Abnormal pupillary responses in myasthenia gravis
A pupillographic study

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Disorders of eye movements are frequent in patients with myasthenia gravis (MG), but abnormalities of pupillary responses are less well known. Previous investigators have examined pupillary responses in relatively few patients and quantitative results have not been reported (Manson and Stern, 1965; Osserman, 1958; Baptista and Souza, 1961; Herishanu and Lavy, 1971).

Electronic pupillography enables one to detect subtle degrees of pupillary abnormalities as well as to quantify pupillary responses. Pupillographic investigations have recently been improved both by using a well-controlled stimulus (open-loop stimulus) and by examining the derivative curves (velocity and acceleration) of pupillary responses (Meyer, Ogle, Hollenhorst, and Moyer, 1969; Morgan, Hollenhorst, and Ogle, 1968). By focusing the stimulus light, the diameter of the light ray can be made smaller than the smallest size of the pupil (Maxwellian view). Hence, pupillary responses (changes in the size of the iris aperture) will not affect the stimulus. This is called an open-loop stimulus and enables one to control the stimulus precisely.

We have investigated pupillary responses in patients with myasthenia gravis and in normal controls both before and after edrophonium chloride injections. By using an open-loop stimulus and measuring the derivative curves of pupillary reaction with infrared video pupillography (Ishikawa, Naito, and Inaba, 1970), involvement of pupillary responses in most of our patients was demonstrated.

Methods and materials

PATIENTS AND CONTROL SUBJECTS

Seven patients ranging from 12 to 45 years of age with myasthenia gravis were examined. Six had ocular myasthenia gravis, and one had generalized myasthenia

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gravis. In each patient, the diagnosis was established by a typical history and physical findings of muscular weakness and fatigue. The diagnosis was confirmed electromyographically by a decline in the amplitude of the action potential and by showing improvement in muscle strength after injection of 10 mg intravenous edrophonium chloride either from skeletal muscle or from extraocular muscle.

In Table I the clinical data are summarized. Only two patients (nos 5 and 6) had been treated with oral anticholinesterase in the past, but none was taking anticholinesterase medication at the time of the examination. The same two patients had been treated with oral prednisolone on alternate days. One patient (no. 5) had had a poor response to prednisolone and therefore it had been withdrawn about one week before measurement of his pupillary response. The other patient responded well to prednisolone and was taking medication at the time of examination (prednisolone 100 mg/day). Five healthy adults were selected for controls with a mean age of 25 years; three of them were given edrophonium injections.

RECORDING OF THE PUPILLARY LIGHT RESPONSE

The pupillary light response curve was recorded using electronic infrared video pupillography (Ishikawa and others, 1970). This system consisted of an infrared-sensitive silicon-vidicon camera (HTV-N-248), a video analysing system with specially designed integrated circuits for calculating the pupillary area, and a monitor scope. Responses were linearly related to pupillary area within ± 1 per cent in the range of 0·01 mm² and 150 mm². System sampling rate was 60 Hz.

Both sinusoidal (0·25 to 3·0 Hz) and pulse (one second) stimuli were used. The stimuli were presented under open-loop condition. The light source was a helium neon gas laser with 6328 Å wave length and 0·8 mm beam diameter, which was less than the smallest diameter of the pupil. The one-second pulse stimulus of 0·05 mW (about five log units above visual threshold) was delivered through a shutter of five-second intervals. The sinusoidal stimulus of zero to 0·0075 mW with varied frequencies of 0·25 to 3·0 Hz was produced by using a neutral density filter, a stationary polaroid filter, and a rotating polaroid filter in the beam path.

Each subject was seated in front of the pupillograph vidicon camera and the head was steadied with a chin and forehead rest. After 15 minutes' dark adaptation, the subject was asked to fixate a small red light (2 mm in diameter) through a half mirror inserted between the

Table I *Clinical manifestations of myasthenia gravis*

Patients no.	Age (years)	Sex	Type of MG	Ptosis	Extraocular muscle involvement	Past treatment	Symbols expressed in figures
1	12	Male	Ocular	Yes	Yes	None	○
2	45	Male	Ocular	Yes	Yes	None	●
3	42	Male	Ocular	Yes	Yes	None	▲
4	25	Female	General	Yes	Yes	None	△
5	39	Male	Ocular	Yes	Yes	Steroid*	☆
6	29	Male	Ocular	Yes	Yes	Steroid†	■
7	14	Male	Ocular	Yes	Yes	None	□

*The results of treatment were poor; corticosteroids were discontinued one week before examination
†The results of the treatment were excellent; corticosteroids were being taken at time of examination

eye and vidicon. The light was 3 m in front of the subject's eye. Only the direct light response of the right pupil was measured. The position of the eye was followed through the monitor scope. A typical pupillary response and derivative curve following a one-second pulse stimulus obtained from a normal subject is shown in Fig. 1. The pupillary response curve represents the actual area of the pupil during various phases of its reaction to a light stimulus. Any point on the derivative curve indicates the rate of change in the pupil at that time during its reaction to light. The slope of any part of the derivative curve reflects the acceleration or deceleration of the change during that phase of the reaction. We measured the following ten parameters by the method described previously (Morgan and others, 1968):

1. P: pupillary area at the moment of the light stimulus (mm^2)
2. ΔP: change in pupillary area caused by the light stimulus (mm^2)
3. ΔP/P $\times$ 100: rate of constriction (percentage)
4. Tc: latency time (ms)
5. MRC: maximal rate of pupillary constriction (mm^2/s)

6. MRD: maximal rate of pupillary dilatation (mm^2/s)
7. Ac: acceleration of pupillary constriction (mm^2/s^2)
8. Dc: deceleration of pupillary constriction (mm^2/s^2)
9. Ad: acceleration of pupillary dilatation (mm^2/s^2)
10. Dd: deceleration of pupillary dilatation (mm^2/s^2)

In order to obtain a preliminary baseline of the pupillary response, at least a five-second interval was given between pulse stimulus and three recordings were obtained. After this procedure, 5 mg edrophonium (half dose of ordinary use) was injected into the cubital vein within 10 seconds. The pupillary responses in each subject were recorded each minute for five minutes. After injection of the drug the response to a series of at least three pulse stimuli was recorded at five-second intervals. Then the above parameters were measured and averaged. The results are presented in graphs in which the averages of the measurements for seven myasthenics and three controls are plotted against the time elapsed since injection of the drug.

Results

PUPILLARY RESPONSES TO SINUSOIDAL INPUTS STIMULI

As the frequency increased from 0·25 to 2·75 Hz, the pupil response decreased in amplitude and its phase increasingly lagged behind the stimulus input. Typical examples of the frequency response of the pupillary reaction in a patient with MG (no. 1) are shown in Fig. 2a. Bode plots of averaged amplitudes and averaged phases obtained from five controls (dotted line) and five patients (solid line), excluding cases 5 and 6, are shown in Fig. 2b. Vertical bars denote standard deviations. For both results, Bode plots were similar to those previously reported (Stark, 1959, 1968) in a group of normal subjects. In addition, no amplitude exhaustion was detected in myasthenia patients.
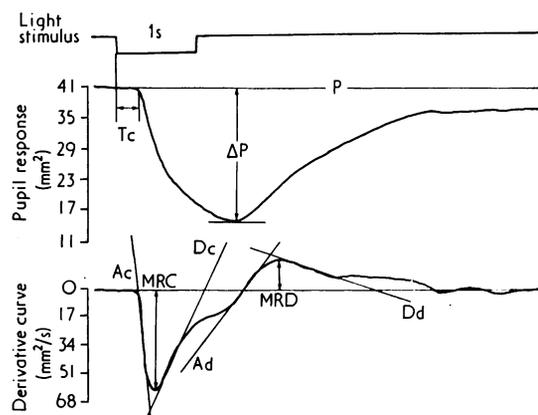

FIG. 1 *Pupillary response curve and its derivative curve obtained from normal subject for one second light stimulus. Methods of analyses of the data are shown*

PUPILLARY RESPONSES TO PULSE STIMULI

Typical superimposed recordings of the pupillary reaction and its derivative curve in response to a
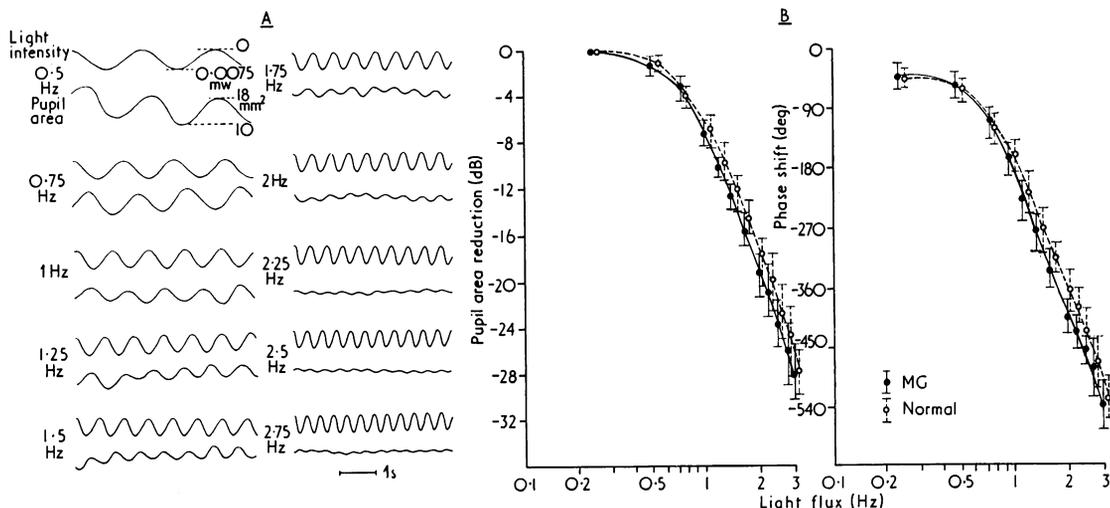
FIG. 2   (a) *Pupillary responses (pupil area) to sinusoidal light stimuli obtained from myasthenia gravis (MG no. 1) with varied frequencies. Light intensity is varied from 0 to 0·0075 mW. Pupil area changed from 18 to 10 mm² at 0·5 Hz. Amplitude of responses gradually reduced and phase lagged with the frequency increase.   (b) Bode plots of averaged amplitudes (pupil area reduction in decibels (dB)) and averaged phase shift in degrees (deg) against light flux in Hz. Solid line: averages of five cases with MG. Dotted line: averages of five normal subjects. Vertical bars denote standard deviations. No abnormal pupil response is seen and no amplitude exhaustion is detected in myasthenic patients*

one-second pulse stimulus in a myasthenic patient both before (solid line) and one minute after 5 mg edrophonium injection (dotted line) are shown in Fig. 3. The wave forms of both the pupillary reaction and its derivative curve are clearly modified by the edrophonium injection. To quantify the response to edrophonium injection in myasthenics and normal subjects, detailed comparisons of the
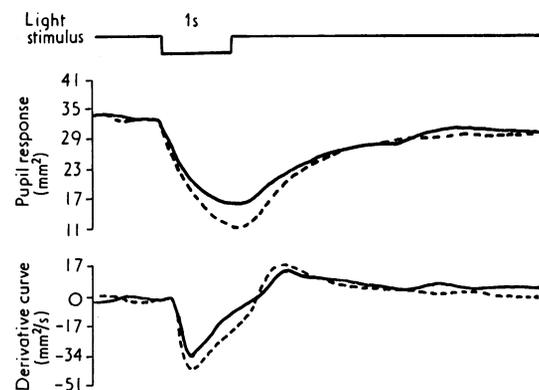

FIG. 3   *Superimposed pupillary responses and their derivative curves in response to a one-second light (pulse) stimulus in MG (no. 1) both before (solid line) and one minute after 5 mg edrophonium (dotted line) administration. The wave forms of both the pupillary responses and derivative curve are clearly modified by intravenous edrophonium injection*

Table II   *Comparison of pupillary light responses before and one minute after the administration of 5 mg intravenous edrophonium in MG (no. 1) and in normal control. Difference in the parameters of ΔP/P, MRC, Ac, Ad, and Tc are apparent*

Parameter		Before edrophonium		One minute after edrophonium	
		MG	Control	MG	Control
P	mm²	32·4	30·1	34·0	32·0
ΔP	mm²	17·1	18·6	21·9	18·5
ΔP/P × 100	Percentage	52·8	62·0	64·4	58·5
Tc	msec	300·0	278·0	282·0	280·1
MRC	mm²/s	35·7	47·5	47·5	49·0
MRD	mm²/s	13·6	15·1	16·1	15·8
Ac	mm²/s²	188·7	300·0	246·5	306·0
Dc	mm²/s²	49·3	98·0	40·8	102·5
Ad	mm²/s²	49·3	42·5	71·4	41·1
Dd	mm²/s²	13·6	14·2	15·4	14·5

time course of the effects of edrophonium on pupillary responses to a pulse stimuli were made. A comparison of MG (no. 1) with a normal control (one minute after edrophonium) is shown in Table II. Difference in the parameters of ΔP/P, MRC, Ac, Ad, and Tc are apparent. All data obtained from the seven cases and three controls before and after edrophonium are given in Figs 4 and 5. Pupillary area (P) showed a very slight increase between one and two minutes after edrophonium injection in myasthenics. Latency (Tc), ΔP/P, and MRC, all of which were moderately abnormal before edro-
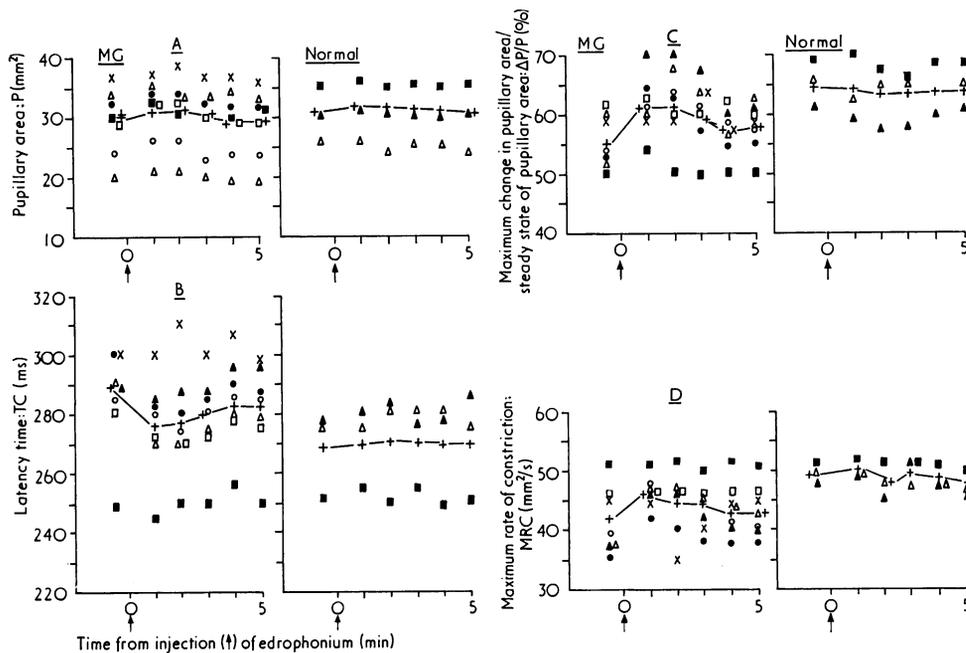
FIG. 4a, b, c, d   *All data obtained from seven cases (different symbols) with MG and three control (normal) subjects before and after edrophonium injection. Arrows indicate the time at edrophonium administration. Mean values are expressed with open star with solid line against time in minutes. A: pupillary area, B: latency time, C: maximum change in pupillary area/steady state of pupillary area, and D: maximum rate of constriction. These are moderately abnormal before edrophonium, approaching nearly normal value one to two minutes after injection*

phonium injection, approached nearly normal values by one to two minutes after edrophonium injection (Fig. 4a, b, c, d). The most striking effect of edrophonium was upon the rate of acceleration of pupillary constriction (Ac) as shown in Fig. 5a. Even one of the treated individuals showed a positive response. Changes in the rate of deceleration of pupillary constriction (Dc) were less than changes in Ac (Fig. 5b). In contrast, changes in the parameters (MRD, Ad, and Dd) of pupillary dilatation were minimal and only Ad showed a very slight increase with edrophonium administration.

In summary, in myasthenic patients edrophonium injections caused marked improvement in the parameters of pupillary constriction (especially Ac) but only minimal changes in the parameters of pupillary dilatation. No response to edrophonium injection was noted in normal subjects.

Discussion

Using electronic pupillography, abnormal pupillary reactions to an open-loop stimulus were observed in a group of patients with myasthenia gravis. Five patients without earlier treatment and one patient with previous corticosteroid therapy showed reduction in the amplitude of pupillary constriction as

well as reduced velocity and acceleration in the pupillary light response. The parameters of $\Delta P/P$, MRC, Tc, Ac, and Ad were abnormal before edrophonium injection and approached nearly normal values after the administration of edrophonium. In contrast, the same dose of edrophonium had no effect upon responses of normal controls. The more severely affected parameters were $\Delta P/P$, MRC, Tc, and Ac which reflected iris sphincter function. In contrast, the parameters of pupillary dilatation, with the exception of Ad, which may reflect iris sphincter relaxation, were unaffected by edrophonium injection. Therefore, it appears that myasthenia gravis primarily affects the sphincter rather than the dilator muscle. This may be related to the differences in innervation to the two muscles; the sphincter is predominantly innervated by cholinergic nerves while the dilator is predominantly innervated by adrenergic nerves (Lowenstein and Loewenfeld, 1969).

Defective accommodation has also been reported in patients with myasthenia gravis, because the ciliary muscle, too, is innervated by cholinergic nerve fibres (Manson and Stern, 1965).

Clinically evident pupillary abnormalities including anisocoria, and sluggish or fatiguable pupillary responses to light have occasionally been reported
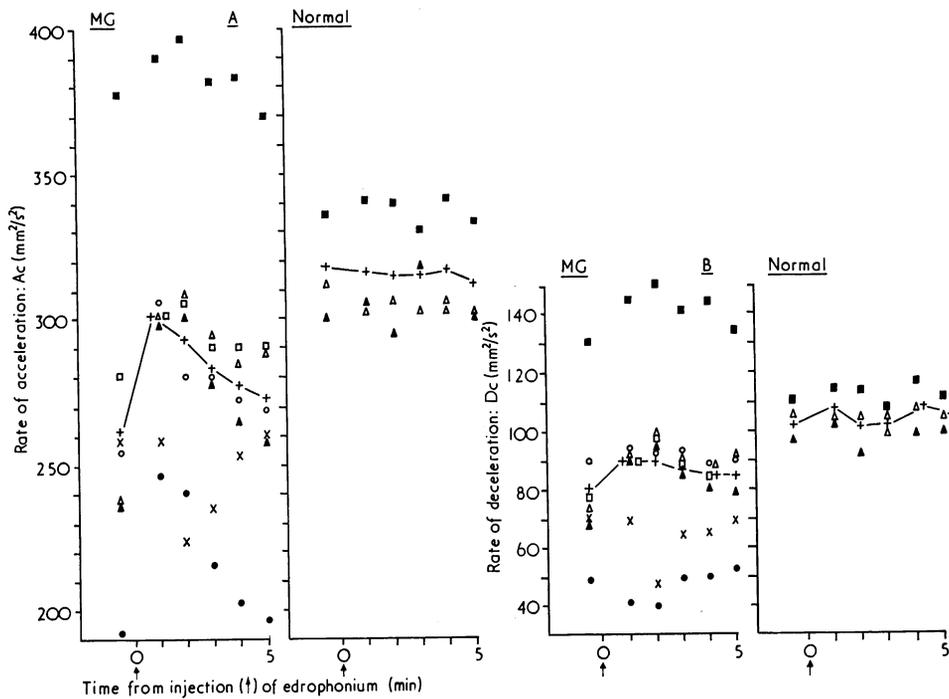
FIG. 5 (a) *Rate of acceleration. Most striking effect of edrophonium, except one case (no. 5), is seen upon rate of acceleration of pupillary constriction.* (b) *Rate of deceleration. Changes in rate of deceleration of pupillary constriction are less than changes in Ac in Fig. 5a. No response to edrophonium injection is noted in normal subjects*

in previous reports (Baptista and Souza, 1961; Herishanu and Lavy, 1971). However, in our patients, only one (no. 5) showed an abnormality—that is, sluggish pupillary light responses that could be observed without pupillography. Similarly, in none of our patients were the pupillary responses fatigued by repetitive stimulation. Whether this is related to a difference between neuromuscular transmission in somatic muscle and the iris or simply to another degree of myasthenic involvement in our patients is not known.

Recent experiments suggest that the number of available acetylcholine receptors at neuromuscular junctions is reduced in patients with myasthenia gravis (Fambrough, Drachman, and Satyamurti, 1973; Satyamurti, Drachman, and Slone, 1975). It is of interest that topical administration of tropicamide, which acts by binding the cholinergic smooth muscle receptor sites blocking the action of acetylcholine, reduces ΔP, MRC, Ac, and Ad without clear mydriasis in normal subjects (Morgan and others, 1968). Since the pupillographic responses in our patients were nearly identical to those in normal subjects treated with tropicamide, it seems likely that the number of available acetylcholine receptors at the pupillary sphincter muscle in patients with myasthenia gravis is reduced. The

positive response to edrophonium supports this idea.

One of two patients treated with oral prednisolone showed increased acceleration of the pupillary response. Further work is needed to explain this phenomenon, although it has been reported that there is a supernormal electroretinogram with increased 'a' as well as 'b' waves in human eyes after the oral administration of prednisolone (Zimmerman, Dawson, and Fitzgerald, 1973).

Finally, our results indicate that recording of pupillary responses in patients with myasthenia gravis provides another means to diagnose myasthenia gravis objectively as well to quantify effects of treatment.

Summary

Using an open-loop stimulus (Maxwellian view), the direct pupillary response to light and its derivative curves (velocity and acceleration of pupillary reactions) were recorded by infrared video pupillography in seven patients with myasthenia gravis and in three normal subjects. Responses before and after intravenous injection of 5 mg edrophonium hydrochloride were determined. Five of the patients had never taken anticholinesterase drugs except for diagnostic injections of edrophonium

while the other two patients had been treated with oral preparations of corticosteroids.

Analyses of the pupillary responses showed reduced amplitude, maximal velocity, and maximal acceleration of pupillary constriction in the myasthenic patients. On the other hand, changes in parameters of pupillary dilatation were minimal. Abnormal values returned towards normal within five minutes after edrophonium injection in all patients except in one individual who was being treated with corticosteroids at the time of examination. These results suggest that involvement of the iris sphincter may be common in patients with myasthenia gravis and this can be demonstrated by analysing the pupillary reaction and its derivative curves in response to an open-loop stimulus.

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