Ocular myasthenia gravis: response to long term immunosuppressive treatment

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Abstract

Objective—Ocular myasthenia gravis is a subtype of myasthenia gravis that causes relatively mild disability, but may convert into severe generalised muscle weakness. A universal management plan for ocular myasthenia gravis has not been established. This study was performed to determine the outcome of ocular myasthenia gravis with the currently available therapeutic options.

Methods—Retrospective analysis of 78 patients with ocular myasthenia gravis with a mean disease duration of 8.3 (range 0.5–58.3) years.

Results—In 54 patients (69%) symptoms and signs remained confined to the extraocular muscles during the observation period. The remaining 24 patients (31%) developed symptoms of generalised myasthenia gravis; 50% of them within two years, 75% within four years after onset. A somewhat reduced risk of generalisation was found in those with mild symptoms, normal repetitive nerve stimulation test, and low or absent antiacetylcholine receptor (AChR) antibodies at the time of diagnosis. Patients receiving immunosuppressive treatment (corticosteroids and/or azathioprine) rarely developed generalised myasthenia gravis (six of 50, 12%). Those without such treatment, usually due to uncertain diagnosis and late referral, converted into generalised myasthenia gravis significantly more often (18 of 28, 64%).

Conclusions—The prognosis of ocular myasthenia gravis is good. A conventional scheme with short term corticosteroids and long term azathioprine seems adequate to achieve remission in most patients. The proportion of patients developing generalised myasthenia gravis was smaller in this population compared with previously published groups (usually 50%–70%). Early immunosuppressive treatment is at least partially responsible for this finding. Thymectomy (performed here in 12 patients with an abnormal chest CT) also correlated with a good outcome, but had no apparent advantage over medical treatment alone.

Myasthenia gravis is caused by autoantibodies against the acetylcholine receptor (AChR) at the neuromuscular junction leading to exertional weakness of striated muscle.^{1,2,3} Its prevalence rate has been estimated to be up to 10 per 100 000 in recent epidemiological surveys, and people of any race at any age may be affected.^{4,5} Due to the currently available treatment options the prognosis of myasthenia gravis has greatly improved during the past 20 years. Anticholinesterase drugs have been used since the 1930s and in the 1960s corticosteroids and other immunosuppressive drugs started to be used.^{3,6,7} Furthermore, the introduction of plasmapheresis, early thymectomy, and improved intensive care facilities has reduced the mortality of myasthenia gravis essentially close to zero since the mid-1970s.^{2,8}

Myasthenia gravis is one of the best studied autoimmune diseases and the remarkable progress in understanding the underlying aetiology and pathogenetic heterogeneity has helped to improve patient management. According to age of onset, thymic abnormalities, and other immune variables patients with generalised myasthenia gravis can be divided into three main groups: (a) "young onset" patients (< 45 years, mainly female), who regularly have thymic hyperplasia; (b) "old onset" patients (> 45 years, slightly more men), who normally have thymic atrophy; and (c) the group of thymoma patients who have no clear age and sex bias.^{1,9} As not all patients with ocular muscle weakness fit into one of these categories, there is often uncertainty about the treatment options which are best in ocular myasthenia gravis. Particularly, there is no clearcut guideline as to the need for thymectomy, mostly performed in groups (a) and (c), or long term immunosuppression, which may be beneficial for all three patient groups with generalised disease.

Apart from symptomatic treatment with anticholinesterase drugs, corticosteroids are regularly considered in all forms of myasthenia gravis, with good results in most patients.^{10–12} The indications for immunosuppressive drugs, such as azathioprine, cyclophosphamide, or cyclosporine are less clear. Although these drugs have clearly been shown to be beneficial in generalised myasthenia gravis,^{6,13,14,15} some neurologists prefer to limit their application to the more severely affected patients.¹⁶ Also, scepticism about the drug treatment is fostered by the fact that very few prospective double blind trials have been performed for any compound.^{10–15} Thymectomy is the generally accepted treatment for patients with thymoma

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and in young onset patients. This is based on immunological evidence that thymic changes play a central part in the pathogenesis of myasthenia gravis, at least in these two patient groups.¹⁷⁻¹⁹ Uncertainty, however, exists as to the value of thymectomy in older patients with thymic atrophy, patients with generalised myasthenia gravis that are negative for serum AChR antibodies, and also in purely ocular myasthenia gravis.²⁰⁻²¹

In this study, we have reviewed patients with purely ocular muscle weakness.

Patients and methods

All patients included in this study were examined in our myasthenia clinic between January 1989 and April 1993 at least twice a year by one of us (NS or AM). In patients with a longer history previous hospital charts were reviewed. In a few patients additional follow up data were collected from referring neurologists.

The diagnosis of ocular myasthenia gravis was based on conventional clinical and laboratory criteria.¹⁻⁷ If AChR antibodies and repetitive nerve stimulation were both negative, then clinical signs, edrophonium chloride (Tensilon) testing, and treatment response, as well as other diagnostic measures (normal CT or MRI and CSF investigation) were re-evaluated carefully to exclude other causes of eye muscle weakness (see also comment on differential diagnosis below). Because of its low specificity, a positive edrophonium chloride test was never used as a single diagnostic criterion.²²⁻²⁵

Patients were only included if symptoms and signs were restricted to the extraocular muscles for at least three months after onset. This arbitrary limit seemed reasonable, because early disease stages (often before referral) were usually not well documented. Also, we thought that the development of generalised myasthenia gravis after a few days or weeks of exclusive weakness of extraocular muscles would not qualify for a diagnosis of ocular myasthenia gravis as a separate entity. In this respect we follow the criteria of Oosterhuis.²⁶ Also, subtle signs of generalised weakness, particularly facial weakness, were sought for and, if present, those patients were not included. Grading of severity of disease was semiquantitative. "Mild", "moderate", or "severe" ocular myasthenia gravis stands for mild, moderate, or severe disability in everyday life, with particular respect to impairment at work and car driving. This seemed more appropriate as the clinically more relevant subjective impairment does not necessarily correlate with the actual degree of extraocular muscle weakness. Improvement was documented when ocular myasthenia gravis was ameliorated by at least one such grade. Remission was stated when there was no remaining disability with or without drug treatment.

Repetitive nerve stimulation was performed according to Schumm and Stöhr²⁷ with minor modifications. The accessory nerve was stimu-

lated behind the sternocleidomastoid muscle with supramaximal intensity at 3 Hz with a bipolar surface electrode and recorded from the trapezius muscle. A decrement of greater than 10% between the first and fifth potential was considered pathological.

Antibodies to AChRs were measured by radioimmunoassay according to Vincent and Newsom-Davis.²⁸ Human amputated leg muscle was used as a source of antigen, incubated with ¹²⁵I- α -bungarotoxin (Amersham-Buchler, Brunswick, Germany) and subsequently with different dilutions of the patients' serum. After thorough washing the bound radioactivity was measured on a γ -counter. Known negative, positive, and equivocal serum samples were run in each assay. Values greater than 0.5 nmol α -bungarotoxin binding sites/l were considered positive, between 0.2 and 0.5 nmol/l equivocal, and less than 0.2 nmol/l negative. To avoid variations between assays, follow up investigations always included retesting of the previous one or two serum samples of a patient together with the new serum.

Results

PATIENTS

We had clinical data from 178 patients with myasthenia gravis; 78 of them (44%; 40 female, 38 male) were diagnosed to have ocular myasthenia gravis according to the criteria outlined above. Mean duration of disease was 8 years 4 months (SD 9 years, range 6 months-58 years 2 months). Twenty four of the 78 patients with ocular myasthenia gravis (31%, 13 female, 11 male) developed symptoms of generalised muscle weakness later during the course (see below). Age and sex distribution of ocular, primary, or secondary generalised patients were not significantly different (age at onset for all 78 patients with ocular myasthenia gravis: mean 50.6 (SD 19.5) years, range 10-84 years; data not shown). Remarkably, the diagnosis of myasthenia gravis in the 78 ocular patients was made only 39.8 (SD 93.5) months after the onset of symptoms.

Concomitant autoimmune diseases were diagnosed in 39 (22%) of all 178 patients with myasthenia gravis reviewed in this study. Thyroid disease was by far the most common condition (33 patients, 19%; female:male ratio 3:1:1). These proportions were not significantly different among the ocular patients (for example, total incidence of thyroid disease 19 of 78, 24%).

Family history disclosed that six of the 178 patients (3%) had a first or second degree relative with myasthenia gravis. Two pairs of siblings (including one pair of monozygotic twins) had generalised myasthenia gravis; another two in the ocular group had relatives with generalised myasthenia gravis who were not part of our sample.

DIFFERENTIAL DIAGNOSIS OF SERONEGATIVE OCULAR MYASTHENIA GRAVIS

In three female patients (ages 45, 57, and 74 years) referred to us with suspected seronega-

tive ocular myasthenia gravis, this diagnosis had to be revised during the course. All three had double vision and unilateral ptosis with mild daily fluctuations and the diagnosis had mainly been based on a positive edrophonium chloride test. AChR-antibodies and electrophysiology were normal. One of the patients had been thymectomised and thymic remnants without germinal centres were found. When re-evaluating the diagnosis, we found unilateral contrast enhancing lesions on CT and MRI in the region of the cavernous sinus in all three. These patients are not included in the present evaluation, but deserve mention, because their history reflects well the diagnostic problems encountered in ocular myasthenia gravis. The MRI of one of the patients has been published previously.⁷

PROGNOSTIC FACTORS

Using secondary generalisation as an end point, no significant prognostic factor could be determined. Nevertheless, mild symptoms at onset, normal results at repetitive nerve stimulation, and negative serum AChR antibody testing were found more often in patients whose myasthenia remained limited to extraocular muscles (fig 1A-C). Patients with mild ocular symptoms developed generalised myasthenia gravis in 14% (three of 22). In moderate and severe ocular myasthenia gravis

these proportions were 36% (15 of 42) and 43% (six of 14) respectively ($\chi^2 = 4.47$, NS; fig 1A).

Patients with a pathological decrement in repetitive accessory nerve stimulation converted to generalised myasthenia gravis in 32% (six of 19), but only 15% (seven of 47) did so with an initially normal electrophysiological result ($\chi^2 = 2.38$, NS; fig 1B).

Among the seronegative patients one of 23 (4%) developed generalised myasthenia gravis. This proportion was significantly higher in the seropositive group (11 of 43, 26%; $\chi^2 = 4.54$, $P < 0.05$; fig 1C). Also, in patients with secondary generalisation the mean antibody titre was significantly higher at the first diagnostic testing (mean 11.9 (SD 14.4), range 0–47.5 nmol/l) than in the permanently ocular patients (mean 4.1 (SD 6.0), range 0–25.9 nmol/l; $t = 3.02$, $P < 0.01$; not shown). As expected, the maximum levels during the whole observation period were tenfold higher in the patients with generalisation (61.6 (SD 116.7) nmol/l) compared with those who remained ocular (6.3 (SD 13.7) nmol/l).

Tensilon testing was positive in 97% of the patients with ocular myasthenia gravis, but was never used as a single diagnostic criterion (see above).

Data on HLA were available in 21 out of the 78 of the ocular patients and there was detectable trend towards a specific association; further investigation was not performed.

COURSE AND TREATMENT OF OCULAR MYASTHENIA GRAVIS

Outcome

Twenty four of the 78 patients with ocular myasthenia gravis (31%) developed secondarily generalised muscle weakness. The median onset of generalisation was 24.5 months (range 3–132) after the first ocular symptoms (fig 2). Among the 54 permanently ocular patients 29 (54%) had reached remission by

Figure 1 Evaluation of prognostic factors in ocular myasthenia gravis. Patients with mild symptoms (A) or normal repetitive accessory nerve stimulation (B) have a somewhat lower risk of developing generalised myasthenia (NS). Detectable AChR antibodies were significantly more frequent in the group with secondary generalisation. The numbers included in the bars indicate the proportion of patients with immunosuppressive drug treatment (for example, 15/19: among 19 patients in this group, 15 received corticosteroids and/or azathioprine). Note that in B and C the total $n = 66$, because data were not available in 12 patients before generalisation.

Figure 2 Cumulative incidence of generalised symptoms in patients with initially purely ocular myasthenia gravis. A shows the patients without, B with immunosuppressive drug treatment. The median time to generalisation was 16 months in A and 33 months in B. The risk of converting to generalised symptoms is greatest during the first years, but is still present after many years.

the end of the observation period. All others improved ($n = 18$) or remained the same ($n = 7$); none of the permanently ocular patients worsened. Although patients after generalisation were not analysed in detail in this study, it is worthwhile mentioning that 11 of the 24 (46%) had also reached remission by the end of the observation time.

Symptomatic treatment

Sixty of the 78 patients received pyridostigmine at some time during their follow up. The maximum individual daily dose was 149.8 (SD 74.2) mg. The duration of pyridostigmine treatment was on average 45.6 (SD 39.9) months. Fourteen patients were treated with pyridostigmine alone for some time. Of those, seven (50%) reported considerable improvement, six (43%) mild improvement, and in one patient no effect was reported.

Immunosuppressive drug treatment

Forty five patients received prednisolone and 27 azathioprine. Figure 3 gives an overview of the various combinations of immunosuppression and thymectomy. Prednisolone was given for an average of 32.3 (SD 32.3) months, with a maximum individual daily dose of 51.9 (SD 26.1) mg. (In those patients who always received alternate day regimens 50% of their maximum dose was used for the calculation.) The mean duration of treatment with azathioprine was 43.7 (SD 35.2) months with a mean maximum dose of 145.3 (SD 25.0) mg. Among the patients who were treated with prednisolone but without azathioprine, a clear positive effect was found in 19 of 22 (86%). Among the four patients treated with azathioprine alone, we found an unequivocally positive effect in three of them. A combination of both drugs was used in 23 and was beneficial in 21 (91%).

Figure 3 Frequency of the different immunosuppressive therapies. Total number of patients = 78. The numbers in parentheses (total = 24) give the numbers of those who developed generalised myasthenia gravis. Note the low proportion of patients with secondary generalisation with any immunosuppressive treatment.

Thymectomy

Thymectomy was performed in 12 patients with purely ocular symptoms, because of an abnormal chest CT (fig 3). Probably due to the late diagnosis (see above) the procedure was performed on average 50 (range 2–253) months after onset of symptoms. Histology was available in 11 and disclosed thymoma in four (three non-invasive, one invasive), lymphofollicular hyperplasia in two, thymic remnants in two, and thymic involution in three patients. Thymectomised patients were followed up for an average of 81 (range 18–190) months after the operation, and all but one were treated with additional immunosuppressants (fig 3). Six patients reached remission during follow up; in another four ocular weakness improved. The remaining two patients (both with thymoma, one non-invasive, the other invasive) developed generalised myasthenia after six or 125 months respectively.

SIDE EFFECTS

No lasting sequelae of thymectomy were reported. Pyridostigmine was associated with side effects in two patients. In one a systemic allergic reaction (generalised exanthema two days after starting the drug) was reported, in another patient bradycardia was ascribed to drug overdose. Corticosteroids led to moderate side effects in 12 patients (cushingoid in five, restlessness and sleeplessness in five, severe acne vulgaris in one, and gastric upset in one), and severe side effects in two patients (one each with decompensation of diabetes mellitus or psychosis). Moderate side effects of azathioprine occurred in six patients (leucopenia between 2000 and 4000/ μ l in two patients, hair loss in two, nausea in one, and skin and nail changes in one). Severe leucopenia ($< 2000/\mu$ l) occurred in one patient. In another two (not considered in fig 3) azathioprine had to be stopped within the first months due to gastrointestinal upset. No severe infections were found under immunosuppressive treatment in this patient group.

Discussion

Ocular myasthenia gravis had a good prognosis in most patients in this study. In 69% the disease remained confined to the extraocular muscles. Of these, 54% were in remission, 33% improved, and 13% patients were unchanged at the end of the study. The most remarkable difference from previous studies is the relatively low fraction of patients converting to generalised myasthenia gravis, which was 31% in our population, but 49–69% in other previous reports. The development of generalised symptoms was used as a major end point by us and others, because it indicates major progression of disease and management has to be re-evaluated.

In the study published in 1983 by Bever *et al*²⁹ 53 of 108 patients (diagnosed 1957–69 in New York City)—that is, 49%—later generalised. Grob reported in his large collective³⁰ that about 40%, and in a later survey³¹ 34% of 202, of his patients with initial ocular myasthe-

nia gravis would remain ocular. The authors of those studies do not report details on possible immunosuppressive treatments applied to patients with ocular myasthenia gravis. As both series started decades ago it might safely be assumed that only a small proportion of patients had corticosteroids and even fewer had azathioprine.

Oosterhuis reviewed an even earlier series of patients who were first documented between 1926 and 1965 in Amsterdam and had to be managed without steroid or other immunosuppressive treatment.²⁶ In this group 24 of 35 (69%) developed generalised myasthenia gravis, probably most realistically reflecting the natural course of the disease. Although patient groups in the various studies may not be comparable with each other, it is evident that there is a gradual evolution towards a lower proportion with secondary generalisation. Common to all studies, including ours, is the finding that the risk of generalisation is greatest soon after onset, gradually declining with time. Of the patients developing generalised myasthenia gravis 50% did so by two years after onset in our study, 88% in Oosterhuis' group,²⁶ 83% in the study of Bever *et al.*²⁹

The proportion of 64% seropositive patients in our group was comparable with most of the previously published results (45%–71%).^{28–32–36} Whereas diagnosis of ocular myasthenia gravis is straightforward in a patient with a compatible history and detectable serum AchR antibodies, diagnostic problems arise in the seronegative patients. Suspicion should be aroused especially if extraocular muscle weakness is unilateral and follows a neurogenic pattern. The briefly summarised history of three patients with fluctuating extraocular muscle weakness and a positive edrophonium chloride test (see above) adds to other reports of patients with a missed tumour of the skull base. The largest such series, consisting of eight patients with extraocular muscle weakness, positive response to anticholinesterase treatment, and intracranial mass lesions was reported by Moorthy *et al.*²³ Thus seronegative ocular myasthenia gravis must, in our opinion, remain a mainly clinical diagnosis after a careful diagnostic work up including skull imaging. The lack of specificity of the edrophonium chloride test has been discussed repeatedly,^{7–22–24–25} and we cannot but repeat the warning not to interpret response to anticholinesterase drugs as a certain diagnostic sign for ocular myasthenia gravis.

The good outcome in patients with ocular myasthenia gravis in this study undoubtedly reflects the overall improvements in the treatment of autoimmune diseases. However, the beneficial effects of the different treatments are difficult to distinguish. Steroids and azathioprine clearly improve symptoms and signs in all forms of autoimmune myasthenia gravis¹² and it would therefore seem natural to give both drugs, steroids for short or medium term treatment and azathioprine for long term immunosuppression. Nevertheless, detailed reports on therapeutic experiences in ocular

myasthenia gravis as a separate entity are rare. Whereas steroids are probably widely applied in ocular myasthenia gravis, the use of other immunosuppressants has hardly been discussed. Evoli *et al* report a series of 48 patients with ocular myasthenia gravis.³⁷ They state that corticosteroids are effective in most cases, but may cause problems when being tapered off. Azathioprine was not considered in those patients followed up between 1968 and 1986.³⁷ Considering the beneficial effect of azathioprine alone or in combination with prednisolone in our patients, we would propose that azathioprine is a valuable immunosuppressant in ocular myasthenia gravis. The steroid sparing effect of the drug is generally accepted,² and side effects are usually tolerable. Haematological (in 11%) and other side effects were rare compared with other studies. Hohlfield *et al*³⁸ reported haematological side effects in 18%, Kissel *et al*³⁹ in 22%, and Witte *et al*⁴⁰ in 17% of their patients. However, all these studies were performed in generalised myasthenia gravis, and often side effects were considered to be dose related in patients requiring relatively high dosage for stabilisation of symptoms (up to 6.6 mg/kg in the study of Hohlfield *et al*,³⁸ and up to 3.4 mg/kg in that of Witte *et al*⁴⁰). In our clinic patients with generalised myasthenia gravis are treated with 2–2.5 mg/kg azathioprine with an increase in dose (usually not above 3.0 mg/kg), if the treatment result is not satisfactory. In patients with ocular myasthenia gravis, however, we find that in most patients 2.0 mg/kg is sufficient to lead to improvement (results not shown in detail).

Thymectomy is now a standard treatment for patients with myasthenia gravis with suspected thymoma and in young onset patients in whom thymic hyperplasia with germinal centres can be expected.^{1–2} However, in most neurologists' opinions thymectomy is not a standard treatment for ocular myasthenia.⁴¹ In our series thymectomy was only performed when chest CT indicated thymoma. Thymoma was found in four of 12 patients, and two of those developed generalised myasthenia gravis, whereas all patients without thymoma remained ocular. Remarkably, in two young onset patients (onset < 45 years) with short duration of disease there was histological evidence for lymphofollicular hyperplasia, whereas in two other young onset patients with much longer duration of disease, similar to those with onset over 45 no hyperplasia was found. This supports the hypothesis that at least a proportion of ocular patients with myasthenia gravis have thymic changes similar to generalised young onset patients, and thus a similar pathogenesis may be assumed. However, evaluation of the retrospective data is difficult, because all except one patient required immunosuppressive drug treatment. In 1985 Schumm *et al* reported a series of 18 mainly young patients with ocular myasthenia gravis who seemed to benefit from thymectomy and 13 of whom showed thymic hyperplasia.²¹ Although immunosuppressants were used in parallel and clear criteria for an expected ther-

apeutic effect could not be identified, the authors concluded that thymectomy should be considered in ocular myasthenia gravis.

What general treatment plan should be followed in ocular myasthenia gravis? Ocular myasthenia gravis is treated as an entity for practical reasons in this study. However, there is ample evidence that in most patients it is probably simply a mild form of myasthenia gravis, without fundamental pathogenetic difference to the three forms of generalised myasthenia gravis outlined above. All clinical findings, such as thymic changes, associated autoimmune disease, and occasional familial occurrence (see results) can also be made in ocular myasthenia gravis with roughly similar frequency as in generalised myasthenia gravis.⁴²⁻⁴³ Therefore, treatment of ocular myasthenia gravis should follow the general principles of myasthenia gravis therapy.

The use of pyridostigmine and corticosteroids is generally accepted in ocular myasthenia gravis. Practically, we start with 20–30 mg pyridostigmine three to four times daily, gradually increasing the dose until symptoms disappear. Normally, 240 mg per day are not exceeded. Most patients will require additional steroids. For mild symptoms we start with 20–30 mg prednisolone on alternate days. This will often lead to considerable improvement after four to six weeks. For more severe ocular symptoms up to 50–60 mg prednisolone daily (or an equivalent steroid) are given for two to three months until improvement is detectable. Dose reduction should not be faster than 5 mg in six to eight weeks. Too fast a reduction of steroids is the most common mistake leading to a relapse.¹⁻⁴⁴

From our experience in ocular myasthenia gravis, we suggest that azathioprine should be used as the immunosuppressant of choice, if ocular symptoms do not remit completely under steroid treatment or cannot be controlled on a very low dose of steroids. Long term azathioprine treatment seems safe, provided blood count and liver enzymes are checked regularly. Thymectomy might be an additional treatment option, but cannot clearly be evaluated on current evidence. A prospective trial could settle this issue and seems most rewarding in patients with onset before 45 years of age. If thymectomy is considered in ocular myasthenia gravis, it should in any case be limited to patients with detectable AChR-antibodies, because seronegative patients virtually never have thymoma in our experience and that of others⁴⁵⁻⁴⁶ and do not normally have lymphofollicular hyperplasia like the seropositive young onset patients.²⁰

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