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The natural course of myasthenia gravis: a long term follow up study

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SUMMARY A long term follow up study is presented of 73 patients with myasthenia gravis, living in Amsterdam between 1926 and 1965. In the period 1961–65 the annual incidence was 3·1, the prevalence 53 per million. Maximum severity of the disease occurred during the first seven years after onset in 87%. Eighteen (29%) patients died, of whom eight had a thymoma (TH). Spontaneous improvement or remission occurred at any time during the follow up. At the end of the study (1985) 16 (22%) patients were in a complete clinical remission, 13 (18%) had improved considerably (3 with prednisone), 12 (16%) had improved moderately, 12 (16%) had remained unchanged and two had deteriorated. If the early deaths are excluded the outcome is similar in the early and the late onset group without TH. Patients with TH had a less favourable course. Associated autoimmune diseases were diagnosed in 25% (n = 58). Because most of these patients were treated with anticholinesterases only, the evolution of their clinical state represents the natural course of MG.

The natural course of myasthenia gravis (MG) is not well known. In the early series the diagnosis was probably limited to the more severely affected patients with mortality rates of 30–40%.[1,2] Since the introduction of anticholinesterases in 1934 the diagnosis was facilitated in less prominent cases although a reaction may be absent in the ocular cases. Thymectomy is generally thought to have improved the natural course in early onset cases without thymoma, but some doubt has been expressed because of the lack of randomised prospective studies. Improved intensive care facilities and the use of prednisone, immunosuppressive drugs and plasma-exchange are of benefit especially to the 20% severely affected patients with intermittent respiratory insufficiency. The use of new diagnostic tools such as single-fibre electromyography, EMG with ischaemia, and the determination of antibodies to acetylcholine receptor proteine (AChR) allow a more accurate diagnosis in mild cases and exclude other myasthenic syndromes and pseudomyasthenia. As a result these procedures include mild cases which probably remained undiagnosed in earlier series, thereby improving the prognosis.

Between 1961–65 I studied 58 patients with MG living in Amsterdam. They probably comprised all the patients diagnosed with MG at that time. This epidemiologically defined cohort was followed until 1985. Since these patients were in part survivors of a larger population of MG patients, all the patients diagnosed in the University Department of Neurology from 1926 and living in Amsterdam, were reviewed retrospectively. Thymectomy in non thymoma patients was not used before 1965 while prednisone and azathioprine were only used after 1970 in some patients and affected the final outcome in only three. Therefore the evolution of their signs might be the natural course of MG if treatment with anticholinesterases is assumed not to influence the outcome. A first report was given in a previous paper.[3]

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Methods

The population studied comprised 73 patients with MG between 1926–65, who were or had been inhabitants of Amsterdam at the onset of their signs. Sixty six patients had initially been referred to the department of neurology at the University Hospital of Amsterdam; seven were known to other neurologists. In two of them the diagnosis was made in 1974. Fifteen of them had died on 1 January 1961 when this study was started. Their disease data were reviewed retrospectively from their hospital records, and in five additional data were acquired from their relatives. All 58 patients alive between 1 January and 31 December 1965 were examined and followed until 31 December 1985 or until their death. On 31 December 1965 (prevalence day) 46 were alive, as were 29 on 31 December 1985. Most of the patients were re-examined at regular intervals, and all relevant medical data were collected from their doctors.

The diagnosis was based on the presence of fluctuating muscle weakness, including at least one muscle group innervated by a cranial nerve, which improved by rest and in specific reaction to anticholinesterases. In four patients who died before 1935 the clinical state alone was convincing. An abnormal reaction to d-tubocurarine confirmed the diagnosis in some patients with ocular MG and an equivocal reaction to anticholinesterases.

Patients were classified according to Osserman[4] as follows: ocular (n = 11), mild (n = 14), moderate (n = 24), severe with rapid progression (n = 15), severe with late progression (n = 9). A personal disability scoring system[5a] was used to indicate disease severity at 0·5, 1, 3, 5, 7, 10 years after onset and every 5 years thereafter. Six global classes were used (0 = remission, no medication, 1 = minimal signs and symptoms, 2 = mildly disabled, 3 = moderately disabled, 4 = severely disabled, 5 = respiratory support needed). "Much improved" implies a change in this scoring system of at least 2 classes (for example, from 4 to 2 or 3 to 1), "improved" is a change of 1 class, deteriorated an increase of 1 or 2 classes.

Antibodies to striated muscle (anti-SM) were determinated with an immunofluorescence technique (on rat diaphragms) (n = 52) and anti-nuclear antibodies with the same technique on various tissues (n = 46). In 26 of 29 patients alive in 1985 antibodies to AChR were determined by immunoprecipitation assay.[6]

Thymomas were detected in six patients by operation, in four at autopsy, in four by radiological investigations diagnosed by exclusion of other diseases that might have caused an anterior mediastinal mass at follow up (table 5). Thymomas were excluded in five severe cases at autopsy; the existence of such tumours was very unlikely in 33 patients who lacked anti-SM antibodies.[5b] In five older patients with anti-SM antibodies in titres of 1:20 to 1:80 no thymoma was detected during the follow up; in 16 patients anti-SM antibodies were not investigated.

Information about the population of Amsterdam was obtained from the Municipal Office of Statistics.

Results

Epidemiology

The newly diagnosed cases of MG in Amsterdam in five year periods from 1926–65 are given in table 1.

Mortality due to MG did not change appreciably if patients with generalised MG only are considered: in the period 1926–45 eight out of 26 (31%) died, in the period 1946–60 seven out of 24 (29%), and in the period 1961–65 three out of 12 (25%).

On prevalence day (31 December 1965) Amsterdam had 852 500 inhabitants (418 800 men, 443 700 women) and at the onset of the last five year period (1 January 1961) this number was 866 300. The estimated migration was 5% per year. The prevalence, incidence and mortality rate are calculated in table 2 and the age adjusted prevalence in table 3.

The distribution according to age, sex, onset of MG, maximum severity, and thymoma are given in figure 1.

The mean follow up was 15·3 years (range 0·5–59) in 26 men, 24·6 years (0·5–50) in 47 women, 28·3 (range 0·5–50 years) in 35 early onset patients (< 39 years) without thymoma, 17·7 (range 0·5–40) years in 24 late onset (> 40 years) patients without thymoma, and 8·6 (range 0·5–21) years in 14 thymoma patients.

Initial signs

The initial signs (that is, within three months from onset) were ocular in 35 patients, oculobulbar in six, bulbar in 11, limb weakness in nine, and generalised in 12. Of the 35 patients starting with ocular signs 11 remained purely ocular, 21 became generalised within two years and in three patients generalisation occurred between 10 and 22 years after onset.

Clinical course

Spontaneous remissions in the first year of the disease occurred in 16 patients; in eight of them the interval to relapse was 3–12 months, in eight more than 12 months, the longest interval being six years in two patients. These early remissions were not related to the ultimate severity of the disease.

The clinical course is schematised in table 4. The worst period including death occurred in 50 patients (87%) within the first seven years, while in 12 patients the clinical condition did not change. In five patients, of whom three had only ocular signs, an exacerbation took place 10 to 25 years after onset. Three patients

Table 1 *Newly diagnosed patients with myasthenia gravis in Amsterdam*

Period	*Inhabitants × 10³*	*Patients*	*Died before 1965*		*Present at*	
			From MG	*From other causes*	*31.12.65*	*1985*
1926–30		8	4	3	1	1
1931–35	782	4		1	3	2
1936–40		6			6	3
1941–45	771	8	4		4	3
1946–50		9	1	2	6	4
1951–55	869	6 (1)	1	2	3	2
1956–60	866	15 (5)	5	1	9	5
1961–65	862	17 (5)	3		14	0
		73 (11)	18	9	46	29

( ): Patients with ocular MG.

Table 2 *Myasthenia gravis in Amsterdam 1961–65*

	Men	*Women*	*Total*
Patients present from 1961–1965	18	40	58
Patients died (MG) before 31.12.1965	8 (5)	4 (2)	12 (7)
Patients present at 31.12.1965	10	36	46
Prevalence per 10^6	24	81	53
95% confidence interval	11–44	57–112	39–71
Onset 1961–1965	4	13	17
Incidence/10^6/year	1·5	4·7	3·1
95% confidence interval	0·4–3·8	2·5–8·0	1·8–5·0
Death rate MG/10^6/year	2·07	0·79	1·4

Table 3 *Age at onset and age adjusted prevalence of myasthenia gravis. Amsterdam 1961–65*

Age at onset	*Men*	*Women*	*Prevalence × 10^6*	
			Men	*Women*
0– 9	2	2	27	29
10–19	1	3	12	39
20–29	3	12	42	174
30–39	1	6	17	101
40–49	3	5	49	74
50–59	5	6	89	92
60–69	2	4	44	71
70–	1	2	30	44
Total	18	40	43	78

had a period of exacerbation in a previously stable course; this could be ascribed to hyperthroidism in one and to emotional stress in two (these exacerbations are not listed in table 4).

Thymomas were detected in nine men and five women; five were present in the early onset group, and nine in the late onset group. In all patients with thymomas MG was generalised; maximum severity was mild in one patient, moderate in four and severe in nine. Further data are summarised in table 5.

Myasthenic crisis and death

Eighteen patients died in a myasthenic crisis, 13 within three years after onset (three in the period before prostigmin), three in the sixth year after onset, and two patients (eight and 17 years respectively after onset) in a crisis precipitated by an operation and an airway infection. Eight of 14 thymoma patients died, four of these shortly after thymomectomy (table 5). Prednisone was not prescribed or intratracheal artificial ventilation given in any of these patients.

One death concerned a boy aged one year who developed a severe bulbar weakness during a varicella infection. The diagnosis was made when his monozygotic twin brother developed the same infection 10 days later. This boy had moderate oculobulbar signs in infancy with a good reaction to prostigmin, and mild intermittent ocular signs thereafter. There were five survivors of a myasthenic crisis (n = 23, table 6). One was a girl aged 17 months, who developed severe oculobulbar weakness and apnoea during an infection. She had mild myasthenic signs in childhood and went into a complete remission at the age of 20. Although no anti-AChR antibodies were found in these two patients as adults, the clinical course and the favourable reaction to anticholinesterases suggests an acquired rather than a congenital myasthenia.

The three adult survivors of the myasthenic crisis were the thymoma patients numbers 13 and 14 (table 5) and a woman aged 60 who improved to stage 2 when treated with prednisone. In this patient a thymoma was excluded at autopsy after cardiac death aged 75.

Final outcome

The final clinical classification in the last year of follow up is given in table 6. In three patients the final outcome was certainly improved by prednisone and in

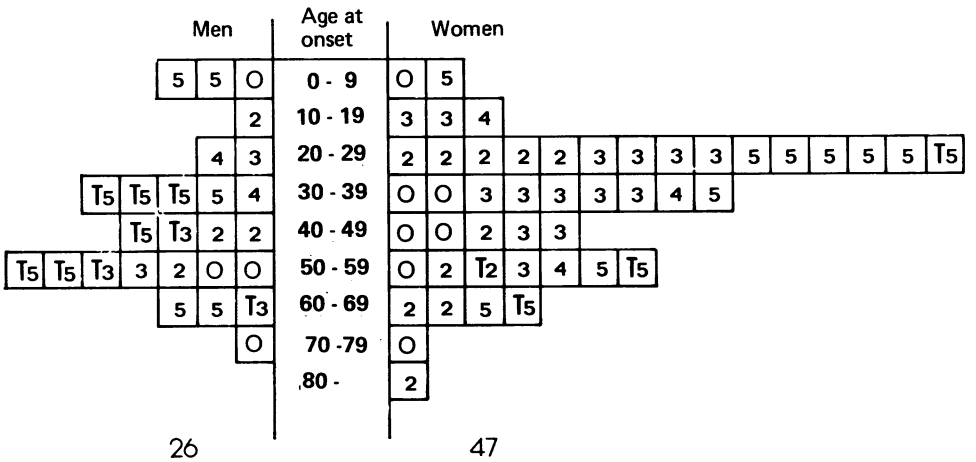

Figure *Each square represents one patient. The number indicates the maximum severity of the MG: 0 = ocular, 2 = mild, 3 = moderate, 4 = severe without respiratory insufficiency, 5 = respiratory insufficiency, T = thymoma.*

Table 4 *Time course of clinical change in MG*

	Years after onset														
	0–½	*½–1*	*1–3*	*3–5*	*5–7*	*7–10*	*10–15*	*15–20*	*20–25*	*25–30*	*30–35*	*35–40*	*40–45*	*45–50*	*Totals*
Remission			1	2	1‡	1	2	2	5				1	1	16
Much improved					1	2*	3*	3*	2	1		1			13
Improved		1	1	2	1	1	4	1							11
Unchanged															12
Deteriorated								2							2
Died	2†	4†	7		3	1†		1†							18
Worst period	7	9	20	8	6	5	2	3	1						61

*One patient treated with prednisone.
†One patient not treated with prostigmine (before 1935).
‡One patient treated with thymomectomy.

Table 5 *Patients with thymomas*

	Sex	*Onset age*	*MG year*	*Maximum severity*	*Operated*	*Follow up*		*Comments*
						Age	*Outcome*	
1	W	28	1941	5	+	28	Died	Postoperative death; autopsy
2	M	56	1943	5	−	59	Died	Irradiation of thymoma; autopsy
3	M	31	1942	5	−	39	Died	Diagnosis thymoma by radiograph
4	M	44	1953	3	+	55	1	Thymoma inoperable: died from aplastic anaemia
5	M	44	1957	5	+	49	Died	Died 1 year after operation
6	M	30	1957	5	−	36	Died	Autopsy
7	M	51	1958	3	+	76	1	Operation 1 year before onset MG; after 9 years ocular → generalised (stage 3) after prednisone → stage 1
8	M	61	1958	3	+	74	0	Remission 1 year after operation systemic lupus erythematosus
9	W	59	1959	1	−	75	1	Thymoma diagnosed by biopsy; aplastic anaemia responded to durabolin
10	M	35	1962	5	+	36	Died	Died 0·5 years after operation
11	M	57	1961	5	+	58	Died	Postoperative death; autopsy
12	W	62	1963	5	−	63	Died	Autopsy
13	W	27	1964	5	−	49	2	Diagnosis by radiograph
14	W	59	1965	5	−	79	1	Diagnosis by radiograph and CT improved from stage 4 → 1 by prednisone; adrenogenital syndrome

Table 6 *Myasthenia gravis in Amsterdam 1926–65. Final outcome.*

Maximum severity MG	*Rem*	*MI*	*I*	*U*	*W*	*Died*	*Total*
Ocular	3	1	1	6			11
Mild (stage 2)	6		6	3			15
Moderate (stage 3 plus 4)	5*	9†	5	3	2		24
Severe (stage 5)	2	3††				18	23
Total	16	13†††	12	12	2	18	73
Early onset 1–39 years, no thymoma	9	7	7	4		8	35
Late onset 40–83 years, no thymoma	6	2†	5	7	2	2	24
Thymoma	1*	4††		1		8	14

*Thymomectomy.
†Patient treated with prednisone.
Rem = remission, MI = much improved, I = improved, U = unchanged, W = worse, died = died from MG.

one probably by thymomectomy; three of these patients had a thymoma. In four other patients (one ocular, three moderate) prednisone had been given for a short time, presumably without effect on the final outcome. All except the four patients who died before 1935 and the two patients for whom the diagnosis was made after death, received anticholinesterases.

Additional investigations

The following data concern the patients (n = 58) in the period 1961–65.

Associated diseases

Associated diseases of probable autoimmune origin are listed in table 7. Their onset had no relation to the onset of MG: in two patients they preceded MG for more than three years, in two patients there was a coincidence within three years and in 10 cases the auto-

Table 7 *Associated autoimmune diseases*

	Male (18)	*Female (40)*
Rheumatoid arthritis	—	6*
Pure red cell anaemia (and thymoma)	1	1
Hyperthyroidism	—	3**
Non toxic goitre		2
Systemic lupus erythematosus (and thymoma)	1	
Sarcoidosis	—	1

*Expected 1·3 (ref 17).
**Expected 1·5 (ref 18).

immune disease started more than three years later. In two patients with rheumatoid arthritis the ocular signs of MG were probably uncovered by the use of quinine type drugs.

Malignancies developed in three women: non-Hodgkin's lymphoma at age 64 (ocular MG since age 49), colon carcinoma at age 71 after 9 years treatment with azathioprine and prednisone (MG since age 59), epithelial cell carcinoma of the nipple at age 40 (MG since age 14).

Muscle atrophy

Muscle atrophy was clinically evident in seven patients. In six women with longstanding disease atrophy was localised in the shoulders and upper arm muscles (n = 4) or in the face and tongue (n = 2). In one young man a generalised muscle atrophy developed within a few months after thymomectomy when he was artificially ventilated. Autopsy showed neurogenic changes in the muscles and normal peripheral nerves.[7]

In 9 of the 20 patients with generalised MG the quadriceps were found to be abnormal at biopsy: lymphorrhages were found in two patients with a thymoma, neurogenic atrophy and lymphorrhages in 5 patients (four with a thymoma) and neurogenic changes only in 2 patients without a thymoma.

Neonatal myasthenia

Two cases of neonatal myasthenia occurred in the offspring of two patients who had previously had one and two normal children respectively during their disease. In total 11 children were born to seven patients during their disease. The incidence of neonatal myasthenia was 18% of the pregnancies during MG. (These cases were not included in the series.) This incidence is not different from the 12% reported.[8]

Antibodies

Antibodies to striated muscle were found in 18 of 51 patients. In all 11 patients with thymomas the titres were much higher than the seven late onset patients without thymomas. Antinuclear factors were found in 18 of the 46 patients; the incidence was higher ($p < 0.05$) in patients with thymomas (seven out of 11), than in patients without thymomas (11 out of 36).

In 1985 antibodies to AChR were found in 18 of 21 patients with generalised MG and in three of the six patients with ocular MG. The seronegative patients in the generalised group included the two patients with onset in infancy and one patient with a mild MG who went into remission.

Discussion

The incidence and prevalence of MG in this study is comparable with data from other recent studies (table 8). The prevalence is higher than that reported by Kurtzke[13] who estimated a prevalence of 40 per million as a result of various previous epidemiological investigations. His estimation of the annual incidence was four per million. The explanation of the higher prevalence is perhaps a more thorough case finding, which included patients no longer receiving specialist care. The higher prevalence in Norway[11] may also be explained in this way. An overall review of the patients with MG, living in Amsterdam and admitted to the neurological department in the periods between 1926–65 (table 1) suggests that the incidence of diagnosed cases with generalised MG and the death rate have not changed. Pure ocular MG was not diagnosed before 1955, possibly due to the difficulty in diagnosis. An alternative explanation is that these patients were not admitted for clinical observation, but this seems unlikely as all patients with uncommon diseases were admitted to hospital.

The predominance of women in the early onset

Table 8 *Survey of recent epidemiological studies of MG*

Origin	*Period*	*Annual incidence per million*	*Prevalence per million*	*Ratio M/F*	*Reference*
Finland	1956–65	2·27	25	0·46	9
Helsinki	1968	3·58	45	—	9
Finland	1976	—	56	0·38	10
Norway	1951–81	4·0	90	0·41	11
Japan	1981		12–51*	0·56	12
Amsterdam	1961–65	3·1	53	0·45	this study

*Various districts.

Table 9 *Natural course in 3 series with generalised MG*

Author	Period of onset	Number of patients	Mean follow up (y)	Outcome (%)			
				R	I	NI	D
Simpson (16)	1934–56	87*	14	19	22	22	37
Grob (2)	1940–60	382	12	11	21	36	32
Present series	1926–65	62	21	21	37	13	29

*Non thymectomised patients of whom data were present.
R = remission, I = improved, NI = not improved (or worse), D = died from MG.

group and of thymomas in the late onset group are common features (fig 1). The main features were ocular in 15% which is in accordance with the frequencies in two other large series[2 14] and of a severe type in 31% which is somewhat higher than the 20% reported by Osserman and Genkins.[14] The prevalence of thymomas has not been reported in epidemiological studies; in large series of MG patients the frequency varies from 9 to 16%.[5c] In this series the prevalence was 19%; only in men was the frequency unusually high (35%). In the 15 patients who died before 1960 the incidence was 20%, but it is possible that some others remained undiagnosed. In my 374 patients[15] with onset between 1965–84 the frequency of thymomas was 19%; the detection rate is likely to increase if all patients with anti-SM are examined with CT scanning of the mediastinum.

This cohort of MG patients, in Amsterdam between 1961–65 (n = 58) is a representative sample. The course of the clinical state of the whole population (n = 73) may be considered as the natural history of the disease, since thymectomy in early onset patients was not performed and immunosuppressive therapy influenced the outcome in only three patients.

The natural history that emerges from this study is as follows. After an uncertain onset, with spontaneous transitory remissions in about 20% of the patients, the disease gradually develops a maximum intensity in the first seven years, although about 15% may have their worst period later. About 25% of the patients will die, mainly in this first period. Spontaneous clinical remissions and substantial improvement may be expected from the second year after onset and may occur at any time thereafter, but the clinical course is unpredictable in the individual patient (table 5). The general trend in the survivors is that of a gradual improvement in the long term, a complete clinical remission (without medication) occurring in more than 20%; approximately 15%, usually with mild symptoms, do not change (table 5). This general improvement was not merely the result of a subjective account by the patients and the improved ability to cope with their handicap. The clinical assessment in this study was based on quantified clinical tests,[5d] for most patients at multiple follow up examinations to assess their muscle strength and endurance.

If patients with thymomas and those who died early are excluded the early onset group had the same prognosis as the late onset group. An early death, without treatment with prostigmine, occurred in four of the early onset patients and in one patient with a thymoma (number 12). Patients with a thymoma usually had severe MG and a higher case fatality (8/14 table 5).

In table nine the results of this study are compared with those of two others from the same period.[2 16] While the myasthenic death rates seem to be similar, the more favourable outcome in the present series is probably the result of the longer follow up.

The impact of new therapies such as thymectomy in early onset patients and prednisone or immunosuppressive therapy in late onset patients, and in patients with thymomas, is reflected in the outcome of a series of 328 patients with generalised MG with onset between 1965–84 and a mean follow up of 12 years.[15] Complete clinical remission, with or without therapy, occurred in 37% and death in 9%. The latter was due to MG in 5·2% of the patients, who were not treated with prednisone, in 1·8% due to the side effects of prednisone or azathioprine and in 2% due to the invasiveness of their thymoma or thymoma associated myocarditis.

Associated diseases of probable autoimmune origin were present in three of 11 patients with thymomas and in 12 of 47 patients without thymomas. This frequency (25%) is probably higher than expected for the whole population although the prevalence of autoimmune diseases in a population studied over a long period is not known. Only rheumatoid arthritis in women had a definitely higher prevalence than expected from a population study[16] which yielded about the same prevalence as that in The Netherlands (expected age adjusted prevalence 3·25% means 15% in this study).

In three women a malignant disease was detected. This figure is not higher than may be expected[19] (age adjusted prevalence 2·4) and does not support the finding that the incidence of extrathymic neoplasms

was three times higher in myasthenic patients who did not have thymectomy.[20] Antibodies to AChR were found in 18 of 21 patients with generalised MG and in three of six patients with ocular MG. This supports our data in recently diagnosed patients.[6] The two patients with onset in early infancy were seronegative and those whose clinical course and favourable reaction to prostigmin indicated that they had an acquired and not a congenital MG; in one patient there was a remission. These findings also confirm our data that antibodies to AChR remain present even if the patient is in a clinical remission. Anti-SM were present in all thymoma patients (n = 11) and in five of 40 patients without detectable thymoma. The titre in the latter were definitely lower than in patients with a confirmed thymoma. The absence of a small thymoma, however, is difficult to prove without a CT scan of the mediastinum or autopsy.

This long follow up study of an epidemiologically defined group of MG patients, most of whom did not receive "modern" treatments, shows that those who survive the signs and symptoms of the disease have a tendency to diminish gradually, although unpredictably in the individual patient. Whether this is caused by a physiologically decreasing immunological activity due to increasing age or to adaptive mechanisms in the acetylcholine receptor turnover, or to both, remains to be elucidated.

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