades had supernormal velocities (Fig. 5). The waveforms consisting of hypometric saccades with dynamic overshoots usually demonstrated higher than normal velocity–amplitude relationships for these saccades. The highest velocities were more than 800°/s for amplitudes of 13° to 15.6°. Occasionally, the first saccade was slower than the second or third; such a case is shown in the inset. The dynamic overshoot velocities were usually normal although some, especially for the first saccade, had higher velocities.

Other commonly occurring responses shown in Table 3 consisted of hypometric saccades some of which were followed by a glissade (HO_nO_u); this was the only pattern in patient 3 and also occurred in patients 5 and 9. Dynamic overshoot of the first hypometric saccade followed by small hypometric saccades to the target ($HO_{do,o}HO_n$---O_n) was the most common pattern in patients 6 and 9, and the second most common pattern in patient 5. Saccades with discrete deceleration ($HO_{dd}HO_n$---O_n; $HO_{dd,do,o}HR_nO_n$; $HO_{dd,do}HO_n$---; $HO_{dd,do,o}HO_n$---O_n; $HO_{dd}HO_oHO_nO_n$) appeared in six patients (4 to 9). Double saccades (HO_mHO_n---O_n; $HO_{m,dd}HO_n$---O_n)

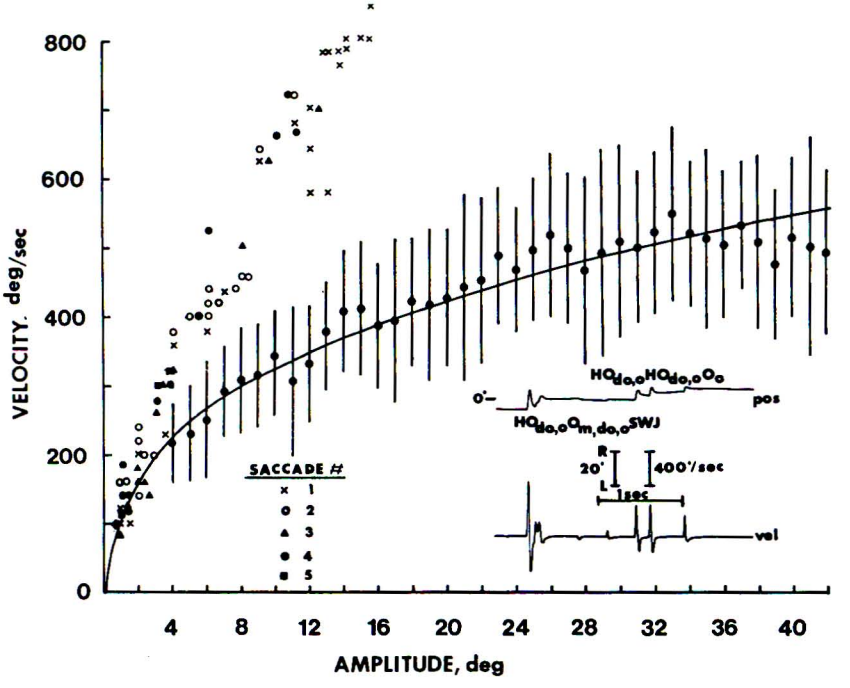

FIG. 5. Velocity–amplitude relationship of the hypometric saccade demonstrated by patient 1. Plotted for comparison is the peak velocity–amplitude curve of a group of normal subjects tested separately. In the inset is shown a typical set of responses made by patient 1 in refixating from left to zero and then from zero to right. Note that the second hypometric saccade in the response going from zero to right has a much higher normalized velocity than the first saccade in that response because, although its absolute velocity is only slightly higher, its amplitude is approximately two-thirds of that of the first saccade. In all figures the fixing eye is shown. pos—eye position. vel—eye velocity in this and subsequent figures.

occurred in three patients (4, 5, and 7). A peculiar phenomenon of hypometric followed by hypermetric saccades ($HO_nHO_nHR_nO_n$) was seen in patients 5, 6, and 10.

In the five patients with orthometric saccades (Table 4) glissades, dynamic overshoots, discrete decelerations, and double saccades were observed. Discrete decelerations or double saccades sometimes appeared (patients 7, 8, and 10) even in hypermetric responses (Table 5). Recordings of commonly encountered waveforms are shown in Fig. 6.

DISCUSSION

We attempted to determine whether the marked intersubject variability could be explained on the basis of the duration of the ocular myasthenia,

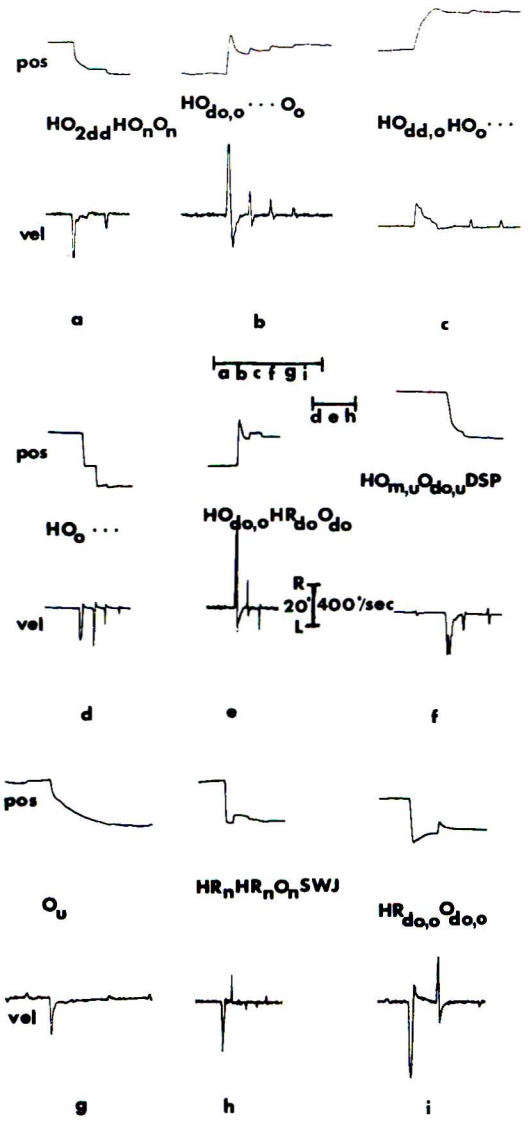

FIG. 6. Recordings of some of the waveforms encountered, as indicated.

recent administration of anticholinesterase medication, or degree of ophthalmoparesis. The only patient without a predominant hypometric pattern was patient 10 (54% of his movements were hypermetric). The duration of his illness was 10 years, which was in the middle of the duration

range and could not explain his uniqueness. He had only a mild paresis of a single extraocular muscle, but other patients such as 2 and 7 also had mild involvement.

The patient with the longest duration of illness (patient 3) had 100% of his movements consisting of small saccades with glissades (HO_nO_u) in his markedly restricted left eye. This response was seen in only two others: patient 5, with a 20-year duration, and patient 9, whose duration was only 1 year. Thus, this waveform cannot be attributed to prolonged illness duration nor marked amplitude restriction as patient 5 had amplitudes in the middle range.

The two patients who took medications closest to the time of recording (patients 1 and 2) had a preponderance (100% in patient 1 and 89% in patient 2) of the $HO_{do,o}HO_{do,o}$---O_{do} pattern. If this was an effect of the medication, one might have expected patient 4, who also had the medication a few hours previously, to have shown this response; he never did.

The intrasubject variabilities in patients 4 through 6 and 8 through 10 could not be explained on the basis of repetition fatigue. That is, the individual patterns had no relationship to their occurrence time during the 3 min of actual recording.

Central and Peripheral Effects. It is now understood that myasthenia gravis is a disease of the receptor sites of the neuromuscular junction which affects, on a probabilistic basis, the number of receptors which interact with released acetylcholine molecules (11, 12). The variability we found in saccadic responses reflects the many factors (chemical and morphological) which contribute to the probability that enough receptors will be involved at a given instant, as well as the central changes which have taken place to overcome the peripheral deficit. Based on our knowledge of ocular motor function in normal subjects and patients with central dysfunction, we can attempt to separate the central and peripheral components of the saccadic responses presented in this paper. Although speculative, the hypotheses that follow are the result of careful analysis of saccadic waveforms and serve to simulate further study of myasthenic muscle function. Table 6 shows the changes primarily responsible (i.e., central, C, or peripheral, P) for the observed metric and trajectory response types. Thus, an O or HR response must reflect central adaptation to the existing peripheral deficit; HO reflects the peripheral deficit despite any secondary gain increase. Similarly for the various trajectories, types n, o, do, and m must be due to central adaptations to the existing deficit and s, u, and dd reflect the peripheral abnormalities caused by the myasthenia (again, despite secondary gain increases).

Peripheral deficits can be reflected by hypometria (HO) or inadequate trajectories (s, u, dd). In the former case, one can postulate a persisting

TABLE 6

Central and Peripheral Effects[a]

	Trajectory[b]						
Metrics	n (C)	s (P)	o (C)	u (P)	do (C)	m (C)	dd (P)
O (C)	C	PC	C	PC	C	C	PC
HR (C)	C	PC	C	PC	C	C	PC
HO (P)	CP	P	CP	P	CP	CP	P

[a] See Results for classifications.

[b] *All* intrusions (saccadic and slow eye movement) reflect central effects. See Fig. 1.

inability of the muscle to contract properly for the given innervation; thus, the eye falls short of its intended position. Trajectory deficiencies reflect more dynamic failures which may indicate differential effects upon the fast ("phasic") and slow ("tonic") muscle fibers involved in executing a saccade. Thus, discrete decelerations (dd) may reflect groups of fibers fatiguing at distinct times during the saccade, (intrasaccadic fatigue) or, slow saccades (s) and undershoots with glissadic tails (u) might reflect the poor efficiency of recruitment of all the muscle fibers required to execute the proper saccades. This gives rise to a pulse–step mismatch of force that results in a saccade which mimics one caused by a central innervational pulse–step mismatch (pulse greater than step in both cases).

Patient 6 demonstrated an intrasubject variability of peripheral deficit when making two saccades in the same direction but with differing points of departure and arrival (Fig. 7). Refixation from left to primary position

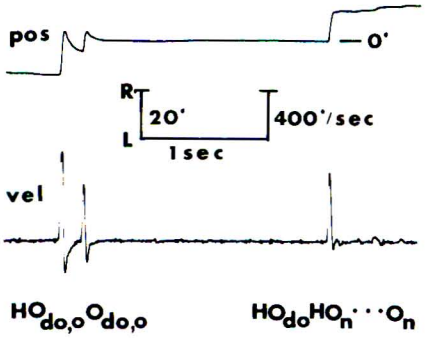

FIG. 7. The intrasubject variability of patient 6 when making two saccades to the right. The waveform going from left to primary was $HO_{do,o}O_{do,o}$ and that going from primary to the right was $HO_{do}HO_{n}$---O_{n}.

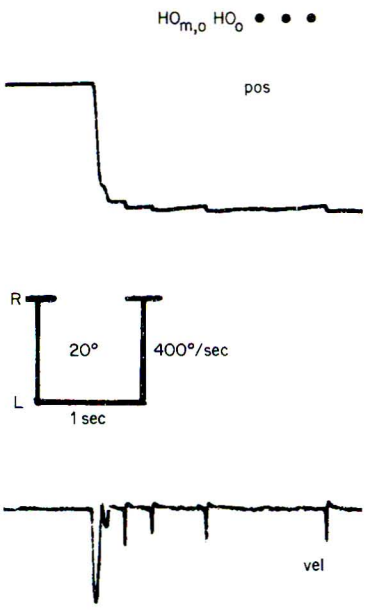

FIG. 8. A recording of muscle–paretic nystagmus in lateral gaze.

showed hypometria with marked overshoot ($HO_{do,o}O_{do,o}$). In contrast, the saccade from primary to the right showed only the hypometria ($HO_{do}HO_n$---O_n). These two different trajectories in the same gaze direction (i.e., the same agonist muscle) reflect the differential deficits in the muscle fibers used for each saccade. Fibers which moved the eye from left to center were much more efficient than those which moved the eye from center to right, resulting in the overshooting trajectory of the former; such difference is not present in normal subjects. The fact that the eye transiently overshot the target probably reflects increased central innervation (see below).

Two patients (7 and 8) showed muscle–paretic nystagmus in lateral gaze (Fig. 8). This waveform $HO_{m,o}HO_o$--- (see Table 3), was due to the peripherally caused gaze-holding failure which resulted in the centripetal drifts and the corrective saccades they initiated.

Examples of the central adaptive effects on waveforms are shown in Fig. 9, some of which also contain saccadic intrusions reflecting the instabilities consequent to an increased central gain. "Supernormal" velocities of hypometric saccades with dynamic overshoots are also due to increased central innervation coupled with the peripheral inability of the muscle to fully contract and move the eye to a position corresponding to this higher

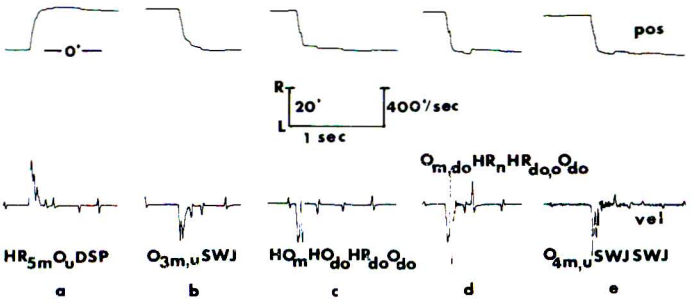

FIG. 9. Recordings which illustrate the effects of increased central gain. a—closely spaced saccades and a double saccadic pulse. b—closely spaced saccades and a square wave jerk. c—closely spaced saccades and hypermetria following hypometria. d—closely spaced saccades encompassing a dynamic overshoot followed by hypermetria. e—closely spaced saccades and square wave jerks.

innervation. It should be noted that all these manifestations of increased central gain were recorded prior to administration of anticholinesterase.

We have not found an increased incidence of multiple, closely spaced saccades or large dynamic overshoots in our recordings of patients with brain stem or cerebellar disease; this is in conformity with most major studies. The increased occurrence in myasthenia gravis is therefore noteworthy. It is quite possible that the peculiar condition of a variable peripheral deficit coupled with a partially adaptive increased central innervational level has stressed the ocular motor system in a manner which may elucidate the role of proprioception in normal eye movements. Consider the stimulus for the closely spaced saccades following the initial hypometric saccade. It cannot be visual or efference copy because of the longer latencies required for those pathways. Efference copy is also improbable because the efferent signal is already larger than that normally required for a saccade of a given magnitude (the high central innervation present is observed as hypermetric saccades after the administration of edrophonium chloride which transiently alleviates the myasthenic condition at the neuromuscular junction). Another possible explanation involves the inherent instability of the pulse generator under the conditions of increased gain (29). However, gain increases associated with internuclear ophthalmoplegia and sixth nerve palsies do not result in multiple, closely spaced saccades. The strong possibility remaining is a fast proprioceptive feedback pathway to the pulse generator. Thus, before vision can confirm the hypometria and despite the fact that the efferent signal is greater than normal, proprioceptive information documents the fact that muscular contraction is inadequate and quickly stimulates the pulse generator to make another saccade or string of saccades. This

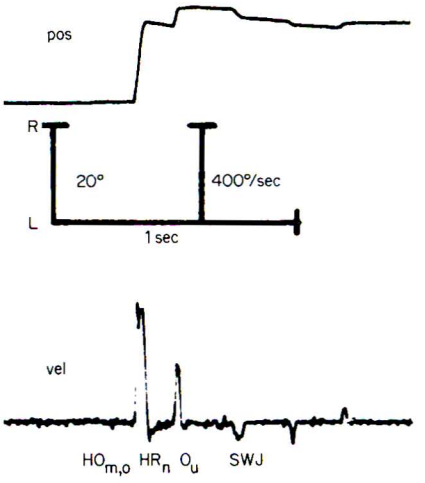

FIG. 10. A recording of hypermetria following hypometria and a square wave jerk.

speculation is supported by the report that closely spaced saccades occur with fatigue in normal subjects (5). If proprioception is functioning, as suggested by these observations, myasthenia gravis apparently does not affect (or has only little effect on) the intrafusal muscle fibers. One could argue that the effects seen in normal subjects with fatigue and in myasthenia gravis are due to the disruption of the normal proprioceptive feedback to the pulse generator. Thus, instead of one pulse, a group of shorter pulses is generated.

An alternative explanation to the involvement of proprioception is that closely spaced saccades reflect a discrete gradation of muscular contraction in response to a single pulse of innervation. This seems very unlikely, however, given the large total duration of the string of movements and the prevalence of dynamic overshoots in myasthenia gravis patients. Dynamic overshoots are merely closely spaced saccades in opposite directions and are due to neurological control signal reversals (4). Thus, proprioception remains as the possible mediator of dynamic overshoots (common in normal saccades of low amplitude) and multiple, closely spaced saccades.

Combinations of central and peripheral changes give rise to many possible waveform combinations as evidenced by the variability we have documented and Table 6. One peculiar response waveform consists of a hypermetric saccade following one or more hypometric saccades (Fig. 10). Here, the $HO_{m,o}HR_nO_uSWJ$ waveform reflects the variable peripheral response (HO to HR) to the increased central innervation (trajectory m, o, and HR_n) as well as the probability of high-gain intrusions SWJ.

REFERENCES

1. ABEL, L. A., D. SCHMIDT, L. F. DELL'OSSO, AND R. B. DAROFF. 1978. Saccadic system plasticity in humans. *Ann. Neurol.* **4:** 313–318.
2. ABEL, L. A., L. F. DELL'OSSO, D. SCHMIDT, AND R. B. DAROFF. 1980. Myasthenia gravis: analog computer model. *Exp. Neurol.* **68:** 378–389.
3. BAHILL, A. T., M. R. CLARK, AND L. STARK. 1975. Glissades-eye movements generated by mismatched components of the saccadic motoneuronal control signal. *Math. Biosci.* **26:** 303–318.
4. BAHILL, A. T., M. R. CLARK, AND L. STARK. 1975. Dynamic overshoot in saccadic eye movements is caused by neurological control signal reversals. *Exp. Neurol.* **48:** 107–122.
5. BAHILL, A. T., AND L. STARK. 1975. Overlapping saccades and glissades are produced by fatigue in the saccadic eye movement system. *Exp. Neurol.* **48:** 95–106.
6. BAHILL, A. T., F. K. HSU, AND L. STARK. 1978. Glissadic overshoots are due to pulse width errors. *Arch. Neurol.* **35:** 138–142.
7. COLLINS, C. C. 1975. The human oculomotor control system. Pages 145–180 in G. LENNERSTRAND AND P. BACH-Y-RITA, Eds., *Basic Mechanisms of Ocular Motility and their Clinical Implications*. Pergamon, Oxford.
8. DAROFF, R. B., AND L. F. DELL'OSSO. 1976. The control of eye movements. Pages 143–170 in *Neurological Reviews*. Amer. Acad. Neurol., Minneapolis.
9. DELL'OSSO, L. F., B. T. TROOST, AND R. B. DAROFF. 1975. Macro square wave jerks. *Neurology* **25:** 975–979.
10. DELL'OSSO, L. F., D. A. ROBINSON, AND R. B. DAROFF. 1974. Optokinetic asymmetry in internuclear ophthalmoplegia. *Arch. Neurol.* **31:** 138–139.
11. DRACHMAN, D. B. 1978. Myasthenia gravis. I. *N. Engl. J. Med.* **298:** 136–142.
12. DRACHMAN, D. B. 1978. Myasthenia gravis. II. *N. Engl. J. Med.* **298:** 186–193.
13. FUCHS, A. F., AND E. S. LUSCHEI. 1970. Firing patterns of abducens neurons of alert monkeys in relationship to horizontal eye movement. *J. Neurophysiol.* **33:** 382–392.
14. KIRKHAM, T. H., AND A. KATSARKAS. 1977. An electro-oculographic study of internuclear ophthalmoplegia. *Ann. Neurol.* **2:** 385–392.
15. KOMMERELL, G. 1975. Internuclear ophthalmoplegia of abduction. Isolated impairment of phasic ocular motor activity in supranuclear lesions. *Arch. Ophthalmol.* **94:** 531–534.
16. KOMMERELL, G., D. OLIVER, AND M. THEOPOLD. 1976. Adaptive programming of phasic and tonic components in saccadic eye movements. Investigations in patients with abducens palsy. *Invest. Ophthalmol.* **15:** 657–660.
17. POLA, J., AND D. A. ROBINSON. 1976. An explanation of eye movements seen in internuclear ophthalmoplegia. *Arch. Neurol.* **33:** 447–452.
18. ROBINSON, D. A. 1970. Oculomotor unit behavior in the monkey. *J. Neurophysiol.* **33:** 393–404.
19. SCHILLER, P. H. 1970. The discharge characteristics of single units in the oculomotor and abducens nuclei of the unanesthetized monkey. *Exp. Brain. Res.* **10:** 347–362.
20. SCHMIDT, D. 1975. Diagnostik myasthenischer Augensymptome. Klinische Symptome und Electronystagmographische Befunde sakkadischer Augenbewegungen. *Klin. Monatsbl. Augenheilkd.* **167:** 651–654.
21. SCHMIDT, D. 1977. Saccadic eye movements in myasthenic ocular muscle pareses. Pages 177–189 in J. S. GLASER, Ed. *Neuro-Ophthalmology*. Mosby, St. Louis.
22. SCHMIDT, D., L. F. DELL'OSSO, L. A. ABEL, AND R. B. DAROFF. 1980. Myasthenia gravis: dynamic changes in saccadic waveform, gain, and velocity. *Exp. Neurol.* **68:** 365–377.

eye movement tracings of several hours' duration from a previously reported [5] hemispherectomy patient and did not find nystagmus. Moreover, we recently recorded tracings from a young woman with a posterior fossa tumor who had a distinct horizontal pursuit asymmetry but no nystagmus. There are factors, as yet undefined, which apparently prevent the manifestation of nystagmus in some patients with pursuit imbalance.

To answer one of Dr Alpert's concerns, there was no increase in slow-phase velocity in darkness. The ranges of velocities found in both light and dark were equivalent. The usual biological variability reflected in slight beat-to-beat differences is evident in our Figure 2B, but the fastest slow-phase velocity in darkness did not exceed the fastest in light. The nystagmus frequency decreased and, secondarily, the amplitude increased, as also reported recently by Mehdorn et al [3]. The increase in fast-phase velocity was commensurate with the amplitude increase. The decrease in nystagmus frequency was due to the fast-phase generator operating on signals other than visual error. As distinct from slow-phase velocity, neither amplitude nor frequency changes are critical variables. When velocity does increase in darkness, such as in vestibular nystagmus, it is presumably caused by removal of a drag upon the slow phase by the intact pursuit system in illuminated conditions. Darkness releases the "true," uninhibited, slow-phase drift.

Dr Alpert's second concern relates to a possible associated vestibular abnormality. The asymmetry of the vestibuloocular reflex during fixation of a stationary object in our Figure 5B was exactly what one would expect, given the absence of rightward pursuit. Pursuit summated with the leftward vestibuloocular response but could not with the rightward response. Irrespective of a possible coexisting vestibular imbalance, our patient had "pursuit defect" nystagmus as defined by Zee et al [6] and supported by subsequent reports from major eye movement laboratories throughout the world [1–4].

Quite recently (since receiving the preceding letters), we have had reason to question the basic concept of "pursuit defect" nystagmus. We recorded eye movements from a patient with spinocerebellar degeneration and periodic alternating nystagmus in whom we found alternating pursuit defects. The unlikelihood of such an alternating defect raised the question of how pursuit should be manifest in the direction of the fast phase of an ongoing jerk nystagmus. The nystagmus persists and pursuit can only be expected to decrease the slow phase velocity (i.e., decrease slope) in the opposite direction. We confirmed this in a normal subject during caloric-induced nystagmus. For pursuit to be regarded as absent, no change in slope should result. This occurred in the computer model of Zee et al [6] but not in their patients, or, convincingly, in any of the others reported. Determination of true pursuit gain would require careful study with varying velocity ramps. This must be done before causality can be established in these cases of "pursuit defect" nystagmus.

References

1. Daroff RB, Dell'Osso LF: Nystagmus—a contemporary approach, in Thompson HS, Daroff RB, Glaser JS, et al (eds): Topics in Neuro-Ophthalmology. Baltimore, Williams & Wilkins (in press)
2. Gilman N, Baloh RW, Tomiyasu U: Primary position upbeat nystagmus. Neurology (Minneap) 27:294–298, 1977
3. Mehdorn E, Kommerell G, Meienberg O: Primary position vertical nystagmus: 'directional preponderance' of the pursuit system. Albrecht von Graefes Arch Klin Ophthalmol 209: 209–217, 1979
4. Sharpe JA, Lo AW, Rabinovitch HE: Control of the saccadic and smooth pursuit systems after cerebral hemidecortication. Brain 102:387–403, 1979
5. Troost BT, Daroff RB, Weber RB, et al: Hemispheric control of eye movements: II. Quantitative analysis of smooth pursuit in a hemispherectomy patient. Arch Neurol 27:449–452, 1972
6. Zee DS, Friendlich AR, Robinson DA: The mechanism of downbeat nystagmus. Arch Neurol 30:227–237, 1974