PAPER

Myasthenia gravis: a long term follow-up study of Swedish patients with specific reference to thymic histology

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Background: Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission. The majority of patients show abnormal thymic histology.

Setting: The study was performed at the Myasthenia Gravis Centre, Karolinska University Hospital, and at the Immunological Research Laboratory, Centre for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden.

Patients and methods: Information was collected retrospectively from 1956 and prospectively from 1975 on clinical data, concomitant diseases, concentration of serum acetylcholine receptor antibodies (AChR-abs), immunosuppressive treatment (IS) and response to it, in 537 patients of whom 326 were thymectomised. Follow-up time was 1.5–50 years.

Results: Age at onset of MG increased from a median age of 24 years before 1975 to a median age of 61 years after 2000. Thymoma was found in 65, hyperplasia (HPL) in 185 and a normal thymus in 76 patients. The trans-sternal surgical approach for thymectomy was used in 255 patients (78%). In five patients with thymoma, MG appeared after thymectomy. Of 537 patients, 466 (87%) had circulating AChR-abs. IS was given to 300 (56%) patients, mostly those with thymoma (85%). In total, 441 patients (82%) showed an improvement. One-third of patients with HPL, a quarter of those with thymoma, one-fifth of those with a normal thymus and one-seventh of those not operated on went into remission.

Conclusion: The prognosis for the majority of patients with MG is favourable, irrespective of thymic histology. The cause may be the use of immunomodulating therapy.

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission.^{1,2} The prevalence of MG in Stockholm is 14.1 per 100 000 (17.1 for women and 10.8 for men).³

The thymus gland plays a central role in the development of the T cell repertoire but its role in MG is not clear.^{4–6} In MG, the thymic gland is normal in 15–20%, shows hyperplasia (HPL) in 65–75% and thymoma in 10–15% of patients.^{1,4} HPL is characterised by lymphoid follicles with germinal centres containing mostly B lymphocytes.^{4,5}

In 1892, Hoppe reported on a 40-year-old man with typical myasthenic bulbar fatigability who died of respiratory paralysis. At autopsy, a large mediastinal tumour was revealed.⁷ In 1944, Blalock described six MG patients without a thymoma, in whom thymectomy was of benefit.⁸ Thereafter, thymectomy has been an accepted therapy for MG. No controlled study of its efficacy has been published but a controlled study was planned in 2000, presented in 2003⁹ and has now started.

Approximately 85% of patients with MG have circulating acetylcholine receptor antibodies (AChR-abs) in serum.¹⁰ Of patients with pure ocular MG, about 30% are seronegative.

Genetic factors contribute to the susceptibility of MG with HPL, but seem to be of minor importance in thymoma associated MG.^{1,11}

The aim of this study was to describe the clinical characteristics, coexisting malignant, autoimmune and endocrine disorders, presence of AChR-abs, use of immunosuppressive treatment (IS) and the response to it, in a population with MG with different thymic gland histology.

PATIENTS AND METHODS

The survey was performed in 2003–2006. A database on patients with MG was started in the 1970s which was approved by the Swedish Data Inspection Board and patients gave

informed consent. Information was gathered retrospectively from 1956 and prospectively from 1975 concerning sex, age at onset of MG, age at thymectomy, method of operation, histology of the thymic gland, concomitant diseases, serum AChR-abs, clinical classification of MG, use of IS and the response to therapy. The information was added to this database after every visit to the MG centre. The majority (n = 426) of patients lived in the Stockholm county area.

This study describes 537 unselected patients with MG from a database of 681 patients. Only patients who were followed for at least 1.5 years were included. Most of the excluded patients lived outside Stockholm and were not available for interview or testing.

The diagnosis of MG was based on abnormal muscular fatigability, positive response to cholinesterase inhibitors, abnormal results on neurophysiological tests and, in most patients, the presence of serum AChR-abs. Before 1970, the neurophysiological test comprised repetitive nerve stimulation with both low and high frequency stimulation, showing a decrement >5% between the 1st and 4th amplitudes of muscle action potentials. In 1970, the single fibre EMG was added. An increased jitter in at least 2 of 20 fibre pairs was considered abnormal.¹² Analysis of serum AChR-abs was performed using a radioimmunoassay described previously.¹⁰ Values >0.2 were considered raised.

At every visit, the clinical investigation consisted of a questionnaire and a muscle fatigability test (MFT) of the following muscle groups:

- (1) ocular: time when ptosis or diplopia appeared at the upward gaze (limit 2 min);

Abbreviations: AChR-ab, acetylcholine receptor antibody; HPL, hyperplasia; IS, immunosuppressive treatment; MFT, muscle fatigability test; MG, myasthenia gravis

Table 1 Demographic data, clinical classification, serum AChR-abs titres, coexisting disorders, immunosuppressive treatment and clinical outcome with specific reference to thymic gland histology in 537 patients with myasthenia gravis

	Thymoma (n = 65)	Hyperplasia (n = 185)	Normal thymus (n = 76)	Unknown (n = 211)
Sex (F:M)	38:27	147:38	32:44	105:106
Age at onset (y) (median (range))	52 (18–77)	22 (5–60)	46 (8–70)	65 (11–90)
Age at thymectomy (y) (median (range))	50 (18–81)	26 (8–61)	53 (17–71)	
Disease duration (y) (median (range))	11.5 (2–37.5)	20.5 (2–50.5)	15.5 (2–66)	9 (1.5–53.5)
Clinical classification (%) at 1st visit				
I	1 (2)	1 (0.5)	5 (7)	43 (20)
II+III	21 (32)	139 (75)	41 (54)	103 (49)
IV	26 (40)	42 (23)	23 (30)	42 (20)
V	17 (26)	3 (2)	7 (9)	25 (12)
AChR-abs (arbitrary units)				
Preoperatively	4.1	3.0	2.9	2.4
Postoperatively	2.6	3.3	1.7	
Extrathymic malignancy (%)	14 (22)	23 (12)	17 (22)	63 (30)
Autoimmune disorder (%)	17 (26)	34 (18)	8 (11)	45 (21)
Endocrine disorder (%)	10 (15)	17 (8)	11 (14)	51 (24)
Immunomodulation (%)	55 (85)	69 (37)	56 (74)	120 (57)
Several drugs	42	48	26	23
Azathioprine 2–3 mg/kg/day	45	52	38	83
Ciclosporin 3–5 mg/kg/day	12	15	6	16
Steroids intermittent	24	41	34	57
Steroids orally >2 mo	19	19	8	10
Other IS drug	12	8	5	5
High dose intravenous IgG	9	11	7	6
Time (y) using IS (median (range))	7 (1 mo–35 y)	5.5 (1 mo–28.5 y)	7.5 (6 mo–30 y)	5.5 (1 mo–36.5 y)
IS withdrawn	10	35	16	19
Need for respirator	29	30	20	26
Outcome at last visit				
Remission (%)	18 (28)	61 (33)	16 (21)	32 (15)
Time after onset of MG (y)	6	8.5	11	4.5
Time after thymectomy (y)	2.5	3.5	5.5	–
Never used IS	6	52	9	20
Continuously IS	8	1	1	10
IS withdrawn	4	8	6	2
Better (%)	30 (46)	101 (55)	38 (50)	142 (67)
Unchanged	12 (18)	17 (9)	20 (26)	19 (9)
Worse	5 (8)	6 (3)	2 (3)	18 (8)

AChR-abs, acetylcholine receptor antibodies; IS, immunosuppressive treatment; MG, myasthenia gravis.

- (2) bulbar: peak expiratory flow with and without noseclips, the nasality of speech when counting from 1 to 100 and the number of chews and smiles (limit 20);
- (3) neck: the number of head lifts from a pillow (limit 30);
- (4) arms: dynamic (A) or static (B) method. (A) A number of arm lifts from 0° to 180° (limit 40 elevations above 90°). (B) Arms stretched forward at 90° (limit 180 s);
- (5) hands: the force at inflation of the sphygmomanometer (limit 300 mm Hg) and fisting/extending the fingers (limit 70);
- (6) legs: dynamic (A) or static (B) method. (A) A number of leg extensions above 45° (limit 35 times). (B) A straight leg elevation at 45° (limit 60 s).

After the visit, the MFT results were scored with the aid of an Excel program. Each test was graded to normal values set at 100%. A summary was made of ocular and non-ocular percentages. MFT scores were used to define the clinical classification which was made modifying Oosterhuis¹³ and Jaretzki and colleagues.¹⁴

- I = pure ocular MG.
- II = mild generalised symptoms (MFT 90–100%).
- III = moderate generalised symptoms (MFT 60–90%).
- IV = severe generalised symptoms (MFT <60%) which interfere with activities of living.
- V = acute, fulminating, progressive form, sometimes needing intensive care.

- Remission = no MG symptoms, no use of cholinesterase inhibitors. IS treatment, an abnormal neurophysiological finding and the presence of serum AChR-abs were allowed.

Groups II and III were combined because of symptom fluctuations throughout the years.

Thymomas were classified into five types¹⁵: spindle cell, lymphocytic, mixed, epithelial tumour and thymic carcinoma (marked cell atypia, necrosis, mitosis). Thymomas with tumour infiltration of the capsule were also classified as malignant. The 1999 and 2004 WHO classification of thymomas could not be used because most of the thymectomies were performed before 1990 and the pathologic anatomic diagnosis (PAD) was given as shown above.¹⁶

Patients were grouped according to the histology of the thymic gland. Non-thymectomised patients (unknown histology) were included as a separate group.

If AChR-abs were measured several times, levels closest to MG onset and at 2–5 years postoperatively were chosen.

In the case of more than one thymectomy in a patient, time to remission after the most recent procedure was calculated.

Statistical evaluation

The non-parametric Mann–Whitney, χ^2 and Fisher's tests were used.

RESULTS

Thymectomy was performed in 326 patients for the following indications: (1) generalised MG, (2) age <70 years and (3)

suspected thymoma irrespective of symptoms or age. Thymectomy was not considered for patients with purely ocular symptoms.

Of the 65 thymoma patients, 17 (26%) also had HPL and nine had a malignant thymoma (table 1). They were included in the thymoma group. In two patients, the thymoma was diagnosed at autopsy.

A mixed tumour was the most common finding ($n = 29$), followed by lymphocytic ($n = 18$) and epithelial ($n = 14$) thymomas. Five patients with epithelial tumours also had spindle cell formations. Thymoma was classified as malignant either histologically or by invasive growth in 27 (42%) patients.

Median time between onset of MG and thymectomy in patients with thymoma was 0.5 years (1 month–15.5 years) and in the two other groups 1.5 years (1 month–44 years). In five patients with thymoma, MG symptoms appeared after a median of 2 years (2 months–26 years) after thymectomy.

In the HPL group, women were overrepresented compared with the other groups ($p = 0.0009$, χ^2) (table 1). Age at disease onset was lowest in the HPL group and highest in the non-operated patients ($p < 0.05$, Mann–Whitney). Age at onset of MG in patients in whom the disease started before 1975 was 24 years (median) and in patients with disease start between 2000 and 2004, 61 years (median). Examining age at onset in 5 year periods, this increase has been insidious (data not shown).

Patients with thymoma had initially more severe MG ($p < 0.05$, χ^2) compared with other groups. The non-operated patients had pure ocular MG (20%) more often than thymectomised patients ($p < 0.05$, χ^2).

Of 537 patients, 142 (26%) died. None had died within 3 months after thymectomy. The cause of death was not analysed in this study.

Thymectomy method

A transcervical approach was used in the 1970s in 71 patients (13%), of whom four had a thymoma. All patients with thymoma later underwent reoperation. In the HPL group, 46 (25%) patients were initially operated on using the transcervical approach and 33 (72%) had to be reoperated. Of patients with a normal histology, 21 (28%) were operated on transcervically and two (10%) needed repeat thymectomy. Indications for reoperation were handicapping symptoms which did not improve after the first operation. The repeat thymectomy was performed by median sternotomy. In all cases the lower thymus lobes were found and removed. In the HPL group, 27 (82%) patients improved after reoperation.

Concomitant diseases

Malignancies (including basalioma and carcinoma in situ of the cervix uteri) were observed significantly more often in non-thymectomised than in thymectomised patients ($p < 0.0001$, χ^2). In 39 patients the malignancy was found before and in 86 patients after the onset of MG. In 44 patients the malignancy appeared during IS therapy. In this group, 18 patients had a skin malignancy of whom 12 had a squamous cell cancer. In patients who did not receive IS, four patients had skin cancer of whom one had squamous cell cancer ($p < 0.01$, χ^2). Other forms of malignancy were not increased in patients with IS.

Autoimmune and endocrine disorders were found at a similar frequency in all groups.

Acetylcholine receptor antibodies

Serum AChR-abs were measured at least once in 530 (99%) patients, of whom 466 (88%) had increased levels. There were no significant differences between preoperative and

postoperative AChR-abs levels or values between different patient groups.

Of the 64 seronegative patients, 28 were thymectomised. Of these, 15 had HPL, 10 a normal thymus and one a thymoma. Of the 37 seronegative patients, one had anti-muscle specific kinase antibodies. There were 11 patients who were seronegative before thymectomy but were found to be seropositive after operation.

Immunosuppressive treatment

In total, 300 patients (56%) (of whom 26 were seronegative) received IS for MG at least temporarily (table 1). In addition, 13 patients were treated with IS because of other autoimmune or malignant diseases. IS treatment was given most often to patients with thymoma and least often to those with HPL ($p < 0.0001$, χ^2). Azathioprine and ciclosporin were the most often used drugs. A combination therapy was given to 139 patients. The indications for other IS were insufficient effect, intolerable side effects or need for more rapid amelioration.

Steroids were given to 212 patients; in 156 patients as a 2 day intensive course (methylprednisolone 30 mg/kg/day intravenously) or as a 7 day adrenocorticotrophic hormone (0.25 mg/day) course, which was repeated if needed.

In the azathioprine group, over 40% of patients improved, less than 20% did not improve and 13% discontinued the drug because of side effects. In the ciclosporin group, 58% of patients improved, 32% did not improve and in approximately one-third of patients the drug was withdrawn.

Seropositive and seronegative patients did not differ in their response to IS.

Drainage of the thoracic duct lymph (1968–1977) and later plasmapheresis were performed in 10 (15%) patients with thymoma, in 20 (11%) patients with HPL, in 12 (16%) patients with a normal thymus and in five (2%) patients with unknown thymic histology.

High dose intravenous immunoglobulin G was given to three patients in 1982. They were investigated clinically, neurophysiologically and with repeated serum AChR-ab measurements. No clinical or neurophysiological benefit was noted and the therapy was rejected. Intravenous immunoglobulin G was restarted after 1996. Eight of 33 patients (24%) showed improvement.

Clinical outcome

Patients with thymoma needed assisted ventilation more often than patients in other groups ($p < 0.0001$). None has been dependent on a ventilator.

Of the 537 patients, 438 (82%) improved or achieved remission, 68 (13%) remained unchanged and 31 (6%) deteriorated (table 1). Age at onset or thymoma histology had no significant effect on outcome. Eight (47%) of 17 patients with both HPL and a thymoma improved compared with 39 (81%) of 48 patients with a thymoma only ($p = 0.0029$).

Remission was transient in two patients. One had been operated on for a thymoma and relapsed after 13 years of remission. The other patient was not operated on and relapsed after 4 years of remission. One man with onset of MG at the age of 63 years started IS and reached remission 1 year later. At the age of 77 years, a malignant thymoma appeared and was removed. MG symptoms did not reappear.

Of the 15 seronegative patients with HPL, 11 improved (four achieved remission), and of the 12 patients with a normal thymus, eight improved (two achieved remission). One man with a thymoma was seronegative. He had only ocular symptoms which disappeared 3 months after thymectomy.

DISCUSSION

This study involved 537 MG patients from a database of 681 patients. Sex distribution and age of onset of MG in patients with different thymic gland histology were similar to those reported previously.^{3, 13} Age at onset seems to be increasing, which has also been noted by others.^{17, 18} One explanation might be that MG in older persons has previously been under-diagnosed.¹⁹

Of our patients, 326 (61%) were thymectomised. In the 1970s, a transcervical approach was used. The most handicapped patients were reoperated trans-sternally; the lower thymus lobes were extirpated, after which 82% of patients improved.²⁰ Since 1979, the transcervical method has been abandoned. Median time for thymectomy after onset of MG was 0.5–1.5 years and this correlates well with WHO recommendations.²¹

Of those operated on, 20% had thymoma, 57% had HPL and 23% had a normal thymic histology. The frequency of thymoma was higher than reported in the literature,^{1, 2, 13} probably because we received more severely ill patients from hospitals outside Stockholm county. In five patients, MG appeared after extirpation of a thymoma, a phenomenon described previously.²²

The increased frequency of autoimmune and endocrine disorders is in line with earlier reports.^{1, 2, 13} Extrathymic malignancies were observed in 25% of all MG patients and this corresponds well to results of a recent report.²³ The highest frequency was noted in non-operated patients, probably because of their older age. Squamous cell skin cancer was found particularly in patients who received IS.

AChR-ab levels did not decrease after thymectomy. Many patients were seronegative at the first visit but became seropositive after several months or years.

The clinical classification at the first contact may have been biased by the fact that the most severely affected patients came to our intensive care unit and their MFT could not be tested during ventilator treatment. Also, patients who came from outside our area had already received anticholinesterase medication before their visit to us.

We have a long tradition of using IS for MG. The majority of our patients received one or more IS drugs for a shorter or longer time. Adrenocorticotrophic hormone and later steroids, as intensive 2 day courses, have been used since 1958,²⁴ azathioprine since 1964 and ciclosporin since 1989. At present, we start IS early in patients with an MG onset over 60 years and in patients with thymoma. The use of plasmapheresis has been rare since the 1990s and has largely been replaced by short courses of methylprednisolone.

In total, 438 patients improved, of whom 127 went into remission. Of the patients in remission, 31% were using or had used IS. Until the 1970s, MG patients with thymoma had a poor prognosis. At present, our patients do well because of early use of IS. In the thymoma group, 74% improved or achieved remission. The best prognosis was found in the HPL group in which 88% improved or achieved remission. Also, patients with a normal thymus and non-operated patients improved over the observation time. Non-operated patients had an older age at onset or had either focal or a mild generalised myasthenia and thus could not be compared with operated patients.

CONCLUSIONS

The prognosis of MG is good for the majority of patients, irrespective of the histology of the thymic gland. Thymoma patients have more severe MG at the onset of disease. Most patients with MG need IS, at least for some of the time. Also,

non-thymectomised patients improved over the observation time.

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