Epidemiology of seropositive myasthenia gravis in Greece

K Poulas, E Tsibri, A Kokla, D Papanastasiou, T Tsouloufis, M Marinou, P Tsantili, T Papapetropoulos, S J Tzartos

Abstract

***Objectives*—To study the epidemiological characteristics of myasthenia gravis in Greece.**

***Methods*—A population based study was carried out of seropositive myasthenia gravis in Greece for the period from 1 January 1983 to 30 June 1997; 843 patients were studied.**

***Results*—The average annual incidence for the period 1992–7, for which the database is complete, was 7.40/million population/year (women 7.14; men 7.66). On 1 July 1997, there were 740 prevalent cases. The point prevalence rate was 70.63/million (women 81.58; men 59.39). The average overall annual mortality rate in the patients was 0.67/million population (women 0.53; men 0.82), and the mortality rate attributed to myasthenia gravis was 0.43/million population (women 0.41; men 0.45). The average age at onset was 46.50 years (women 40.16; men 54.46), and the mean age of the prevalent patients was 52.58 (women 47.65; men 59.48). The women:men incidence ratio was 1:1.04, and the prevalence ratio was 1.41:1. It is predicted that the prevalence and women: men prevalence ratio would increase if the patient list included all patients with a date of onset before 1983.**

***Conclusions*—The largest epidemiological study ever performed on myasthenia gravis is presented. The most important epidemiological indexes are provided.**

(*J Neurol Neurosurg Psychiatry* 2001;**71**:352–356)

Keywords: myasthenia gravis; neuromuscular disease; epidemiology

Department of Biochemistry, Hellenic Pasteur Institute, 127 Vas Sofias Avenue, Athens 11521, Greece
K Poulas
A Kokla
D Papanastasiou
T Tsouloufis
M Marinou
P Tsantili
S J Tzartos

University Department of Neurology, Medical School of Patras University, Regional University Hospital of Patras, PO Box 1045, 26500 Rion, Greece
E Tsibri
T Papapetropoulos

Correspondence to:
Dr S J Tzartos
tzartos@mail.pasteur.gr

Received 28 September 2000
and in revised form
22 January 2001
Accepted 26 April 2001

Myasthenia gravis is an organ specific autoimmune disorder characterised by weakness and fatiguability of the voluntary muscles and caused by autoantibodies against the muscle nicotinic acetylcholine receptor (AChR) at the neuromuscular junction.[1 2] Binding of these autoantibodies to the AChR leads to loss of AChR molecules and direct block of function of the remaining AChRs at the neuromuscular junction, resulting in impaired neuromuscular signal transmission. Such antibodies are detected in 80%-90% of patients with myasthenia gravis (seropositive myasthenia gravis).[1] Myasthenia gravis is a relatively rare disease that affects all ages, but not uniformly. Disease incidence is age and sex related with two peaks, one in the 2nd and 3rd decades, seen mainly in women, and one in the 6th and 7th decades, seen mainly in men.[1] Epidemiological studies on myasthenia gravis have been carried out since 1950[2] and have provided useful information for health service planning.

A review of the international literature, shown in table 1, which includes epidemiological studies of more than 50 cases, suggests that there is a wide range in the reported frequency of myasthenia gravis.[3–19] In these studies, the annual incidence was reported to range from 1.0 to 15/million and the point prevalence rate from 3.05 to 175/million.[20] This variability may be due to the fact that most of these studies are clinical reports based on few patients, usually treated in a hospital, the data then being extrapolated to the entire population. The number of patients with myasthenia gravis reported has increased from the 1950s to the 1990s, partly as a result of improved diagnosis and reduced mortality due to more effective

Table 1 Epidemiological studies on myasthenia gravis 1912–97. Surveys with more than 50 cases are included

First author	*Year*	*Region*	*No*	*Population*	*Incidence*	*Prevalence*
Storm-Mathisen[3 4]	1912–52	Norway	90	3700000	1	21
Garland[5]	1955	Yorkshire, UK	60	3500000	5	26
Giagheddu[6]	1961	Sardinia, Italy	110	1500000	2.6	7.7
Oosterhuis[7]	1965	Amsterdam, Netherlands	73	850000	3.1	53
Giagheddu[6]	1971	Sardinia, Italy	110	1500000	2.6	17.6
Pirskanen[8]	1976	Finland	264	4700000	ND	5.6
Storm-Mathisen[9]	1981	Norway	458	3700000	4	90
Phillips[10]	1984	Virginia, USA	112	550000	9.1	142
Giagheddu[6]	1986	Sardinia, Italy	110	1500000	2.6	45
Micaglio[11] (abstract)	1987	North east Italy	128	1820000	ND	70.3
Somnier[12 13]	1987	Eastern Denmark	229	2320000	4.4	77
Yu[14]	1987	Hong Kong	262	5610000	4	53.5
Christensen[15] (abstract)	1990	Western Denmark	290	2800000	5	78
Lavrnic[16]	1992	Belgrade, Yugoslavia	124	1495000	7.1	121.5
Kyriallis[17]	1994	Cyprus	105	600000	15	175
Tola[18]	1994	Emilia Romagna, Italy	86	2925000	14.7	ND
Robertson[19]	1997	Cambridgeshire, UK	100	685000	11	150

treatment.[20] We think that the real epidemiology of myasthenia gravis has not yet been identified and larger population based studies are needed.

To investigate the epidemiological characteristics of myasthenia gravis and refine the various epidemiological indexes, we have undertaken a large national study. Both the number of patients included in this survey and the population size are almost double the maximum used in previous studies.[9 14] Most previous studies have involved only small groups of patients, but accurate epidemiological analysis of diseases with low frequency—such as myasthenia gravis—requires large populations in order to identify the real epidemiological characteristics and provide useful data on the natural history of the disease. It should be noted, however, that this study only involved patients with seropositive myasthenia gravis—that is, about 85% of the total patients.

Methods

We conducted a population based study of the frequency of seropositive myasthenia gravis between 1 January 1983 and 30 June 1997 in the whole of Greece. Information about the Greek population was obtained from the National Office of Statistics. The total population of the country in 1997 was 10 475 878 (women 5 307 186; men 5 168 692),[21] whereas the mean population for the period 1983–97 was calculated to be 10 180 913 (women 5 156 632; men 5 024 281).

The Hellenic Pasteur Institute is the only institution in Greece in which human serum samples have been analyzed for anti-AChR antibodies since 1983; as a consequence, it receives blood samples and patients' details from most hospitals and practising neurologists throughout the country and keeps computerised records of patients' details.

Serum samples are tested by a conventional radioimmunoassay for the presence of antibodies against human AChR.[22] Amputated human leg muscle or the human rhabdomyosarcoma cell line, TE671, are used as the AChR source. Antibody titres are expressed as mol ^{125}I-α-bungarotoxin labelled AChR bound/l serum.[22] Normal human serum samples have titres of 0.2 nmol/l or less, samples with titres of 0.4–0.9 nmoles/l are considered as ambiguous, and samples with titres of 1 nmol/l or more are considered positive. Only seropositive patients were included in the survey.

Incidence was based on the year of clinical onset. Myasthenic patients were considered prevalent if they were living in Greece on 1 July 1997 (prevalence day). All patients with seropositive myasthenia gravis sent from the whole of Greece to our laboratory for anti-AChR antibody testing between 1 January 1983 and 30 June 1997 were screened. In the next 3 years (1 July 1997 to 1 July 2000), all newly identified seropositive patients were also interviewed to identify those with a date of onset before 30 June 1997. These patients were also included in the prevalence date.

A positive anti-AChR antibody assay was sufficient for inclusion in the group of patients with myasthenia gravis. However, for many patients, the diagnosis of myasthenia gravis was already confirmed or supported by pharmacological tests or neurophysiological examination in parallel with clinical findings (history of muscle weakness, recovery of muscular strength at rest, and improvement after administration of cholinesterase inhibitors). For each patient, a registration form was completed which included details of name, sex, date of birth, age at onset and diagnosis, main symptoms at onset, results of various clinical tests and examinations, clinical course and therapies, thymectomy, presence of other (especially autoimmune) diseases, and relatives with myasthenia gravis. The basic data in this study were obtained by personal interview or by telephone and letter contact. Patients with penicillamine induced myasthenia gravis (10 cases) or transient neonatal myasthenia gravis (two cases) or who were not Greek citizens (five cases) were excluded.

Confidence intervals were calculated using the Poisson distribution. The difference between two or more frequencies was estimated using the χ^2 test. For all tests, p values<0.05 were considered significant.

Results

CASE ASCERTAINMENT

A total of 843 patients with myasthenia gravis (474 women and 369 men) were found to be seropositive. A total of 733 patients (389 women and 344 men) with onset between 1 January 1983 and 30 June 1997 and 110 (85 women and 25 men) with onset before 1983 (earliest onset in a woman 1956; in a man 1957) were identified.

INCIDENCE

Figure 1 shows the number of annually identified incident cases in Greece over the period 1983–97. The average annual incidence rate/million population in Greece was 4.80 (95% confidence interval (95% CI) 4.11–5.49), 5.03 for women (95% CI 4.33–5.73), and 4.56 for men (95% CI 3.89–5.23, table 2). The rates for the first years of the survey (1983–91) were lower than those for the period 1992–7 (see discussion). In the 6 year period between 1 January 1992 and 31 December 1997, 452 new diagnoses of myasthenia gravis were made (women 221; men 231), giving an average annual incidence rate of 7.40/million population/year over this period (95% CI 6.54–8.26), 7.14 for women (95% CI 6.30–7.98) and 7.66 for men (95% CI 6.79–8.53). The women:men incidence ratio for this period was 1:1.04.

Figure 2 shows the number of incident patients according to age at date of onset. The mean age at onset was 46.50 years (95% CI 45.07–47.93), 40.16 for women (95% CI 36.28–44.04) and 54.46 for men (95% CI 52.48–56.54). This difference was significant. Figure 2 clearly shows that the previously well described bimodal distribution pattern[1] was also seen in the Greek population. The bimodal pattern was significant, whereas population distributions for men only and women

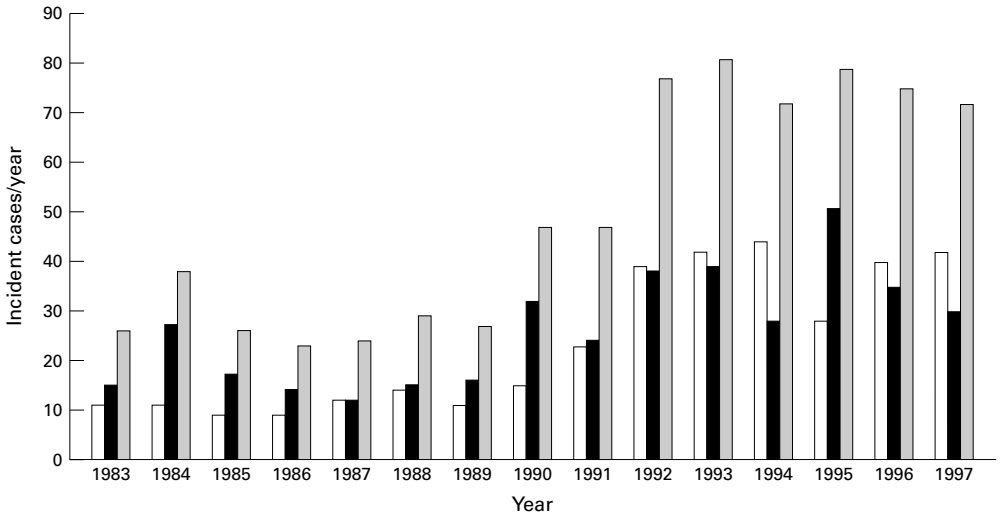

Figure 1 Incident cases of myasthenia gravis in Greece/year during the survey years (white column men; black column women; grey column both sexes).

only were unimodal. In the total population, age and sex specific incidence was highest in the age group 60–69 years. In men, the incidence rates were very low in the younger age groups (<50 years) and increased to a peak in age groups older than 60 years. In women, a different pattern was seen, with the highest rate in the age group 20–29 years. The differences between sexes were significant for all age groups, except for the groups 0–9 years and 50–59 years. This sex specific bimodal pattern in the Greek population has been shown previously in a study of 266 patients from the Athens University Neurological Clinic.[23]

PREVALENCE

The day chosen for prevalence determination was 1 July 1997, on which date 740 patients (433 women and 307 men) diagnosed with myasthenia gravis were living in Greece. The point prevalence rate on this day was 70.63/million population (95% CI: 62.23–79.03), 81.58 for women (95% CI 72.55–90.61), and 59.39 for men (95% CI 51.69–67.09). The mean age of the prevalent patients was 52.58 (95% CI 51.13–54.03), 47.65 for women (95% CI 45.25–50.05) and 59.48 for men (95% CI 57.63–61.33). This difference was highly significant ($p<0.001$). The women:men ratio was 1.41:1. Table 3 shows the age and sex specific prevalence of the disease in Greece. For both sexes combined, the highest prevalence rate was seen in the group older than 70 years. In women, the prevalence rate showed a rather stable plateau between the ages of 20 to older than 70 years, whereas, in men, a continuous increase that became more dramatic after the age of 60 was seen (fig 3).

Table 2 Incident cases of seropositive myasthenia gravis (MG) in Greece

Period	*Women*	*Men*	*Total population*
1983–97	389 (5.03 ± 0.70)*	344 (4.56 ± 0.67)	733 (4.80 ± 0.69)
1983–91	168 (3.62 ± 0.43)	113 (2.49 ± 0.49)	281 (3.06 ± 0.38)
1992–97	221 (7.14 ± 0.84)	231 (7.66 ± 0.87)	452 (7.40 ± 0.86)

*Mean annual incidence rate, expressed as MG incident cases/million population/year, with 95% confidence intervals.

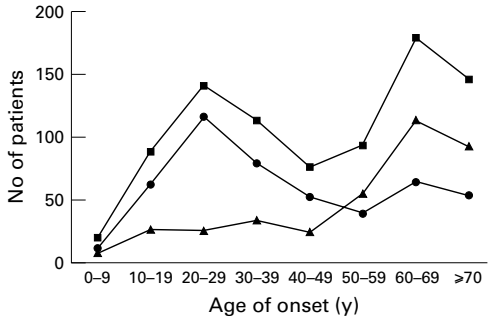

Figure 2 Age specific and sex specific onset of myasthenia gravis in Greece. Circles=women; triangles=men; squares=both sexes.

MORTALITY: OTHER CLINICAL FEATURES

In the whole 15 year period (1983–97), 103 patients died (women 41; men 62), 66 of these deaths being attributed to myasthenia gravis (women 32; men 34). The annual average overall mortality rate/million population was 0.67 (wome: 0.53; men 0.82), whereas the myasthenia gravis mortality rate (with myasthenia gravis as an underlying or contributory cause) was 0.43 (women 0.41; men 0.45). The age at time of death for myasthenia gravis related cases varied from 17 to 87 for women and 26 to 85 for men, with an average of 60.77 and 64.65, respectively.

Other autoimmune diseases were found among the patients with myasthenia gravis, the most common being thyroid disorders (table 4). Associated autoimmune diseases were seen more often among women patients. Overall, 11.62% of the patients had associated autoimmune diseases.

Discussion

As far as we are aware, this is the largest epidemiological study ever performed on myasthenia gravis and one of very few on an entire nation. It is the first epidemiological study on myasthenia gravis ever conducted in Greece, although clinical data for 266 patients[23] and results on beneficial effect of early thymectomy[24] have been published. We included all

Table 3 Age and sex specific prevalence

	Women			*Men*			*All*		
Age	*Population*	*No*	*Prevalence**	*Population*	*No*	*Prevalence**	*Population*	*No*	*Prevalence**
0–9	514449	2	3.88	546099	3	5.49	1060548	5	4.71
10–19	686080	13	18.94	725767	8	11.02	1411847	21	14.87
20–29	784094	76	96.92	810345	15	18.51	1594439	91	57.07
30–39	755499	73	96.62	752233	24	31.90	1507732	97	64.33
40–49	680624	68	99.90	682823	25	36.61	1363447	93	68.20
50–59	625513	58	92.72	600974	40	66.55	1226487	98	79.90
60–69	641252	74	115.39	581046	70	120.47	1222298	144	117.81
≥70	619675	69	111.34	469405	122	259.90	1089081	191	175.37
Total	5307186	433	81.58 (±9.03)†	5168692	307	59.39 (±7.70)†	10475878	740	70.63 (±8.40)†

*Prevalence rates are expressed as myasthenia gravis patients/million population.
†95% confidence intervals.

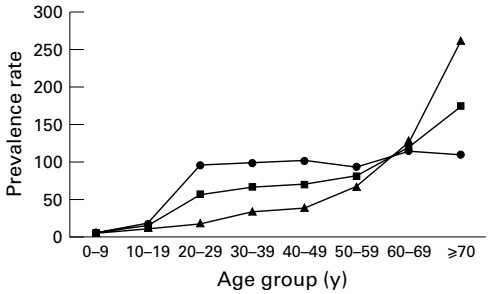

Figure 3 Myasthenia gravis in Greece on 1 July 1997. Age and sex specific point prevalence rates/million population. Circles=women; triangles=men; squares=both sexes.

known seropositive patients identified by our diagnostic unit.

Only a few population studies on myasthenia gravis have included a sufficient number of patients to obtain reliable epidemiological indices. The small size of these studies is probably partly responsible for the large variation in their epidemiological indices (table 1). However, the bimodal pattern of the age and sex specific incidence seems to be a universally identified epidemiological characteristic of the disease and was confirmed in the present study (fig 2).

The annual incidence, shown in figure 1, seems to present two different patterns, being low for the period 1983–91 (mean 3.06) and high for the period 1992–7 (mean 7.40), the overall average being 4.80/million. The reason for the low annual incidence in the first period is that Greek neurologists were not all aware of the diagnostic unit at that period and we therefore suggest that the most representative average annual incidence is that for the period 1992–7 (mean 7.40), rather than that for the whole period 1983–97. In fact, the annual incidence has remained relatively stable during 1992–97 (figure 1).

The crude prevalence rate for the Greek population was 70.63/million, which is within the limits of prevalence rates obtained in recent studies in various countries.[11–13 15] Due to the longer life expectancy after onset of disease for women than for men, when we study the entire population, the prevalence rates increase with age, peaking in the group over the age of 70 (mainly due to an increase of male patients). In women, the rates are roughly stable after the age of 20 (fig 3).

The data presented in this study agree with our previous report,[25] which stated that the incidence in men and women is equal. We had estimated that, with a women:men incidence ratio of 1:1, the prevalence ratio would be 1.74:1, as women patients with myasthenia gravis have a much longer average life expectancy and disease duration after onset (women:men myasthenia gravis life expectancy=40:23 years or 1.74:1).[25] In this study, we found a women:men prevalence ratio of 1.41:1. We think that this difference (1.41 compared with 1.74) is due to several older patients diagnosed before 1983 (and some between 1983–92) not having been referred to our diagnostic unit. Most recently diagnosed myasthenic patients, both men and women, fall into the lower range of the predicted life expectancy range, and therefore the overrepresentation of patients with recent onset in the studied myasthenia gravis population should reduce the calculated 1.74:1 ratio. Further support for this explanation comes from the finding that the group of patients with onset before 1983 was heavily dominated by women patients (85 women; 25 men: ratio 3.40:1). The mortality rate of myasthenia gravis was low (0.43/million), close to previously reported values.[20] Close follow up and advanced treatment of patients with myasthenia gravis explain the low rate and increased mean age of death.

Our conclusions should be considered in the light of several limitations.

(1) we excluded patients with seronegative myasthenia gravis, as, although our database contains a few such patients, it is currently impossible for us to evaluate most of them. Furthermore, seronegative myasthenia gravis has recently been shown to be a different entity

Table 4 Associated autoimmune diseases in 843 patients with myasthenia gravis (MG)

	Number of cases among:		
Autoimmune disease	*Women MG patients*	*Men MG patients*	*Total (% of all MG patients)*
Thyroid disorder (TD)	47	13	60 (7.11)
Rheumatoid arthritis (RA)	17	9	26 (3.08)
Systemic lupus erythematosus (SLE)	10	2	12 (1.42)
Ankylosing spondylitis	1	—	1 (0.11)
Crohn's disease	2	—	2 (0.22)
Ulcerative colitis	—	3	3 (0.33)
SLE+RA+TD*	1	—	1
SLE+TD*	3	—	3
RA+TD*	1	—	1
RA+SLE*	1	—	1
Total	71 (14.97%)	27 (7.31%)	98 (11.62)

*Patients with two or three associated autoimmune disorders are included several times—that is, in each single disorder and in the disorder groups.

from the seropositive disease, being caused by antibodies to the MuSK protein,[26]

(2) Some patients diagnosed with myasthenia gravis were not included in our survey. There are Greek patients diagnosed by radioimmunoassay abroad, others who were diagnosed before 1983 (before our unit was established) and whose follow up was not based on this test, and patients whose physicians (often non-neurologists), for various reasons, do not consider this test critical for the final diagnosis of myasthenia gravis. In addition, although our unit is widely known within the country, some neurologists may still not be aware of its existence.

(3) It is likely that some patients have never been properly diagnosed. In Greece, almost everyone has access to health care services, which ensures that the great majority of patients will be identified by neurologists and finally reach our unit. However, in some regions, because of social, economic, and geographical reasons, it is not as easy to receive medical advice as in the cities and thus such patients may have been omitted from our survey, although the number should be relatively small.

(4) We did not examine any regional variations, but treated the country as a whole. We realise that it would be useful to study topological differences within the country, but this is very difficult, as Greece is divided into 52 provinces, most of which would have too few patients to allow statistical evaluation.

Taking into account the fact that only patients with seropositive myasthenia gravis, who are generally considered to be about 85% of the total patients, were included in our survey[1] the above values for incidence and prevalence should be increased by a factor of about 1.18 to include all patients. Therefore the incidence of seropositive plus seronegative myasthenia gravis in Greece must be about 8.73/million/year and the prevalence 83.34/million.

We thank the Greek neurologists for informing their patients of our diagnostic unit and for providing occasional clinical data. We also thank all the patients for completing the questionnaire. This work was supported by the Hellenic Pasteur Institute.

1 Drachman D. Myasthenia gravis. In: Rose N, Mackay I, eds. *The autoimmune diseases.* 3rd ed. San Diego: Academic Press, 1998:637–62.
2 Tzartos SJ, Barkas T, Cung MT, *et al.* Anatomy of the antigenic structure of a large membrane autoantigen, the muscle-type nicotinic acetylcholine receptor. *Immunol Rev* 1998;**163**:89–120.
3 Storm-Mathisen A. Epidemiological and prognostical aspects of myasthenia gravis in Norway. *Ann N Y Acad Sci* 1966;**135**:431–5.
4 Storm-Mathisen A. Epidemiological and prognostical aspects of myasthenia gravis in Norway. *Acta Neurol Scand* 1976;**54**:120.
5 Garland H, Clark ANG. Myasthenia gravis: a personal study of 60 cases. *BMJ* 1956;i:1259–62.
6 Giagheddu M, Puggioni G, Sanna G, *et al.* Epidemiological study of myasthenia gravis in Sardinia, Italy (1958–86). *Acta Neurol Scand* 1989;**79**:326–33.
7 Oosterhuis HJ. The natural course of myasthenia gravis: a long term follow up study. *J Neurol Neurosurg Psychiatry* 1989;**52**:1121–7.
8 Pirskanen R. Genetic aspects in myasthenia gravis: a family study of 264 Finnish patients. *Acta Neurol Scand* 1977;**56**:365–88.
9 Storm-Mathisen A. Epidemiology of myasthenia gravis in Norway. *Acta Neurol Scand* 1984;**70**:274–84.
10 Phillips LH, Torner JC, Anderson MS, *et al.* The epidemiology of myasthenia gravis in central and western Virginia. *Neurology* 1992;**42**:1888–93.
11 Micaglio G, Sartori V, Brazzo F, *et al.* Epidemiology of myasthenia gravis (MG) in northeast of Italy [abstract]. *Neurology* 1991;**41**(suppl 1):243.
12 Somnier FE, Keiding N, Paulson OB. Epidemiology of myasthenia gravis in Denmark: a longitudinal and comprehensive population survey. *Arch Neurol* 1991;**48**:733–9.
13 Somnier FE. Myasthenia gravis. *Dan Med Bull* 1996;**43**:1–10.
14 Yu YL, Hawkins BR, Ip MS, *et al.* Myasthenia gravis in Hong Kong Chinese. 1. Epidemiology and adult disease. *Acta Neurol Scand* 1992;**86**:113–19.
15 Christensen PB, Jensen TS, Tsiropoulos I, *et al.* Incidence and prevalence of myasthenia gravis in western Denmark: 1975–1989. *Neurology* 1993;**43**:1779–83.
16 Lavrnic D, Jarebinski M, Rakocevic-Stojanovic V, *et al.* Epidemiological and clinical characteristics of myasthenia gravis in Belgrade, Yugoslavia (1983–92). *Acta Neurol Scand* 1999;**100**:168–74.
17 Kyriallis K, Hristova A, Middleton L. What is the real epidemiology of myasthenia gravis? *Neurology* 1995;(suppl 4):A351.
18 Tola MR, Casetta I, Granieri E, *et al.* Incidence of myasthenia gravis in the Emilia-Romagna region: a prospective multicenter study. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. *Neurology* 1998;**51**:255–8.
19 Robertson NP, Deans J, Compston DAS. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. *J Neurol Neurosurg Psychiatry* 1998;**65**:492–6.
20 Phillips LH, Torner JC. Epidemiologic evidence for a changing natural history of myasthenia gravis. *Neurology* 1996;**47**:1233–8.
21 Statistical yearbook of Greece: year 1997. Athens: National Statistical Service of Greece, 1997.
22 Lindstrom J, Einarson B, Tzartos SJ. Production and assay of antibodies to acetylcholine receptor. *Methods Enzymol* 1981;**74**:432–60.
23 Tsakanikas C, Karandreas N, Lygidakis C. Remarks on the sex, the age and the form of myasthenia of Greek patients. *Materia Medica Greca* 1984;**12**:65–70.
24 Bramis J, Pikoulis E, Leppaniemi A, *et al.* Benefits of early thymectomy in patients with myasthenia gravis. *Eur J Surg* 1997;**163**:897–902.
25 Poulas K, Tsibri E, Papanastasiou D, *et al.* Equal male and female incidence of myasthenia gravis. *Neurology* 2000;**54**:1202–3.
26 Hoch W, McConville J, Helms S, *et al.* Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* 2001;7:365–8.