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The Contribution of Oculography to Early Diagnosis of Myasthenia Gravis

A Study of Saccadic Eye Movements using the Infrared Reflection Method in 22 Cases

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Summary. Saccadic eye movements were examined by infrared reflection oculography in 22 patients with suspected myasthenia gravis. In all of them the diagnosis was confirmed either by electromyography, by the presence of acetylcholine-receptor antibodies (15 cases), by a positive clinical Tensilon test (4 cases), or by the course of the disease (3 cases). The aim of the study was to find out which of the saccade disorders described in myasthenic patients can be found in the early stage of the disease, and to discover their diagnostic value. Typically, saccade abnormalities were also seen in clinically uninvolved eyes. Intrasaccadic disorders mainly consisted of "decrescendo" of the velocity profiles (two-thirds of the cases) and „hypometria" (half of the cases). Postsaccadic "waver" was present in about two-thirds of the patients. The most frequent finding was "intersaccadic variation" (i.e., variation between repeated corresponding saccades) which occurred in 18 of the 22 patients, and particularly affected the velocity profiles. A standardized fatigue test proved to be useful in accentuating mild, or provoking latent pathology in most of the patients. A standardized combined examination of saccades with Tensilon yielded pathological results less frequently than hitherto described in the literature. In 4 of the 9 patients with purely ocular myasthenia gravis oculography led to the diagnosis. The problems in attempting to delimit the observed saccade abnormalities from those found in other eye movement disorders are discussed.

Key words: Myasthenia gravis, early diagnosis – Ocular myasthenia gravis – Saccadic eye movements – Infrared reflection oculography (IROG) – Fatigue test – Tensilon test

Introduction

Eye movement disorders are very frequent in myasthenia gravis. In large series ocular symptoms were found to be present at onset in 65%–84% of the patients, and in 40%–53% of all cases the initial symptoms were purely ocular (Bever et al. 1983; Grob et al. 1981; Oosterhuis 1982).

Oculographic studies have documented and defined various abnormalities of saccadic eye movements in patients with myasthenia gravis (Feldon et al. 1982; Schmidt et al. 1980a, b; Spooner and Baloh 1979; Yee et al. 1976). Yee et al. (1976) described three pathological waveforms: hypometric, glissade-like, and hypermetric. Large saccades were mainly hypometric or glissade-like, but their maximum velocities were not significantly different from those in normal individuals. The duration of the glissade-like saccades, however, was prolonged, which was attributed by the authors to intrasaccadic fatigue. Small saccades, on the other hand, often had abnormally high velocities and were often hypermetric. Similar observations have been made by other authors (Feldon et al. 1982; Schmidt et al. 1980a, b; Spooner and Baloh 1979) Schmidt et al. (1980a and b) made detailed analyses of eye movements in myasthenic patients. They defined several subtypes of saccadic trajectories, and additionally studied eye position during maintained gaze. Feldon et al. (1982) distinguished five abnormalities reflecting fatigue in the saccadic system, three of them were intrasaccadic and two postsaccadic. Intrasaccadic abnormalities of the velocity profiles included stutter, decrescendo, and slowing. Postsaccadic fatigue consisted of backdrift and waver. Some authors also observed the effects of Tensilon on saccadic eye movements (Huber 1980; Schmidt et al. 1980b, Spooner and Baloh 1979; Yee et al. 1976). After intravenous injection of Tensilon they often found an increase of the saccadic amplitude.

Bearing in mind the high frequency of early clinical eye movement disorders and the variety of oculographic saccade abnormalities, the question arises, how far oculographic examination of saccadic eye movements could contribute to early diagnosis of myasthenia gravis. Since the above mentioned oculographic studies had been performed in patients with advanced disease, it is unclear as to which of the described saccade disorders can be found in the early stage, and the level of their diagnostic value. To answer these questions we recorded horizontal saccadic eye movements in patients with suspected myasthenia gravis.

Patients and Methods

A total of 22 patients with suspected myasthenia gravis were examined by means of infrared reflection oculography (IROG). The diagnosis was confirmed in 15 of the patients by other laboratory examinations, in 4 of them by a positive clinical

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Tensilon test, and in the remaining 3 (Cases 1, 5, and 9) by the course of the disease. The age of the 11 women and 11 men ranged from 20 to 77 years (mean 54.7 years). At the time of their first neurological examination the symptoms in 14 cases had lasted from 1 to 4 months (mean 2.4 months), and in 8 cases from 6 to 72 months (mean 21.6 months). In all patients except Case 5 an electrophysiological examination (Oezdemir and Young 1976; Slomić et al. 1968) was performed. This included repetitive stimulation of an ulnar, a facial, and/or an axillar nerve with recording from the m. adductor pollicis, the m. orbicularis oculi and the m. deltoideus respectively. When examining the ulnar nerve the isometric contractions of m. adductor pollicis were also recorded. In 19 patients serum was examined for the presence of acetylcholine-receptor antibodies. The IROG recordings were performed in 14 patients within 10 days, and in the other 8 patients between 2 months to 2 years (mean 7.8 months) after the first neurological examination.

Recording of Eye Movements

Horizontal eye movements were recorded from each eye separately with an improved version of the infrared reflection method (Bahill et al. 1975; Meienberg and Burkhalter in press). The eye was diffusely illuminated with (invisible) infrared light. While the subject was looking straigt ahead, a pair of photosensors mounted on a head-fixed frame was aimed at the iris-sclera border, one on each side of the iris. When the eye was turned, e.g., to the right, the right photosensor which was exposed to the dark iris picked up less light than the left photosensor which was exposed to the white sclera. The difference in the currents from the photosensors was a measure of the eye position. To obtain saccadic velocities, the position signals of each eye were differentiated electronically. The differentiators were calibrated with a series of ramp signals of different velocities between 50 and 750°/s. Amplification was 10 mm = 10° for eye position signals, and 15 mm = 750°/s for saccadic velocity. Both position and velocity signals were linear within the range of eye movements examined. Blinks were continuously monitored on a separate channel. A rectilinear chart recorder was used. The whole system had a bandwidth from DC to 70 Hz.

Protocol

The patients were sitting in a dimly lit room on a modified dental chair with neck and forehead fixation at a distance of 1 m from a featureless semitranslucent white screen containing red light emitting diodes which served as targets. The patients fixated the targets binocularly. In the presence of ptosis the eyelid was raised with adhesive tape.

(1) Fatigue test: 30° saccades (± 15°) to targets presented at intervals of 1.5 s were continuously recorded during 2 min at a paper speed of 100 mm/s.

(2) Tensilon test: 20° saccades (± 10°) were examined in the following manner: immediately before the injection of 10 mg Tensilon i.v., at least 10 saccades of 20° in each direction were recorded to obtain baseline values. After the injection, saccades to targets presented at intervals of 1.5 s were continuously recorded at a paper speed of 10 mm/s during the first 5 min, and additionally during the 7th and 9th min. For further details of the examination procedure see Sonderegger et al. (in press).

Normal values and evaluation

The recordings from our patients were compared with normative data obtained from 40 eyes of 20 healthy subjects (9 females and 11 males, 4 subjects per decade from 20 to 70 years). These data included age specific normal values for accuracy, peak velocity and duration of the saccades, as well as for the standardized Fatigue and Tensilon tests (Sonderegger et al. in press). For the Tensilon test an amplitude increase of 20° saccades of more than 20% was abnormal. In addition, the recordings were compared qualitatively with various saccade disorders previously described in patients with myasthenia gravis (Feldon et al. 1982; Schmidt et al. 1980a, b; Spooner and Baloh 1979; Yee et al. 1976).

Results

Table 1 summarizes the clinical and laboratory findings of the 22 patients with myasthenia gravis. In group-1 with purely ocular myasthenia gravis the clinical Tensilon test was positive in 6 of the 7 patients in whom it was performed. The laboratory examinations in most subjects of this group were negative except for oculography which was pathological in all 9 cases. In 4 of them the oculographic findings led to the diagnosis: in 1 patient (Case 4) the diagnosis was confirmed by further examinations, while in the other 3 (Cases 1, 5, 9) it was proven by the course of the disease only. In Case 2 the first oculography 1 month after the beginning of symptoms was normal, as were all other laboratory findings, then 6 months later it was pathological. In group-2 with combined ocular and extraocular myasthenia gravis the clinical Tension test was abnormal in 5 of the 6 patients in whom it was performed. In all except 1 of the patients of this group the conventional laboratory findings (electromyography (EMG), acetylcholine-receptor antibodies) were positive, and in 8 of the 10 patients oculography was also abnormal. In group-3 with purely extraocular myasthenia gravis the conventional laboratory findings were mainly positive, whereas oculography was pathological in 1 case only.

Case report

A 43-year-old man (Case 4) complained of horizontal diplopia for several weeks. On examination, adduction of his left eye was completely restricted, while with attempted convergence some movement seemed to be possible. All other eye movements were normal, and there was no ptosis. Internuclear ophthalmoplegia was suspected. Correspondingly, IROG revealed a marked slowing of the adduction saccades of the left eye (Fig. 1). But in addition, abnormalities of all other saccades of both eyes were found which were characteristic for myasthenia gravis (Fig. 2). Therefore a Tensilon test was performed, which showed a pathological amplitude increase of the adduction saccades of the left (+55%) and abduction saccades of the right (+24%) eye. By means of oculography the diagnosis of myasthenic pseudo-internuclear ophthalmoplegia (Glaser 1966; Pierrot-Déseilligny and Michelin 1983; Spooner and Baloh 1979) was made. Figure 3 shows the result of a Tensilon test in another patient (Case 15) who had a less marked, but still pathological response.

Table 2 gives an overview of the oculographic findings. Principally three types of abnormalities, intrasaccadic, post-

Table 1. Clinical and laboratory findings in 22 patients with myasthenia gravis at the time of the first neurological examination

Case	Age	Sex	Duration of symptoms	Symptoms and signs		Clinical laboratory findings						
				Ocular[a]	Other[b]	Tensilon[c] test	EMG			Acetyl-choline-receptor antibodies	Enlarged tyhmus (CT)	Oculo-graphy
							a	b	c			
Group-1: Purely ocular myasthenia gravis												
1	77	M	1 months	++	−		−	−		−	−	+
2	47	M	a) 1 month	++	−	+	−	−		−	−	−
			b) 7 months	+++	−	+					−	+
3	77	F	3 months	+	−	+	−	−	−	+	−	+
4	43	M	3 months	++	−	+	−	−	−	+	−	+
5	71	M	3 months	+++	−						−	+
6	69	F	4 months	+++	−		+					+
7	59	M	6 months	++	−	+	−	−		−	−	+
8	72	M	11 months	+	−	+	−	+		−	−	+
9	34	F	a) 18 months	++	−	−	−	−		−	−	+
			b) 40 months	+++	−					−		+
Group-2: Ocular and extraocular myasthenia gravis												
10	69	F	1 month	++	+	+	+	−			−	+
11	24	F	1 month	+	++	+	+	+		−	+	+
12	31	M	2 months	+	+++	−	+	+	−	+	+	−
13	35	F	4 months	+	+		+	+		+	+	−
14	31	F	4 months	++	++		+	−	+	−	−	+
15	23	M	4 months	+++	++	+	+	+		+	−	+
16	75	F	6 months	++	++		+	+		+	−	+
17	68	F	6 months	++	+		+	+		+	−	+
18	63	F	4 years	+++	+	+		−		−	−	+
19	20	F	6 years	++	+++	+	+	+		+	−	+
Group-3: Purely extraocular myasthenia gravis												
20	71	M	1 month	−	++			−		+	+	−
21	75	M	2 months	−	++		+		+	+	−	+
22	70	M	6 months	−	++		+	+		+	−	−

[a] + Mild ptosis, no diplopia
++ Diplopia without visible restriction of eye movements
+++ Mild to moderate restriction of eye movements
[b] + Mild weakness of skeletal muscles
++ Moderate weakness of skeletal muscles
+++ Severe weakness of skeletal muscles
[c] Repetitive stimulation of:
a N. facialis with recording from m. orbicularis oculi
b N. ulnaris with recording from m. adductor pollicis
c N. axillaris with recording from m. deltoideus
− Negative result of examination

saccadic, and intersaccadic, were identified, which were also present in clinically unaffected eyes at varying levels. The subtypes of intrasaccadic disorders occurred with different frequencies. "Decrescendo" was found in 14, and "hypometria" in 10 of the 22 patients. "Stutter" and abnormally "slow" saccades were observed in only 1 and 3 cases respectively. Of the postsaccadic abnormalities "waver" (inability to hold steady eye position) was present in 16 cases, while "backdrift" was only found 5 times. Intersaccadic disorders consisted of "variation" between repeated corresponding saccades (e.g., all rightward saccades of the right eye). Intersaccadic variation was present in 18 of the 22 patients, and particularly affected the velocity profiles (Fig. 2).

The Fatigue test (results between brackets in Table 2) proved to be useful in accentuating spontaneous pathology, or in making latent pathology become manifest. Intrasaccadic abnormalities were stressed in 10 patients; postsaccadic disorders became more manifest in 11, and intersaccadic variation was markedly increased in 10 patients. A continuous decrease or increase of any saccadic parameter toward the end of the test could not be observed on our patients. Altogether the Fatigue test accentuated or provoked pathology in 17 of the 22 patients.

During the Tensilon test the characteristic pathological finding was hypermetria or an abnormal increase of the saccade amplitude (Fig. 3). In all patients the response to Tensi-

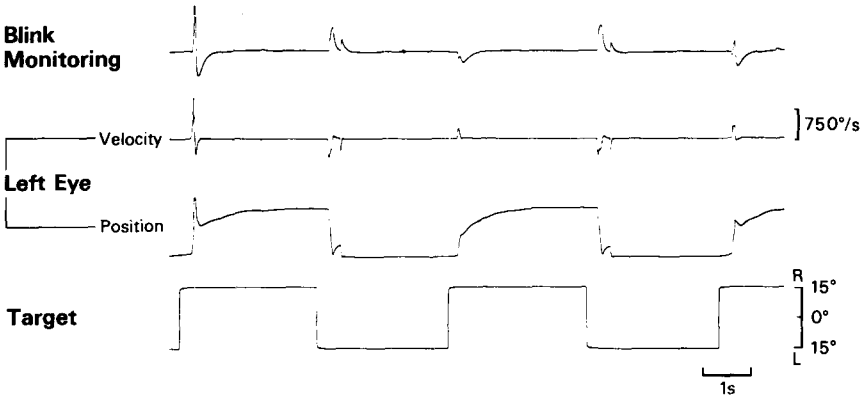

Fig. 1. Recording of saccadic eye movements (Case 4): marked slowing of rightward saccades, moderate slowing of leftward saccades with backdrift and corrective saccade. Note the two blinks (triphasic transients) which accompany the first and third rightward saccades, producing artifacts, that by themselves cannot be distinguished from real postsaccadic backdrift. (The biphasic transients of the blink monitoring trace are due to a slight deviation of the photocells from the horizontal plane)

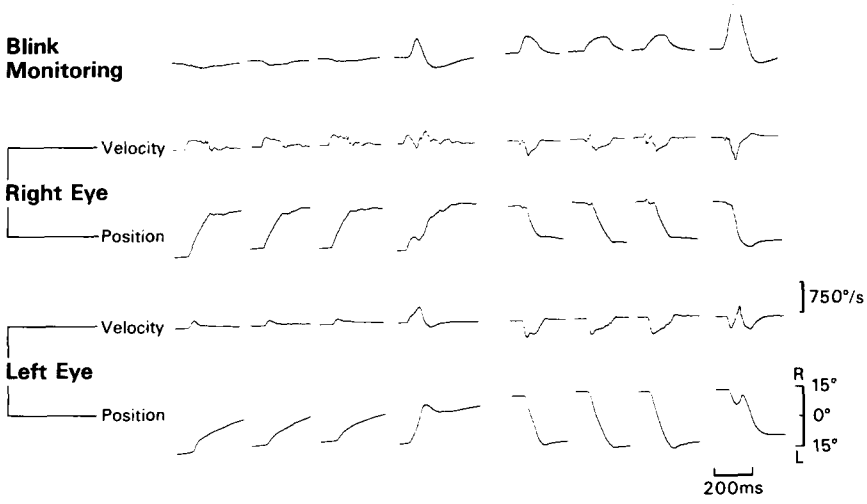

Fig. 2. Fatigue test (Case 4): rightward saccades are shown in the left, leftward saccades in the right half of the Figure. For comparison a saccade each contaminated with a blink artifact is shown. Characteristic intrasaccadic abnormalities of the velocity profiles such as decrescendo (leftward saccades of both eyes) and stutter (rightward and leftward saccades of the right eye) are also present in clinically unaffected movements. Additionally, the repetition of saccades during the fatigue test reveals intersaccadic variation between corresponding velocity profiles (e.g., all leftward saccades of the right eye).

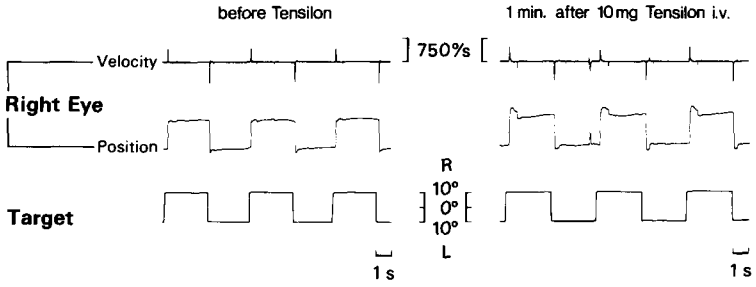

Fig. 3. Tensilon test (Case 15): before Tensilon the saccades are normometric, 1 min after 10 mg of Tensilon i.v. the saccades have become pathologically hypermetric to both sides (+35% to the right, +24% to the left; upper limit of normal: 20%), as inferred from the relatively large correction saccades to the target in the opposite direction 200 to 400 ms after the main saccade.

lon began within the first 2 min after the injection. The maximum effect in most of them was reached around the 2nd min, with no further increase observed after the 3rd min. In 2 patients (Cases 9 and 14), after the decline of the Tensilon effect a marked hypometria appeared in the 7th and 9th min respectively. Altogether the Tensilon test was positive in 7 of the 22 patients only. In 8 other patients a mild hypermetria was present which, however, still fell within the normal range. In most patients Tensilon produced burning and tearing of the eyes. In some of them this led to artificial reduction of amplification due to changes of reflection. When they were allowed to blink a few times while continuing the test, the artifact generally disappeared. In 2 patients the artificial amplitude reduction of the saccades transiently fell below the normal range. Since they were not followed by corrective movements, these reductions of amplitude could be distinguished from true hypometric saccades.

Discussion

It is a well known fact that the diagnosis of myasthenia gravis can at times be difficult (Engel 1984; Kelly et al. 1982; Osserman 1967). This is particularly true for the purely ocular form of this disorder, where extended EMG examinations have been found to be negative in 23%–83% (Kelly et al. 1982; Oh et al. 1982) and acetylcholine-receptor antibodies were absent in 30%–50% of patients (Grob et al. 1981; Limburg et al. 1983; Oda and Ito 1981). In some of these cases EMG of the extraocular muscles can still yield the diagnosis (Huber 1980). It is, however, inconvenient and not without risk for the patient. As our results have shown, oculographic examination of saccades may represent a welcome noninvasive alternative, since in 4 of the 9 patients with purely ocular myasthenia gravis oculography led to the diagnosis.

Table 2. Oculographic saccade abnormalities in 22 patients with myasthenia gravis

Case	Intrasaccadic				Postsaccadic		Intersaccadic variation	Tensilon test
	Hypometria	Stutter	Decrescendo	Slow	Backdrift	Waver		
Group-1: Purely ocular myasthenia gravis								
1	−	−	−	−	−	−	+ (++)	−
2a)	−	−	−	−	−	− (+)	−	−
b)	+++	+ (++)	+++	++	+	+	++ (+++)	+++
3	−	−	−	−	−	− (+)	−	+
4	++	− (+)	++ (+++)	+	− (+)	+	++	++
5	++	−	−	−	− (+)	+ (++)	+ (++)	−
6	++	−	+	−	+	+	+ (++)	−
7	+	−	++ (+++)	−	− (+)	+	+ (++)	−
8	−	−	+	−	−	+	+	−
9a)	+ (++)	−	+	−	+	+ (++)	+ (++)	−
b)	++	−	+	−	+	+ (++)	− (++)	+
Group-2: Ocular and extraocular myasthenia gravis								
10	++	−	+	+	−	+ (++)	+	−
11	−	−	+	−	+	+	+ (++)	−
12	−	−	−	−	−	−	−	−
13	−	−	−	−	−	−	− (+)	−
14	− (+)	−	+	−	−	+	+	−
15	− (+)	−	+	−	−	+	++	+
16	+	−	+	−	−	+	++	−
17	−	−	+	−	−	+	++	−
18	− (+)	− (+)	++	−	− (+)	++	++ (+++)	++
19	+ (++)	−	++	− (++)	+ (++)	+	++ (+++)	−
Group-3: Extraocular myasthenia gravis								
20	+	−	−	−	−	+	−	−
21	− (+)	−	−	−	−	− (+)	+	++
22	− (+)	−	−	−	−	− (+)	+	−

\+ Mild
++ Moderate
+++ Severe
− Negative result of examination
( ) Acentuation by Fatigue test

Some of the previous studies of saccadic eye movements in myasthenia gravis have been performed with DC-electro-oculography (EOG) (Spooner and Baloh 1979; Yee et al. 1976), and some with IROG (Feldon et al. 1982; Schmidt et al. 1980a, b). We used IROG because of its baseline stability, low noise level, and high accuracy in reproducing horizontal saccades. Baseline stability is a prerequisite for reliable recognition of postsaccadic fatigue such as waver and backdrift. The low noise level of IROG yields optimal saccadic velocity profiles. For detection of minor disorders, high accuracy of reproduction is of particular importance. As has recently been demonstrated, IROG more accurately reproduces horizontal saccades of 20° and 30° than EOG (Hess et al. 1986). Continuous monitoring of lid blinks during the recordings is mandatory, since otherwise blink artifacts cannot be distinguished from true intrasaccadic or postsaccadic myasthenic fatigue (Figs. 1 and 2). The observation that patients with myasthenia gravis (own experience), as well as patients with other eye movement disorders (Zee et al. 1983) more often make spontaneous blinks associated with saccades than healthy subjects, underscores the importance of this postulate.

Qualitatively, our oculographic findings were identical with those described previously (Feldon et al. 1982; Schmidt et al. 1980a, b; Spooner and Baloh 1979; Yee et al. 1976). Similarly, saccade abnormalities were also often seen in clinically uninvolved eyes. The frequency of the saccade abnormalities we found, however, was different from previous studies. This is probably explained by the fact that these authors had examined patients with more advanced disease. In our patients, of the intrasaccadic disorders decrescendo was found in about two-thirds and hypometria in about half, whereas stutter and abnormally slow saccades were almost never observed. Of the postsaccadic abnormalities waver was frequently present, while backdrift was only occasionally found. Variation between repeated corresponding saccades, i.e., intersaccadic variation, was the most frequently encountered finding. The standardized Fatigue test we employed, proved to be useful in accentuating mild or provoking latent pathology in most of our patients. This virtually important aspect has hitherto not been sufficiently appreciated. On the other hand, we did not observe any continuous change of saccade parameters during the repeated refixations of the 2-min

Fatigue test in our patients with early myasthenia gravis. While some authors have made similar observations (Schmidt et al. 1980b; Yee et al. 1976), others found a progressive decrease of amplitude and velocity during a 3-min period of refixations (Huber 1980; Spooner and Baloh 1979). Whether this discrepancy is due to the longer duration of the test or to more advanced disease in the patients of these authors remains open. Nevertheless, combining a 2-min Fatigue test with IROG, we detected a number of other important abnormalities.

Some authors have used oculographic examination of saccades in combination with a Tensilon test (Huber 1980; Schmidt et al. 1980b; Spooner and Baloh 1979; Yee et al. 1976). After the injection of Tensilon they observed an increase in the saccade amplitude, often with hypermetria. In the present study an abnormal increase of the amplitude was found in 7 of the 22 patients only. In 8 of our patients a mild hypermetria was present after Tensilon, but the increase of the amplitude still fell within our normal range. It cannot be excluded that, as mentioned above, tearing artificially reduced the Tensilon effect on the saccades. On the other hand, it must be remembered, that healthy subjects can also show some hypermetria after Tensilon. Therefore it is necessary to refer to normative data for the Tensilon test (Sonderegger et al. in press). Moreover, one has to consider that pure ocular myasthenia gravis sometimes shows no Tensilon response (Oosterhuis 1982). The clinical Tensilon test was more often positive in our patients than the oculographic one. This is not surprising, as with IROG only horizontal saccades are recorded and an evaluation of the Tensilon effect on lid and vertical eye movements is not possible. However, in contrast to the clinical test, the evaluation of which is subjective and sometimes remains uncertain, the oculographic Tensilon test allows an objective quantification.

The saccade abnormalities found oculographically in myasthenia gravis, though highly characteristic, are not specific. Identical or similar findings have been observed in Guillain-Barré syndrome (Feldon et al. 1982), Eaton-Lambert syndrome (Dell'Osso et al. 1983) and in cephalic tetanus (Meienberg and Burgunder 1985). Considering the clinical features of these disorders, together with an EMG examination, a distinction from myasthenia gravis should be possible without major problems. Brainstem lesions occasionally can produce saccade disorders similar to the "decrescendo" and "stutter" of myasthenia gravis (Feldon et al. 1980, and own unpublished data). In our experience they generally do not show the characteristic intersaccadic variation of myasthenia. At times, however, a definite distinction between the two is not possible without additional paraclinical examination. In ocular myopathies such as progressive external ophthalmoplegia (Oohira et al. 1985, Yee et al. 1976) or myotonic dystrophy (Oohira et al. 1985) saccadic velocities are typically reduced over a wide range of amplitudes. In addition, the abnormality is continuous and shows no intersaccadic variation (own unpublished data). In endocrine ophthalmopathy saccadic eye movements generally are little affected, even in the presence of exophthalmus. With the Fatigue test sometimes a saccade disorder can be provoked which, in contrast to myasthenic intersaccadic variation, continuously increases during the test (Mauri et al. 1984). Neurogenic palsies of extraocular muscles also lead to reduction of saccade velocity. In contrast to myasthenia gravis it is, however, confined to the clinically affected muscle and to the area of the restriction of movement (Oohira et al. 1985, and own unpublished data). Sedative drugs can also be the cause of slowing and prolongation of saccades with decrescendo deformation of the velocity profiles (Bittencourt et al. 1981; Jürgens et al. 1981; Rothenberg and Selkoe 1981; Schlaginhaufen et al. 1984). This possibility must carefully be excluded, before conclusions on existing pathology are made. Identical findings can occur, when the patient becomes mentally tired (Jürgens et al. 1981; Mauri et al. 1984; Schmidt et al. 1979). It is therefore important to pay attention to the state of alertness of the patient during the recording of saccades. In cases where reduction of amplitude or velocity, or an increase of duration is observed, the examiner must encourage the patient to concentrate on his task. If fatigue was the cause, the changes immediately disappear.

As our study demonstrated, examination of saccadic eye movements with IROG detected a number of characteristic abnormalities in the early stage of myasthenia gravis. Although such abnormalities are not specific, they represent a useful contribution to the diagnosis of myasthenia gravis.

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