Article abstract—Accurate ocular motility recordings were made of the saccadic responses of five patients with Eaton-Lambert syndrome (ELS). It was found that, contrary to common belief, the ocular motor system is affected. The saccades of ELS patients mimicked those of patients with myasthenia gravis (MG). Both groups exhibited hypometria and multiple, closely spaced saccades. Two patients demonstrated both saccadic facilitation and positive edrophonium tests. The ELS patients had slow or normal saccadic velocities, not the "super-fast" velocities found in patients with ocular MG.

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Edrophonium test in Eaton-Lambert syndrome: Quantitative oculography

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The Eaton-Lambert syndrome (ELS)[1] is attributed to impaired release of acetylcholine from nerve terminals.[2] Unlike myasthenia gravis (MG), the weakness primarily involves proximal limb muscles, sparing cranial muscles.[2,3] The response to edrophonium is slight or absent in most cases, but occasionally positive.[4] Also, ELS shows facilitation both electronically and clinically,[5,6] in contrast to the decremental response of MG. We have reported oculographic studies of saccadic eye movements and the response to edrophonium in ocular myasthenia.[7,8] Many of the abnormalities seemed due to increases in central ocular motor gain in compensation for the peripheral defect.

We now report quantitative oculographic studies of saccadic eye movements and the effect of edrophonium in five patients with ELS. None of the patients had obvious eye movement abnormalities when examined clinically by neuro-ophthalmologists. The study was prompted, in part, by reports of subclinical eye movement abnormalities uncovered by oculography in MS,[9] amyotrophic lateral sclerosis,[10] and Alzheimer's disease.[11]

Case reports. Patient 1. For 6 months, this 66-year-old woman noted progressive weakness of all four limbs, dysphagia, and dry mouth, but no ptosis, diplopia, or dysarthria. The diagnosis of MG had been made by a neurologist after a "positive edrophonium test." She was treated with pyridostigmine (120 mg, four times a day for 8 weeks) without benefit.

Examination was normal except for proximal limb weakness. Few brief contractions of the proximal muscles appeared to result in transient improvement of strength. Tendon reflexes were absent. Intravenous administration of 10 milligrams of edrophonium did not improve muscle strength. AChR antibodies were not detected in serum by radio immunoassay.

Neuromuscular transmission studies revealed markedly decreased amplitude of the compound muscle action potential (CMAP) of the abductor pollicis brevis (0.4 mV). After 10 seconds of maximal contraction, there was an increment of 1,000% in the amplitude of the CMAP. Two-per-second stimulation showed a decremental response of 25% in the same muscle. Similar findings were noted in other muscles. Nerve conduction studies were normal. On electromyography, there was moment-to-moment variation in the amplitude of the motor unit potentials, but the amplitudes and durations were normal.

Roentgenogram of the chest revealed a large hilar and paratracheal mass on the right side. Biopsy of the lymph nodes during mediastinotomy revealed metastatic oat cell carcinoma. She was given guanidine hydrochloride, 15 mg/kg body weight/day. Dysphagia, proximal muscle strength, and the neuromuscular transmission studies improved. She was started on chemotherapy and discharged on guanidine, with no side effects, and maintained improvement.

Patient 2. A 55-year-old man noted muscle soreness and weakness. He could walk only a few paces with difficulty. He had occasional transient diplopia for about 3 months before evaluation, but no cranial symptoms other than dry mouth. On examination, he could not rise from a bed or a

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chair. There was moderate weakness of the trunk and pelvic girdle muscles, and mild weakness of the shoulder girdle muscles. Tendon reflexes were absent, and sensation was normal.

The amplitude of the hypothenar CMAP to supramaximal stimulation of the ulnar nerve was decreased to 1.6 mV (normal > 5.6 mV). Supramaximal stimulation of the nerve after 10 seconds of maximal voluntary contraction increased the amplitude to 9.0 mV. Two-per-second repetitive stimulation resulted in 20% decrement of the CMAP, but on 30-per-second stimulation, the amplitude increased from 1.6 to 25 mV in 20 seconds.

Guanidine hydrochloride therapy (15mg/kg body weight/day) increased his strength dramatically, but the drug had to be discontinued because of dermatitis. Intravenous edrophonium tests were negative, and AChR antibodies were absent. Chest radiograms revealed a hilar mass. Bronchoscopy and biopsy confirmed the diagnosis of oat cell carcinoma of the lung. He was treated with radiotherapy and chemotherapy.

Patient 3. For 12 months, this 48-year-old man had progressive weakness of the legs. A few months after the onset, his arms were also weak. The weakness was much worse in the afternoons and evenings. He also complained of dry mouth, but no diplopia, dysarthria, dysphagia, or respiratory difficulty.

Examination revealed mild bilateral ptosis and facial weakness. The weakness included neck flexion and extension, proximal arm muscles, and all muscles of the legs. On testing grip strength, there was an overt delay before maximal strength was attained. Few quick repetitive contractions of the proximal limb muscles improved strength. Tendon reflexes were present. Several intravenous edrophonium tests were negative, and AChR antibodies were absent in the serum.

Roentgenogram of the chest showed a paratracheal mass. Biopsy revealed an oat cell carcinoma. Brain CT was normal. Nerve conduction studies were normal except for the decreased amplitudes of the evoked CMAP. The amplitude of the abductor pollicis brevis CMAP was 2.5 mV. Two-per-second repetitive stimulation resulted in a decremental response of 38%; 40-per-second stimulation caused an incremental response of 490%. After a maximum contraction of the muscle for 10 seconds, there was an incremental response of 230%. Similar abnormalities were noted in other muscles. He was given guanidine hydrochloride (15 mg/kg body weight, increased to 35 mg in three divided doses) with improvement of strength. The carcinoma of the lung was treated with radiotherapy and chemotherapy.

Patient 4. A 50-year-old woman had a 6-month history of progressive proximal muscle weakness of the legs. Examination revealed profound weakness confined to the proximal muscles of all four limbs. On testing hand grip, there was a delay before maximal strength was attained. A few brief contractions of proximal muscles increased strength for several minutes. Tendon reflexes were absent. Nerve conduction studies were normal. Electromyography revealed moment-to-moment variation in the amplitude of the motor unit action potentials. Neuromuscular transmission studies revealed low amplitude of the evoked CMAP in thenar muscles (0.75 mV). Two-per-second repetitive stimulation gave a decremental response of 20%. Maximal contraction resulted in an incremental response of 800%. An edrophonium test was negative, and AChR antibodies were absent. She was given guanidine (15 mg/kg body weight) with improvement in strength, but after a few days, anemia necessitated cessation of the drug. She was later given prednisone (30 mg every other day) and guanidine (15 mg/kg body weight daily) together, and is still tolerating the drugs quite well. The muscle strength and the neuromuscular transmission studies showed considerable improvement. Extensive investigations to rule out underlying carcinoma were negative.

Patient 5. Except for bronchial asthma since childhood, this 52-year-old man was asymptomatic until May 1978, when he noted occasional blurred vision and "stiffness" of his legs. All four limbs became weak in November of 1978, and he also noted intermittent diplopia. Neurologic examination in April 1979 revealed slight bilateral ptosis, symmetrical proximal weakness of all four limbs, and absent tendon reflexes. Edrophonium tests were negative, and a neostigmine test was "equivocal."

Repetitive stimulation studies demonstrated moderate facilitation after brief exercise with subsequent decrement greater than 10%, with a marked increment on tetanic stimulation. The findings were regarded as consistent with ELS. Work-up for a malignancy was negative except for an anterior superior mediastinal mass on CT, which was thought to be a thymoma. On May 8, 1979, a sternal splitting thymectomy was performed, and the pathologic diagnosis was "thymic hyperplasia." Pyridostigmine, 60 mg five times daily, provided some subjective and objective improvement.

A diagnosis of hyperthyroidism was made in May 1980, and he was treated with ^{131}I followed by levothyroxine.

When we examined him in September 1980, he was taking pyridostigmine, 180 mg four times daily, and 180 mg Timespan at bedtime. He denied ever having the symptom of dry mouth. Examination revealed slight proximal and distal weakness in the arms and minimal leg weakness, which improved with repetition. Tendon reflexes were absent. No cranial nerve abnormalities were noted. He was advised to decrease the pyridostigmine therapy to 90 mg four times daily for several weeks, with no clinical change.

Laboratory studies and chest x-ray on admission were normal. AChR antibody was not detected. On September 23, 1980, transmission studies showed a significant decrease in the amplitude of the CMAP of the abductor digiti minimi (3 mV). After maximum voluntary contraction for 30 seconds, the amplitude increased to 10 mV—an increment of 230%. Two-per-second stimulation of the abductor pollicis brevis showed a decremental response of 30% in the CMAP; pyridostigmine had been discontinued 16 hours before the test. He was given guanidine hydrochloride on September 25, and the dose was gradually increased to 500 mg four times daily. On that dose, he was distinctly stronger, and on October 2, 1980, stimulation studies after maximal voluntary contraction for 30 seconds showed only a 30% compound muscle action potential increment. Pyridostigmine, 30 mg every 3 hours, was added before discharge on October 3.

Paresthesia of fingers and face prompted decrease in guanidine dose to 375 mg every 3 hours, with an increase in the pyridostigmine to 60 mg every 3 hours. He was stable until early May 1981, when he had a flu-like syndrome with shaking, chills, fever to 102 °F, and diarrhea. He became progressively weaker and was readmitted May 29, 1981. Relevant laboratory studies included hematocrit 29 vol %,

hemoglobin of 9.7 g/dl, BUN 46 mg %, and creatinine 3.6 mg %. He had a grand mal seizure shortly after admission and was given 1.5 g phenytoin intravenously. The anemia, azotemia, and seizure were attributed to guanidine, which was discontinued. Bone-marrow examination was normal. As he began to improve, he complained of blurred vision that was not corrected with reading glasses. The symptom varied and responded only equivocally to increasing doses of pyridostigmine. He also described difficulty focusing when he refixated from the end of a line on the right to the beginning of the next line on the left.

On July 1, 1981, quantitative oculograpy was performed at the ocular motor neurophysiology laboratory of the Cleveland Veterans Administration Medical Center. Pyridostigmine was discontinued 16 hours before these studies. Results of the studies are detailed below. The test showed bilateral slowing of adduction, with abduction overshooting. When he was then examined clinically, the disconjugacy (medical rectus weakness) was overt, especially with optokinetic stimuli. Increasing weakness prompted restarting pyridostigmine therapy at 60 mg every 3 hours, and this resulted in improved strength.

Methods. Horizontal eye movement recordings were made using infrared oculography, in subdued light, with a full-system bandwidth (position and velocity) of DC to 100 Hz (Biometric Model-200 and rectilinear Beckman Type-R Dynograph—both modified to achieve the described bandwidths). Each patient was seated in a chair with a head brace and a chin rest at the center of a 1.14-m arc containing red light-emitting diodes. The recordings of the first two patients did not include a specific test for facilitation, but the repetitive saccades required for the calibration procedure would have revealed obvious facilitation. When recording the second two patients, we inserted a specific protocol for facilitation, consisting of a series of 40° refixations every 1 to 2 seconds across the center, lasting for approximately 1 minute. With the fifth patient, we added a 2-minute rest period preceding the repetitive refixation test. All patients were then administered edrophonium while they were making repetitive refixations between target lights at ±20°.

Saccadic metrics and trajectory classification. The abbreviations used in this paper to describe saccadic metrics and trajectories were developed as part of a classification of eye movements in MG.[7] Proper description of complex saccadic waveforms requires separation of metrics (ie, actual final position) from trajectory (ie, path taken to final position). The recursive classification scheme provides an accurate description of all possible waveform combinations. Since a saccade is the movement resulting from a pulse-step of neural innervation, neither the pulse nor the step alone can produce a normal and accurate saccade. In normal people, there is considerable intra- and intersubject variation in the relative strengths of these two innervational components, resulting in both trajectory and metric variations. The metrics of a saccade are determined by the eye's final position with respect to both the target and the initial position of the eye; metrics depend solely on the step of innervation. The relative size of the pulse cannot affect final eye position, but does affect the trajectory. Thus, mismatches due to an incorrect pulse and a correct step can cause different trajectories, but the movement will be orthometric. In normals, most refixations are accomplished by one (orthometric) or two (hypometric or hypermetric, followed by orthometric) saccades. In patients with ocular motor disorders, a refixation may consist of many saccades of differing metrics and trajectories. Therefore, the only accurate way to characterize such a refixation is to describe completely (metrics and trajectory) each constituent saccade in the refixation. For example, if a patient with hypometria accomplishes refixation by making five saccades (the first four hypometric and the last orthometric), all separated by the normal latency for a corrective saccade, the trajectories and metrics of each of the five separate saccades must be described to characterize the refixation fully. This reasoning is the foundation for our recursive classification scheme and nomenclature.

The abbreviations are as follows: HO-hypometric, O-orthometric, and HR-hypermetric. When describing a paretic, nonviewing eye, metrics lose their meaning, and X is used. For trajectories: m-multiple, closely spaced saccades; do-dynamic overshoot; o-overshoot; u-undershoot; dd-discrete decelerations; and s-slow. In addition, SWJ (square wave jerks) and MSO (macrosaccadic oscillations) describe specific fixation instabilities.

Conjugacy. There is confusion in the use of the terms "conjugacy" and "disconjugacy." We have found it helpful in classifying nystagmus movements to use a conjugacy scale, because the nystagmus in the two eyes may be unequal in amplitude, but equal in direction. Similar difficulties arise in pathologic conditions that cause paresis of eye movement. Table 1 contains a scale of conjugacy that was developed for congenital nystagmus and was used to describe the conjugacy variations of MG and ELS. Many of the eye movements in these two diseases are only directionally conjugate (+1), because the yoke agonist muscles responsible for them may be unequally paretic. Thus, despite conjugate (ie, +2) innervation to both eyes, movements of *unequal* amplitude but *equal* direction (ie, +1) result. Also, any +1 movement can be expressed as a linear combination of a +2 and a 0 movement, and these can be plotted as orthogonal components. Similarly, any −1 movement can be expressed as the sum of a −2 and a 0 movement. At present, the utility of orthogonal mappings of eye movements on these "conjugacy planes" is unclear; these maps may help differentiate the eye movements of different pathologic conditions.

Results. *Saccadic refixations.* The saccadic refixations exhibited by ELS patients were analogous to

Table 1. Conjugacy scale

+2	Perfectly conjugate	$\bar{e}_{OD} = \bar{e}_{OS}$
+1	Directionally conjugate	$\lvert e_{OD}\rvert \neq \lvert e_{OS}\rvert$, $\measuredangle e_{OD} = \measuredangle e_{OS}$
0	Uniocular	$\bar{e}_{OD}$ or $\bar{e}_{OS} = 0$
−1	Directionally disconjugate	$\lvert e_{OD}\rvert \neq \lvert e_{OS}\rvert$, $\measuredangle e_{OD} = -\measuredangle e_{OS}$
−2	Perfectly disconjugate	$\bar{e}_{OD} = -\bar{e}_{OS}$

Where, $\bar{e}_{OD} = \lvert e_{OD}\rvert \measuredangle e_{OD}$ and $\bar{e}_{OS} = \lvert e_{OS}\rvert \measuredangle e_{OS}$

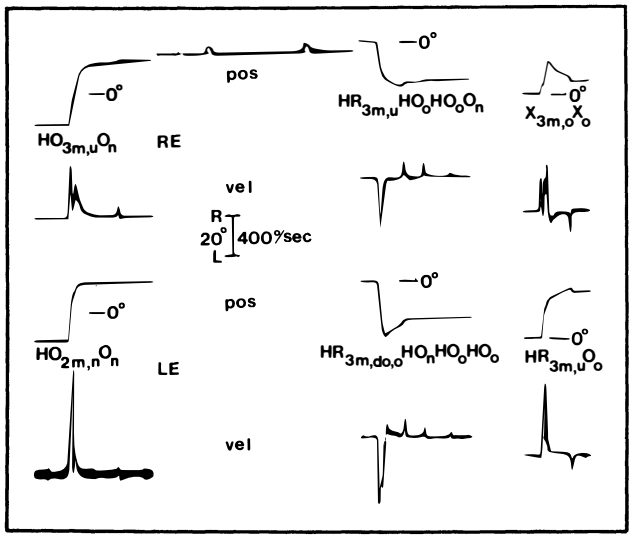

Figure 1. Illustrations of hypometria (HO) and multiple, closely spaced saccades (m) in ELS in three separate saccades. These were found in all five patients. Note that although closely spaced saccades result from conjugate central innervation, the resulting eye movements can be quite disconjugate. These eye movements are indistinguishable from those of MG patients. In this and other figures, RE-right eye, LE-left eye, pos-eye position, vel-eye velocity, R-right, L-left, and time markers denote 1-second intervals.

those of MG patients in two predominant characteristics. All five ELS patients made HO saccades and had m trajectories (figure 1). Although the central innervation for each of these movements was +2, the responses were all +1; this was also characteristic of the saccadic responses of MG patients.[7] As a result of the +2 innervation, the presence of both m and dd saccades can be detected by accurate ocular motility recordings as occurring simultaneously, albeit not necessarily equally (ie, of equal magnitude) in both eyes (table 2). Dynamic overshoots (do) and square wave jerks (SWJ) were common.

Saccadic velocities. Figure 2 shows a slow saccade and a plot of peak velocities versus amplitudes of the saccades of patient 1. He was the only patient with truly slow saccades whom we have found in either ELS or MG. Most MG patients, but none of our ELS patients, exhibited "super-fast" saccades[7] (table 2).

Facilitation. Ocular motor facilitation was found in two of the five patients (table 2). Both transition from HO to HR and increase in peak velocities were evident (figure 3).

Edrophonium effect. A positive response to edrophonium was found in two of the five ELS patients. Pre-edrophonium HO saccades became HR postedrophonium, and peak velocities increased as a result of the HR (figure 4). Note the presence of m saccades with +1 conjugacy in both the pre- and postedrophonium responses. Edrophonium caused transient esotropia (ET) in two patients (table 2); this was not taken as a positive edrophonium response.

Discussion. ELS regularly involves the ocular motor system by oculography, even though there may be no clinical abnormality. We found a plastic increase in the central gain, due to the peripheral abnormality of ELS, analogous to that in MG. Also, there was a preponderance of HO and m-saccades in both disorders. Moment-to-moment variation of the abnormalities may differ in MG and ELS, but further studies are needed.

The striking difference between the eye move-

Table 2. Summary of ocular motor findings in E-L syndrome

Pt	Age	Sex	Saccades: Metrics	Saccades: Trajectories	Saccades: PV	Tensilon test	Facilitation	SWJ
1	66	F	HO	m, do, dd, s	▼	−	−	+
2	55	M	HO, HR	m, do, o	N	+	+	+
3	48	M	HO, HR	m, do, o, u	N	−	−	+
4	50	F	HO, O	m, u	N	−(ET)	−	+
5	52	M	HO, O, HR	m, do, o	N	+(ET)	+	−

PV Peak velocity.
ET Esotropia.
SWJ Square wave jerk.
m Multiple closely spaced saccades.
do Dynamic overshoot.
dd Discrete deceleration.
s Slow.

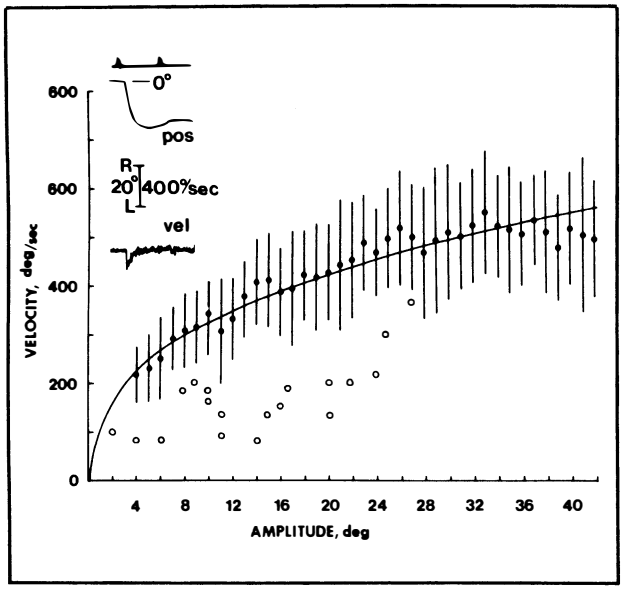

Figure 2. An example of a slow saccade (amplitude-24°, peak velocity-200°/sec) found in one of our ELS patients (patient 1). Open circles show peak saccadic velocities of this patient. The normal curve with standard deviations is for comparison (Schmidt et al, 1979).

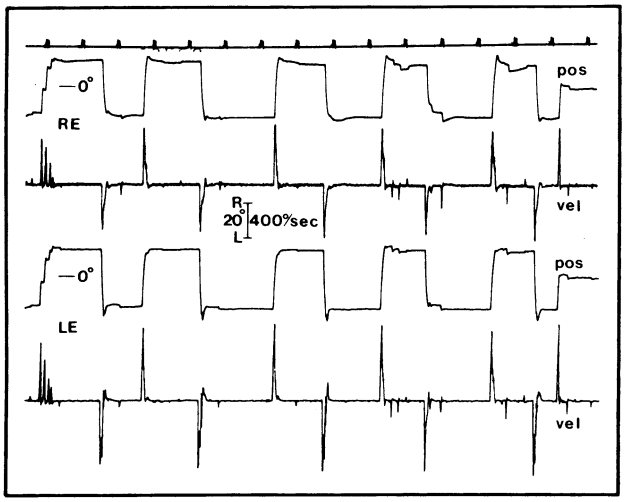

Figure 3. A demonstration of ocular motor facilitation in patient 5. Note the transition from hypometria to hypermetria and the increases in the velocity traces during 10 saccades over a 15-second interval.

ments of ELS and MG affected peak velocities, which were slower than normal in one ELS patient and normal in the others (table 2). In contrast, MG patients have[7,12] many super-fast saccades, attributed to selective sparing of fast muscle fibers in MG.[13] This implies a difference between the effects of presynaptic and postsynaptic disorders of ocular muscles. MG and ELS affect different muscles in different ways. MG almost always affects the eyes clinically. ELS rarely does, requiring quantitative

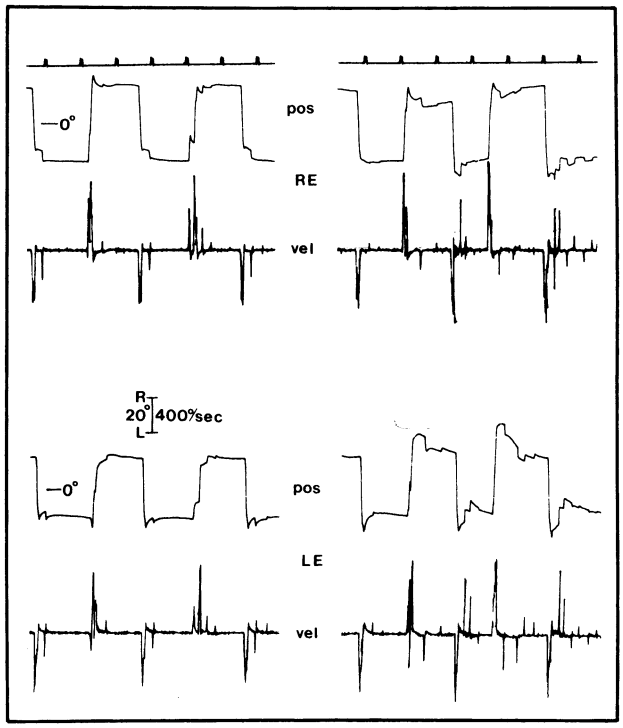

Figure 4. One of the two positive edrophonium tests (patient 5). Pre-edrophonium (on left) shows hypometria (many times with overshoot trajectories); postedrophonium (on right) shows hypermetria and macrosaccadic oscillations. Note multiple, closely spaced saccades in both pre- and postedrophonium tracings.

oculography to uncover the abnormality. In ELS, the increased central gain is probably inadequate to increase the reduced saccadic velocity because of the basic deficit in acetylcholine release.

From the point of view of the "command center" of the ocular motor control system, there is no difference between MG and ELS. The system has access to both efferent signals going to the ocular muscles and to afferent information from the proprioceptors in the ocular muscles and from vision. No information of the actual site of the problem (ie, pre- or postsynaptic) is available to "command center." Therefore, eye movements produced by pre- or postsynaptic deficits should be similar. In both ELS and MG, the central gain has been turned up in response to a peripheral abnormality that causes increased innervation bilaterally in a given direction. However, due to the differential nature of the deficit in the agonist eye muscles of each eye, the resulting eye movements are usually not equal in magnitude (this results in a +1 type movement). With the use of high-bandwidth recordings and velocity as well as position channels, it can be determined that, although the eye movements are not of equal magnitude, their timing is simultaneous.[7]

Facilitation occurred in two of our ELS patients, sometimes resulting in the transition from HO to HR

and increased peak velocities of these saccades (figure 3).

Two of the five patients had a positive response to edrophonium, in which HR-saccades replaced the pre-edrophonium HO-saccades (figure 4). However, all five patients had ELS as defined by electrodiagnostic tests of limb muscles, and none had detectable AChR serum antibodies. The two patients with positive edrophonium tests also showed saccadic facilitation, an unequivocal sign of ELS. Edrophonium responses in ELS patients have been reported.[4,14] We cannot determine whether these two patients had both ELS and MG.[15-20]

The only method that distinguishes between ELS and MG is microelectrode study, which has not been reported in patients with evidence of both disorders. Our patient 5 improved with pyridostigmine and had hyperplasia of the thymus gland. Malignant thymoma was reported in one case of ELS,[21] but thymus hyperplasia, a characteristic finding in MG, has not been reported previously in ELS.

Although the edrophonium caused the manifestation of the internal high gain (HR replacing HO), m-saccades with +1 conjugacy were evident both pre- and postedrophonium. These adaptive changes in the brainstem pulse generator (where the neural package for saccades is initiated), in response to peripheral disease, imply that these trajectories, simultaneous in both eyes, were due to pulse generator changes. If they were secondary to the problem in neuromuscular transmission, as suggested in MG,[22] they should have been eliminated in the positive edrophonium tests in patients 2 and 5, but m-saccades (present in both ELS and MG) were unaffected by edrophonium.[7] Given the unequally affected muscles in each eye, it is not surprising that their common innervation resulted in movements that were only directionally conjugate. As with MG, patients with ELS also had MSO after edrophonium, a reflection of the high central gain in both conditions.

Four of the five patients showed frequent SWJ. This type of saccadic intrusion is not specific for any neurologic condition and is seen in many normals.[23]

For both MG and ELS, we can attribute some of these findings to changes in the ocular motor system at either a central or peripheral level.[8] Specifically, HO results from a low peripheral gain (G_P) due to the neuromuscular deficit. HR (after edrophonium) is due to the increased central gain (G_c) resulting from the plastic adaptation in attempts to overcome the low G_P. The HR of facilitation in ELS also reflects the high G_c, because the initially low G_P increases with each movement. As in MG, we believe that the m-saccades of ELS may be due to increased central innervation mediated by a fast proprioceptive loop[7,8] (table 3). Our studies in MG gave rise to an unanswered question about the functional integrity of the spindle neuromuscular junction; the same question is posed for ELS. Specifically, is there an abnormality of the intrafusal junction that would affect proprioceptive information from the muscles in ELS or MG? Is the ocular motor system getting accurate information about a malfunctioning muscle, or inaccurate information from that same muscle? The end result in both MG and ELS is high central gain and the occurrence of m-saccades.

Table 3. Central and peripheral effects

OM sign	ELS	MG
HO	↓ G_p	↓ G_p
HR (+ Tensilon test)	↑ G_c	↑ G_c
HR (facilitation)	↑ G_c	—
m (central innervation)	Proprioception	Proprioception

G_p Peripheral gain.
G_c Central gain.

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