The ocular signs and symptoms of myasthenia gravis

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Abstract. Myasthenia gravis is a chronic disease characterized by a fluctuating weakness of voluntary muscles, with a preference for the muscles innervated by the cranial nerves. Ocular symptoms (ptosis, diplopia) were present at onset in 65% of 432 own patients and in 10% of these patients the disease remained confined to the extrinsic eye muscles. A complete remission occurred in 30% of the purely ocular cases within 10 years of onset. The diagnosis depends upon the pattern of weakness, the spontaneous or provoked fluctuation of the symptoms and the favourable response to anticholinesterases. The presence of antibodies against acetylcholine receptor protein is the most recent tool to confirm the diagnosis, but they are absent in 10–20% of the patients with generalized MG and in 20–50% of the purely ocular cases. As the reaction to anticholinesterases in ocular MG is sometimes equivocal or even absent auxillary investigations (electromyography, tonography, nystagmography, curaretest) may be necessary. Oral anticholinesterases (Pyridostigmin, Prostigmin, Ambenomium) usually have a moderate effect on the ptosis and a poor effect on the diplopia so that other measures (ptosishooks, covering one eye) are necessary. In selected patients alternate-day Prednisone is the therapy of choice.

Introduction

Myasthenia gravis (MG) is characterized by a fluctuating weakness of voluntary muscles, caused by a failure of neuromuscular transmission. Recent investigations (review Engel, 1979) have demonstrated that this failure is due to a loss of acetylcholine receptors at the postsynaptic membrane as a result of an autoimmunological mechanism. The disease may involve all voluntary muscles, but a striking preference exists for the muscles innervated by the cranial nerves and especially for the extrinsic eye muscles and the m. levator palpebrae. In 60–70% of patients the first complaints are diplopia and/or ptosis of one of the upper eye lids. Since the signs and symptoms are fluctuating, especially at onset, and may be absent in the morning, the diagnosis is frequently overlooked by both ophthalmologists and neurologists at the first consultation. Even in patients with prominent and lasting symptoms the diagnosis is delayed and made after a series of negative investigations including computertomography of the brain and orbita and arteriography, in order to exclude aneurysms and space-occupying lesions. This neglect may be explained by the relative rareness of MG. In an epidemiological

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investigation in Amsterdam between 1961 and 1965 (Oosterhuis, 1977) the total prevalence was 5.6/100.000 (2.4/100.000 men and 8.4/100.000 women). This implies that the incidence of new cases is 0.4/100.000/year, so that the average peripheral ophthalmologist or neurologist may expect 1 new patient in 2–3 years. The purpose of this article is to give an overview of the ocular signs and to indicate the procedure needed to reach the diagnosis. Although the pathogenesis is still a matter of speculation, some valuable therapeutic measures are available.

Signs and symptoms

In the last 20 years I have seen about 500 patients with MG of whom 432 were followed up for at least 3 years after onset (mean 11.6 years, range 3–48 years). In 40% the initial symptoms were purely ocular, in 11% ocular and bulbar and in another 14% generalized so that ocular symptoms occurred at onset in 65% of the patients. At the end of the follow-up only 10% remained purely ocular (*Table 1*). In 12 patients (3%) the involvement of

Table 1. Myasthenia gravis. Follow-up > 3 years

Age at onset	men	women	total
0–9	10 (2)	8 (3)	18 (5)
10–19	19 (2)	71 (1)	90 (3)
20–29	21 (1)	86 (2)	107 (3)
30–39	15 (1)	45 (2)	60 (3)
40–49	22 (7)	34 (4)	56 (11)
50–59	21 (5)	30 (3)	51 (8)
60–69	15 (5)	17 (2)	32 (7)
70	9 (2)	9 (1)	18 (3)
	132 (25)	300 (18)	432 (43)
% ocular MG	19%	6%	10%

In brackets ( ) the number of cases included in the previous number that remained purely ocular at the end of the follow-up period (range 3–48 years, mean 11.6 years)

non-ocular muscles took first place after the third year of the disease. In 5 other patients the disease remained ocular during the follow-up of 20 years, with the exception of a short period of more generalized weakness e.g. some weakness of the upper arms or of the bulbar muscles. From the data in Table 1 the preponderance of women in the age-group of 10–40 years can be seen, which is a general feature in other large series. The purely ocular MG was significantly more represented in men than in women and also more prevalent in the older age groups.

Another well-known feature is the presence of thymomas in about 10–15% of the patients, but especially in the patients with an onset between 40 and 70 years. Thymomas were detected in 20 out of 132 men and 42 out

of 300 women in this series but *never* in patients in whom the MG remained purely ocular for 3 years. The most obvious and frequent complaint due to ocular MG is diplopia, caused by paresis of one but usually of several external eye muscles of one or both eyes. The medial recti are most commonly affected followed by the elevators of the eye with a preference for the superior recti. Diplopia is relatively rare on downward gaze but any combination of palsies may be seen. Especially at onset but also in the course of the disease the diplopia may occur without visible squinting or disturbance of movement if the inspection is done routinely and without provocation. A simple provocative test is to ask the patient to sustain the gaze in one of the horizontal or vertical directions for at least 30 seconds. It is usual for diplopia to appear within that time during which the failure of sustained movement becomes visible. When the patient looks to the side some other remarkable features may appear. At first it may be noted that adduction fails and the patient indicates diplopia; at the same time or some seconds later the abducting eye shows nystagmoid movements which gradually become coarser and end in a visible paresis of the external rectus of the abducting eye. This syndrome may be named pseudo-internuclear ophthalmoplegia (Glaser, 1966). Sustained lateral gaze during 30 seconds may also provoke ptosis, especially of the abducting eye, even if ptosis is not a spontaneous complaint. In some patients I have found that sustained lateral gaze more easily evokes ptosis than looking upwards (Fig. 1). It is not unusual for ptosis in some degree to be present from the onset of diplopia, but this sign may remain unnoticed by the patient if the upper lid does not cover more than 25% of the eye. On the other hand ptosis may be a very prominent sign from the onset, so that it obscures the diplopia. The ptosis may be present on one eye or on both, but if on both eyes it is nearly always asymmetrical. It is not rare for the ptosis to fluctuate rapidly, e.g. during the interview, a feature already reported by Oppenheim (1901), so that it may be falsely interpreted as a sign of 'nervousness'. Cogan (1965) described the same feature as lid-twitching when the patient is asked to look upwards. Even more strange but less common is a rapid shift of the ptosis from one eye to the other, which is considered by Osserman (1958) as pathognomonic for MG. This shift is not uncommon over longer periods of observation. Patients with a purely ocular MG try to correct the ptosis by contraction of the mm. frontales, but this sign may be absent in patients with facial weakness. Both the ptosis and the diplopia increase if the patient looks at the bright light or even on sunny days, so that many patients prefer to wear sunglasses even at home. Ptosis and diplopia usually increase in the course of the day, but about 10% of patients report that these symptoms are present on awakening in the morning or after a short nap in the afternoon and diminish subsequently in the next 30–60 minutes without medication. Simpson (1960) was the first to mention this. The ptosis increases on staring intently at a fixed point (Fig. 2) and decreases after 3 minutes of eye closure (Fig. 3). After this rest period another symptom

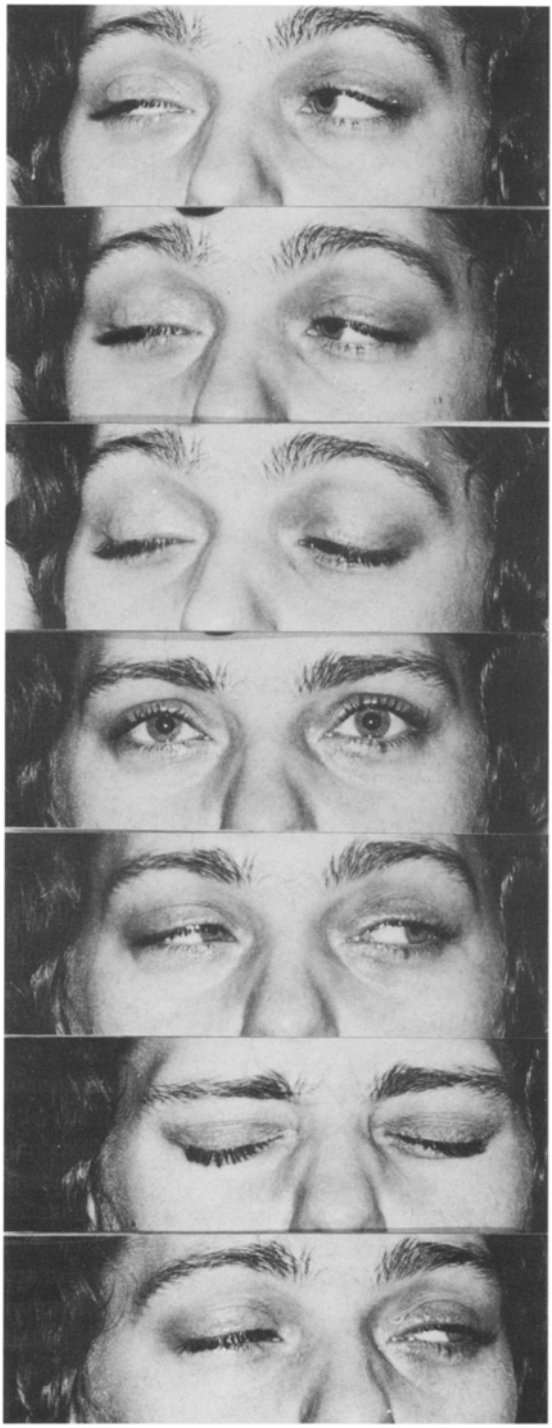

Figure 1. Fluctuating ptosis provoked by looking to the side. A) after 10 seconds; B) after 20 seconds; C) after 30 seconds; D) after 40 seconds; E) after 10 seconds; F) after 20 seconds; G) after 30 seconds

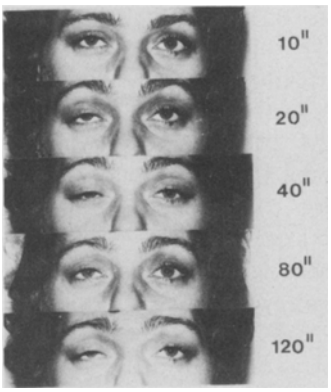

Figure 2. Fluctuating ptosis during 2 minutes of staring at a fixed point

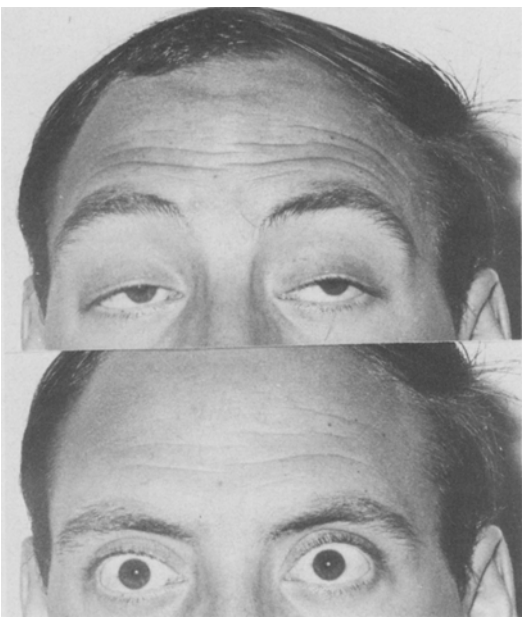

Figure 3. A) ptosis partially relieved by contraction of the m. frontalis; B) after 3 minutes of eye closure the ptosis has disappeared and the palpebral fissure is widened due to the weakness of the m. orbicularis oculi

is sometimes seen: widening of the palpebral fissure due to weakness of the orbicularis oculi muscle which was obscured by the ptosis. Some weakness of eye closure is present in half of the patients with a purely ocular MG and is nearly always detectable in patients with facial and bulbar weakness. If the

strength of the m. orbicularis is tested, the examiner may see that the physiological elevation of the eye is absent due to the weakness of the elevator eye muscles. In some of these patients the eye cannot be fully closed so that they complain of irritated eyes in the morning. This orbicularis fatigue is also the mechanism underlying the 'peek' sign: in trying to keep the eyes gently closed the palpebral fissure widens and the patient seems to 'peek' at the examiner (Osher and Griggs, 1979). Many patients without obvious ptosis or diplopia complain of the same irritation or a somewhat blurred vision after reading, car-driving or watching the television. These complaints are probably due to a slight intermittent eye muscle paresis. A curious phenomenon may be exemplified with the case history of a 60-year-old man, who suddenly acquired a vertical diplopia, followed soon by a horizontal deviation. Later he also acquired a bilateral ptosis, the right side being more severely affected than the left (Fig. 4).

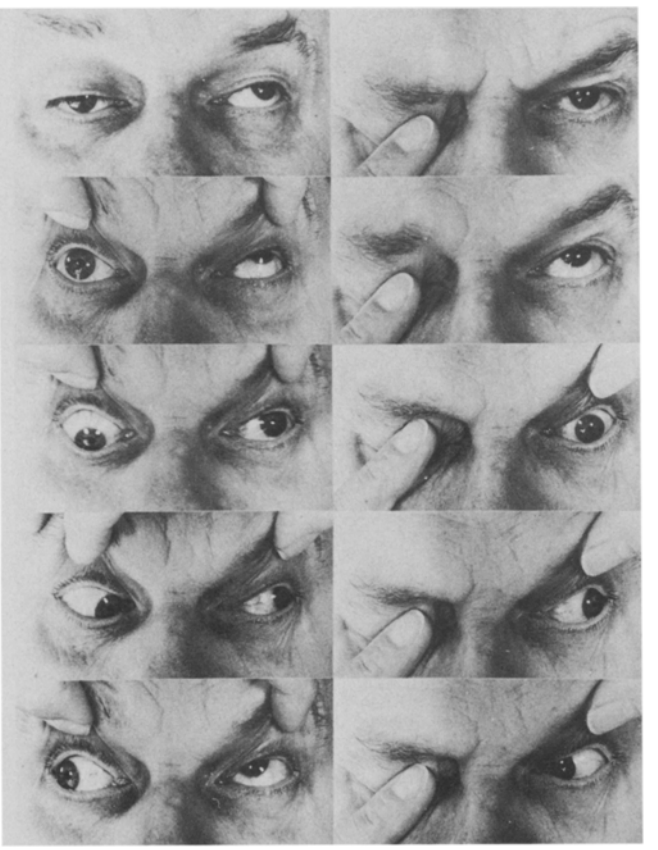

Figure 4. Difference between fixation with the right eye (both eyes open) and with the left eye (right eye closed)

At examination the elevation of the right eye was impaired, whereas the left eye could not be depressed. All other movements appeared to be nearly normal. During preferred fixation with the right eye, the left eye's position was in outward and extremely upward direction. However, during closure of the right eye, the left eye could easily maintain the primary position, while downward gaze remained restricted; the occluded right eye's position was then downward and outward. The extremely large vertical deviation of the left eye may be explained on the grounds of Hering's law of equal distribution. To keep the dominant right eye in the primary position an increased innervation to the right elevator muscle is needed. The same increase of innervation is provided to the non-paretic contralateral synergist of the left eye, which is not counteracted by the paretic homolateral depressor muscle. The same mechanism also explains the observation that passively closing the ptotic lid of the fixing eye may cause some ptosis in the other eye. It is important to note that no weakness of the sphincter pupillae is detectable by clinical methods. I could not confirm the observations of Baptista et al. (1961) who reported diminished pupillary contractions on repeated exposure to light, nor the complete lightstiffness after 2–3 minutes of repeated illumination reversed by edrophonium, as described by Herishanu et al. (1971). However, with infrared pupillography, Yamazaki et al. (1976) and Lepore et al. (1979) demonstrated about 30% slowing of the pupillary contraction-dilatation cycles.

Diagnosis

The essential features of myasthenic paresis are the pattern of involvement and the fluctuation over short and long periods (Fig. 5). This fluctuation may be spontaneous but is nearly always provoked by exertion and diminished by rest. Rapid 'spontaneous' fluctuation indicates that the periods of rest may be very short, even as short as seconds. Evidence that ocular signs are due to MG may further rely on the demonstration of fluctuating weakness outside the ocular muscles, particularly of the bulbar muscles, or on the detection of antibodies against acetylcholine receptors which are present in 85–90% of patients with generalized MG and in 43–70% of patients with purely ocular symptoms (review Vincent and Newsom Davis, 1980). If the diagnosis is suspected on the basis of the history and the findings at clinical examination, a favourable reaction to anticholinesterases, either edrophonium chloride (Tensilon®) or prostigmine, is considered to be a final proof. Indeed an unequivocal reaction to either of these drugs is specific for MG, but especially in the ocular pareses some pitfalls should be mentioned that impede a proper interpretation and not seldom lead to a false negative conclusion. The following precautions should be taken:

(1) The fluctuating muscle function in a period without anticholinesterases should be compared with the function in a similar period after injection

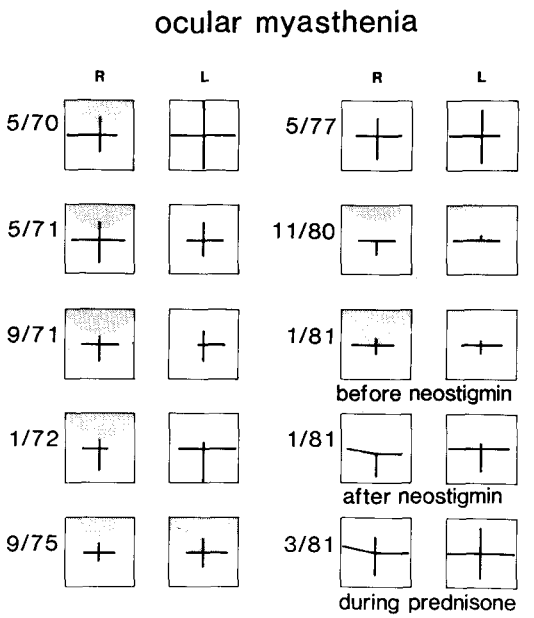

Figure 5. Ptosis and global range of eye-movements in 4 directions over a 10-year period. Spontaneous fluctuations, incomplete reaction to Neostigmin and rapid amelioration after alternate-day Prednisone treatment

of anticholinesterases and preferably also in a period after injection of a placebo. A common finding is that the ocular weakness reacts only partially so that some ptosis or diplopia is still left. If the change in diplopia is not analyzed properly, e.g. with a Lancaster red-green test (Retzlaff et al., 1969), the patient may deny any effect of anticholinesterases although the distance between the double images has decreased. On the other hand a negative Tensilon test may be present in longstanding cases with nearly complete external ophthalmoplegia.

(2) The ptosis may fluctuate rapidly and increase in bright light, or on looking intently at a certain point, or under the influence of emotions. These factors may obscure the influence of anticholinesterases.

(3) Tensilon® intravenously and to a lesser degree Neostigmin i.m. may give rise to muscarinic side effects such as lacrimation, abdominal cramps, diarrhoea and bradycardia (very rarely asytole), so that the interpretation of the nicotinic effect becomes difficult. Personally I prefer the Atropin-Neostigmin test (Viets and Schwab, 1935) to the Tensilon test because the effect of Neostigmin lasts longer so that more time is available for detailed testing.

Several auxillary test procedures have been described for the acquisition of

objective data, including the effect of anticholinesterases (Tensilon®). The tests most frequently used are:

(1) Electromyography of the m. orbicularis oculi (or of some limb muscle).
(2) Electromyography of the extrinsic eye muscles e.g. the m. rectus lateralis.
(3) Tonography.
(4) The registration and analysis of eye movements ('nystagmography').

ad 1 The 'fatiguability' of m. orbicularis oculi can easily be demonstrated with surface electrodes: the patient is asked to keep his eyes tightly closed. The compound muscle action potentials decrease gradually and show fluctuations (Bothello et al., 1952). Before and after this voluntary contraction a myogram with repeated supramaximal stimulation (1–3/sec) of the facial nerve can be made which shows the typical decrement, that is maximum at the 5th stimulus (Fig. 6).

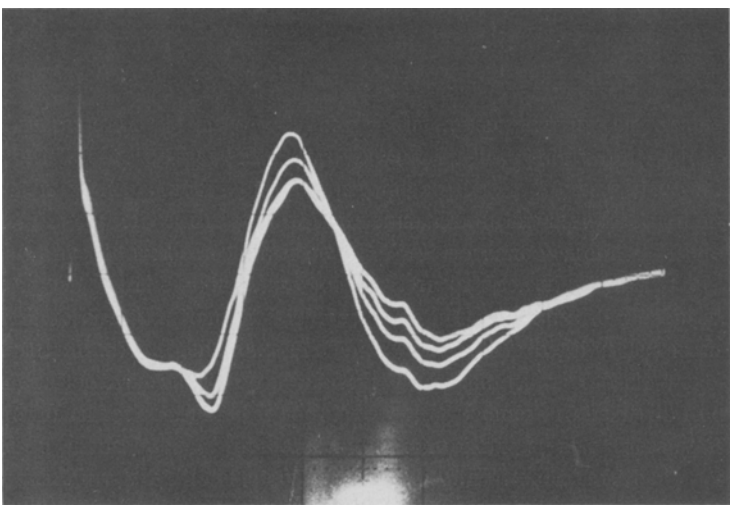

Figure 6. Electromyogram of the m. oribicularis oculi obtained with surface electrodes. Supramaximal stimulation of the facial nerve with 3/sec. Decrement of the 4th compound action potential of 18%

ad 2 Electromyography of the extrinsic eye muscles under conjunctival anaesthesia (Breinin, 1957) may show a decreased fire frequency of the motor units at rest, or in some direction of gaze, which increases after Tensilon. The difference compared with the EMG of the limb muscles is that not only the amplitude but also the frequency increases after Tensilon. This test may be useful if the eye muscle paresis has not changed after injection of anticholinesterases, as the effect of Tensilon may be the activation of several functioning motor units which can only be recorded with a needle electrode (Marek and Szobor, 1966). This test is uncomfortable for the patient.

ad 3 Tonography is based on the increase in intraocular pressure caused by contraction of the extrinsic eye muscles. In 16 out of 17 patients with MG Campbell et al. (1970) found a mean increase in pressure of 1.6 mm Hg after an injection of Tensilon®, with a maximum effect after 35 seconds. In controls the intraocular pressure did not react to Tensilon but showed a physiological spontaneous decrease of 1.6–1.8 mm Hg in 60 seconds.
ad 4 The analysis of eye movement recordings ('nystagmography') may document in detail some abnormalities such as paretic nystagmus, predominantly of the abducting eye, and dissociated saccadic movements if one eye moves faster than the other. After Tensilon injection hypermetric saccades may be seen (Schmidt, 1975). Yee et al. (1976) found that the maximum velocities of 20° and 40° voluntary saccades were not decreased in MG, although the eye movements had a limited range. In some of their patients small amplitude saccades were hypermetric and had high velocities. These are clinically known as 'quiver' movements, considered to be characteristic for MG. These 'supernormal' saccadic velocities were also found by Schmidt et al. (1980) and could be explained as a relative sparing of the phasic (twitch) muscle fibres. Baloh and Keesey (1976) found a decrease in amplitude and velocity of voluntary saccades after their patients had performed pursuit eye movements during 4 minutes. An improvement was found after Tensilon. The difference compared with the forementioned authors may be explained by the longer period of exertion and by the fact that 9 of their 12 patients had no clinical eye muscle paresis. With the same technique Mastaglia et al. (1977) also found an abnormal saccadic velocity in half of their patients, with an increase of the saccadic velocity after Tensilon. A 50% increase of saccadic velocity was also found in a patient with multiple sclerosis. Spector and Daroff (1977) used infrared optokinetic nystagmography and found an average increase of 85% in the amplitude of the optokinetic nystagmus after Tensilon in all their 40 MG-patients, without false positives in 25 controls and 18 patients with non-myasthenic ocular palsies. They state that this method is superior to the commonly used technique, because no electrodes are used. This is important because Tensilon causes sweating and a decreased resistence between the electrodes, so that the amplitude is diminished and false negative findings occur.

In most centres only one or two of these tests are used, so that their relative sensitivity and specificity are not well known. Again it should be emphasized that the fluctuations, either spontaneous or induced by exertion, are the key-stone of the diagnosis. Repeated clinical observations will be sufficient in most of the patients. If the patient has no ptosis or orbicularis weakness and only eye muscle paresis or diplopia, and if the reaction to Neostigmin or Tensilon is negative, a localized (hand muscles, Horowitz and Sivak, 1978) or systemic (Hertel et al., 1977) curaretest may be necessary.

Pathogenesis

The cause of MG is unknown but the pathogenesis is the loss of postsynaptic acetylcholinereceptors to less than 20–30% so that the safety margin of neuromuscular transmission is lost. It is probable that the function of the remaining acetylcholine receptors is impaired by antibodies against receptor protein, which can be demonstrated in the serum of 80–90% of the patients with a generalized MG and which are highly specific for the disease. (Recent review Vincent and Newsom Davis, 1980). The exact role of these antibodies is not known. Their concentration is highly variable in a group of MG patients and not related to the severity of the disease. However in the individual patient a global relation exists between the antibody concentration and the disease activity (Seybold et al., 1981; Limburg et al., 1981). The role of cellular immunity and that of the thymus is still more uncertain but the hypothesis includes an autoimmune disturbance directed against the acetylcholine receptor protein, initiated or not suppressed by the thymus.

One of the intriguing features of the disease is the preference for the muscles innervated by the cranial nerves and especially for the external eye muscles, the levator palpebrae and the orbicularis oculi muscle. These muscles are more sensitive to curare than the limb muscles. (The resemblance of MG to a partial curareintoxication inspired Mary Walker (1934) to try the effect of physostigmin). According to Esslen (1977) the following factors have to be considered:

(a) The maximal innervation rate of the twitch fibres in the external eye muscles is 300–400/sec which is 6–8 times as frequent as the rate of the limb muscles.

(b) The external eye muscles are continuously active: the electrical activity of a muscle only ceases at the moment the maximum activity of its antagonist is reached.

(c) The external eye muscles have a limited peak activity: they cannot easily perform long-lasting movements such as convergence.

(d) The external eye muscles are small. The motor units consist of 4–12 fibres, compared with the 400–600 motorunits of the limb muscles. This implies that a process which impairs the function of half of the muscle fibres at random has a greater chance of blocking some motor units completely.

(e) The equal innervation of the eye muscles implies that a minor deficit in innervation of one muscle cannot be compensated, so that diplopia results. A limb muscle may loose 20–30% of its strength before this bothers the patient, unless this muscle is used very intensively.

Considering the probable role of circulating antibodies I should like to add another possible factor. The arterial blood supply of the eye muscles is part of the internal carotid circulation which receives 20% of the cardiac output.

This is a ten-fold of the volume to the other parts of the body at rest. One may suppose that the antibody supply is also ten-fold, as compared to the muscles of the other parts of the body. As these antibodies seem to have a direct influence on the destruction of the postsynaptic acetylcholine receptors, this circulatory factor may be of decisive importance. Reports on the histology of the eye muscles in myasthenia are scarce. Sakimoto and Cheng-Minoda (1970) reported elongation of the terminal axons and changes in the junctional folds in fibres with a 'Fibrillen'-structure in the extraocular muscles of 10 patients. Remus and Lahl (1974) found lymphorrhagic infiltrates, and cloddy-granular muscle fibre necrosis in a patient with a thymoma. In 2 out of 5 autopsies we found lymphorrhagic infiltrates (Oosterhuis and Bethlem, 1973). Hoogenraad et al. (1978) reported widespread atrophy of muscle fibres in the biopsies of inferior oblique muscles of 3 patients. Notwithstanding these arguments it is far from understood how the big differences in the intensity of involvement of the ocular muscles in individual patients are to be explained.

Therapy

It is common experience that the paresis of the extraocular muscles reacts poorly to anticholinesterases. The ptosis reacts more favourably but seldom completely disappears. In some patients oral anticholinesterases have no effect at all. As was mentioned before, the ocular symptoms may fluctuate in the course of the day and over longer periods and spontaneous remissions are not rare. In 30% of the 43 purely ocular cases in my series (Oosterhuis, 1981) a lasting complete remission occurred within 10 years of the onset. This is also the case in patients with a generalized MG. The eye muscle paresis may disappear spontaneously, even when the bulbar and limb muscle weakness remains. It is not unusual for spontaneous improvement to be attributed to the therapy, with the consequence that anticholinesterase therapy is continued without adequate proof of its efficiency. If the diplopia becomes troublesome, covering of one eye is the best initial measure. Prisms are seldom useful, because of the fluctuation in the angle of squint. Eye muscle corrections are not advisable for the same reason. The ptosis may be relieved with a ptosis hook (Fig. 7). Patients like to wear sunglasses, even at home, because ptosis and diplopia increase in bright light. If the ptosis is chronic and does not fluctuate any more, the patient may be helped with ptosis surgery. If the patient needs reading glasses, bifocals are usually not well tolerated. If these measures are unsatisfactory and a tendency to improvement is not obvious within one year, treatment with corticosteroids may be considered. A fairly good reaction of the eye muscle pareses is usually seen within a few weeks of the start of Prednisone therapy (Fisher and Schwartzman, 1976). Older patients with a purely or mainly ocular myasthenia are the category that is likely to have most benefit. My own experience of this therapy in

Table 2. Effect of corticosteroïds on ocular myasthenia gravis

Case no	207	216	334	364	434	463	508	509	522	524	544	546
sex	F	F	M	M	M	M	F	F	M	M	F	M
age at onset MG	19	50	61	49	67	56	70	73	49	53	53	47
duration MG (years)	20	2	3	2	1	2	17	4	2	6	12	$\frac{3}{4}$
Cs: initial dose mg/2d	30	30	3[2)]	3[2)]	30	60	30	60	30	30	60	60
Cs: lowest dose mg/2d	15	20	$1\frac{1}{2}$[2)]	1[2)]	10	30	30	25	30	30	40	60
Cs: effect on MG[1)]	+	+	++	++	++	+	+	++	—	+	++	++
Cs: duration (years)	3	3	7	7	$2\frac{1}{2}$	3	$1\frac{1}{2}$	2	1	1	$\frac{1}{2}$	$\frac{1}{2}$
Cs: side effects[3)]	—	—	—	—	—	—	—	C	—	—	W	—
Cs: relapse after termination	+	+	+		—	?	?	?	?	?	?	?
anti Acetylcholine receptor antibodies	+	?	?	—	—	+	+	+	—	—	—	—

MG: myasthenia gravis CS: corticosteroïds
1) ++ = remission + = amelioration — = no effect
2) Dexamethasone
3) C = Cushing face W: weight gain

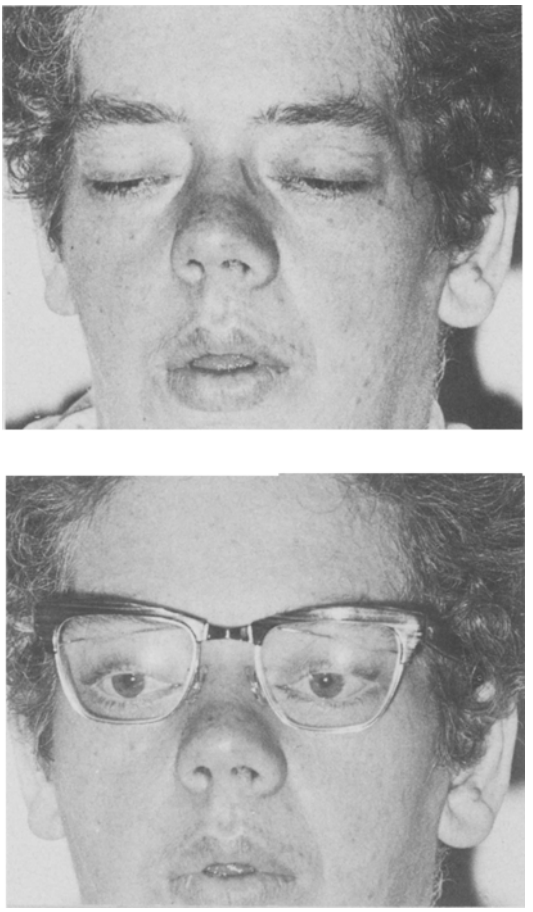

Figure 7. A) Severe ptosis not corrected by contraction of the m. frontalis in a patient with severe generalized myasthenia. The mouth cannot be closed; B) Partial correction of the ptosis with ptosis 'hooks'

12 patients is summarized in Table 2. In 6 patients a complete remission ensued, in 5 patients considerable improvement and in 1 patient the result was insufficient. The first effect was usually on the ptosis and occurred 1–2 weeks after the onset of treatment. The eye muscle paresis followed after 2–3 weeks with gradual improvement during 2–3 months. The initial dose varied from 30–60 mg on alternate days. It was tapered off gradually to the lowest maintenance dosage when the maximum effect seemed to have been reached. This varied from 15–30 mg Prednisone (1–1½ mg Dexamethasone) on alternate days. No serious side effects from this maintenance dose were seen. It is advisable to reduce this dose gradually after one year, to see if the symptoms reappear, so that treatment during a possible spontaneous

remission is avoided. The results of this therapeutic scheme are very encouraging and seem to outweigh the small risk of alternate-day steroids in selected patients. Whether thymectomy is of use in purely ocular myasthenia is not known. As this condition is very rare in patients between 15 and 45 years, sufficient data are lacking.

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