PAPER

Causes of death among patients with myasthenia gravis in Norway between 1951 and 2001

J F Owe, A K Daltveit, N E Gilhus

J Neurol Neurosurg Psychiatry 2006;**77**:203–207. doi: 10.1136/jnnp.2005.072355

See end of article for authors' affiliations

Correspondence to: Dr J F Owe, Department of Clinical Medicine, Section for Neurology, University of Bergen, 5021 Bergen, Norway; jone.furlund.owe@helse-bergen.no

Received 18 May 2005
Revised 4 July 2005
Accepted for publication 10 July 2005

Objective: This study investigated the causes of death among patients with myasthenia gravis (MG), with emphasis on respiratory tract and cardiac disease.
Methods: The Norwegian Cause of Death Register contains information on all deaths among Norwegian citizens. In total, 249 deceased patients with MG were identified (1951–2001). These were compared with 1245 controls deceased in the same period and matched for sex and year of birth.
Results: The death certificates of patients with MG had a significantly higher occurrence of respiratory tract disease as cause of death than controls (28.1% *v* 20.9%, p = 0.012). The difference was most pronounced for male patients, for patients dying between 30 and 69 years of age, and for deaths occurring before 1996. For cardiac disease there was a significantly lower occurrence among patients with MG than among controls at 50–69 years of age, for both men (19.4% *v* 52.0%, p = 0.001) and women (14.6% *v* 29.6%, p = 0.036). Age and year of death were important determinants for the causes of death, but could not account for the differences between the patients with MG and controls.
Conclusions: This study shows that patients with MG dying between 1951 and 1995 had a higher occurrence of respiratory tract disease listed as cause of death than had a matched control group. The lack of difference after 1995 probably reflects improved treatment of MG and its complications. The reduced occurrence of cardiac disease among patients with MG is probably explained by competing factors (respiratory tract disease) causing death.

Myasthenia gravis (MG) is an autoimmune disease causing increased fatigue and weakness in voluntary muscles. About 85% of patients with MG have circulating antibodies against postsynaptic nicotinic acetylcholine receptors (AChR) in the neuromuscular junction.[1] Six MG subgroups have been identified:[2] (*a*) ocular MG has purely ocular symptoms; (*b*) early onset MG starts before the age of 40–50 years, has a 2:1 female predominance, and is associated with thymus hyperplasia; (*c*) late onset MG, starting after 40–50 years of age, is associated with thymus atrophy and is equally common among men and women; (*d*) thymoma MG is a paraneoplastic disease and accounts for 10–15% of patients with MG; seronegative MG includes (*e*) the anti-muscle specific receptor tyrosine kinase (MuSK) and (*f*) non-AChR-non-MuSK antibody forms of MG and accounts for 10–20% of patients with MG. Patients in the anti-MuSK group have antibodies to MuSK in the cell membrane[3]; non-MuSK seronegative MG is probably caused by as yet unidentified muscle antibodies.[4]

The prevalence of MG has been reported to be up to 17.5 per 100 000, with a rise in prevalence over time, caused by prolonged patient survival not accompanied by a rise in incidence.[5] The reported prevalence of MG in Norway in the time period examined was 9.0–9.6 per 100 000.[6 7] The disease has two prevalence peaks, one between 20 and 40 years, dominated by women, and the other between 70 and 80 years, without any gender predominance.

Life expectancy among patients with non-thymoma MG has previously been shown to be slightly reduced compared with the general population.[8] Although routinely performed, the beneficial effect of thymectomy for non-thymoma MG has not been proven by randomised and controlled studies.[9] Patients with MG caused by thymoma have a less favourable survival than patients with non-thymoma MG, due to malignancy from the thymic changes with higher incidence of a second malignancy, complications of surgery, and associated autoimmune diseases.[10–12] Up to 40% of patients with MG experience respiratory problems during their disease period.[13] Treatment with ACh-esterase inhibitors, immunosuppressants, plasma exchange, and intravenous IgG has dramatically changed the life of patients with MG, with a decrease in mortality and an increase in prevalence. Of similar importance is modern intensive medical care. Nevertheless, respiratory function remains a major challenge in the management of MG.

The Norwegian Cause of Death Register has registered all deaths for the Norwegian population since 1951. With data collected over a period of more than 50 years, the register makes it possible to examine causes of death and changes of these causes within a complete population.

In this study, we examined all deaths between 1951 and 2001 of patients with a diagnosis of MG on their death certificate. Our aim was to investigate whether patients with MG had different causes of death than comparable controls, whether or not these causes could be linked to the patients' MG, and whether or not the causes of death for patients with MG have changed over the years because of improved treatment.

METHODS

The Norwegian Cause of Death Register registers all deaths among people recorded as having their permanent residence in Norway at time of death, whether they died in Norway or abroad. It contains electronically stored reports of all deaths since 1951. By the Norwegian Health Personnel Act, doctors are obliged to report deaths on a standardised form, sending the information to the Cause of Death Register.[14 15] To ensure accurate and complete information, the information gained

Abbreviations: AChR, acetylcholine receptor; ICD, International Classification of Diseases; MG, myasthenia gravis; MuSK, muscle specific receptor tyrosine kinase

through death certificates is cross linked to deaths registered in the Central Population Register. In instances where the death certificate contains inadequate information, this information will be retrieved by the Cause of Death Register, and the municipality doctor in the area where the death occurred will be prompted to clarify the medical history and correct diagnoses. A medical consultant is engaged to ensure that the information on the certificates is adequate.

The diagnoses on the death certificates were given in accordance with the latest available version of the International Classification of Diseases (ICD) at the time of death. During the period 1951–2001, different ICD versions were used: ICD 7 (1951–1968), ICD 8 (1969–1985), ICD 9 (1986–1995), and ICD 10 (1996–2001). Major revisions of the classification were performed in 1969 and 1996, and a minor revision in 1986.

The search was conducted among the 1 992 342 deaths registered during 1951–2001, using the ICD specific diagnosis for MG through the consecutive versions of the classification: 744.0 (ICD-7), 733.0 (ICD-8), 358.0 (ICD-9), and G70.0 (ICD-10). In total, 249 patients (149 female and 100 male patients) were identified with a diagnosis of MG on their death certificate. For each patient, five deceased controls of the same sex and with the same year of birth were selected, regardless of year of death, giving a total of 1245 controls (745 female and 500 male patients). If a control also had MG (thus also being found among the patients) they would have been excluded as a control and a new control drawn, but in fact, there were no such cases. Of the 249 patients, 13 (5.2%) were reported with a thymoma. These patients were included in all analyses.

The register provided information about sex, years of birth and death, one underlying cause of death, and contributing cause(s) of death (0–2 up to 1968, 0–4 between 1969 and 1995, and 0–6 after 1996). In the raw data, causes of death were presented as individual diagnoses according to the ICD classification. The diagnoses of interest were then grouped together into several major categories for further examination. Each individual patient and control could be included in more than one category, but could only count as one in each category; for example, a patient dying from pneumonia as an underlying cause of death, and having heart infarction and asthma as contributing causes, would count as one in the respiratory tract disease category and as one in the cardiac disease category. Patients and controls were also grouped into four categories based on year of death; 1951–1968, 1969–1985, 1986–1995, and 1996–2001, corresponding to the periods where different ICD versions were used. Patients and controls were also grouped according to age at death: 0–29, 30–49, 50–69 and ⩾70 years.

Differences in causes of death between patients and controls were examined using the χ^2 test. Two sided p values <0.05 were considered statistically significant. For comparison of the number of diagnoses, the Mann-Whitney U test was used. Unconditional logistic regression analyses were performed to adjust for age at death where data were stratified for year of death and to adjust for year of death for data stratified for age at death. In this analysis, age at death and year of death were included as categorical variables. The statistical analyses were performed with SPSS software (version 12.0.1; SPSS Inc., Chicago, IL, USA).

Table 1 Frequencies of underlying and contributing causes of death reported on death certificate

Disease category	Patients (n = 249)	Controls (n = 1245)	p
Respiratory tract	70 (28.1)	260 (20.9)	0.012*
Cardiac	72 (28.9)	540 (43.4)	<0.001*
Malignant	22 (11.2)	339 (27.2)	<0.001*
Cerebrovascular	25 (10.0)	227 (18.2)	0.002*
Gastrointestinal	12 (4.8)	67 (5.4)	0.72
Neurological, not MG	11 (4.4)	50 (4.0)	0.78
Diabetes mellitus	13 (5.2)	86 (6.9)	0.33
Urinary tract	4 (1.6)	44 (3.5)	0.12

Number (%) is given for each group (patients or controls). The two groups were compared with the Pearson χ^2 test. *Statistical significance.

RESULTS

Our data show a higher occurrence of respiratory tract disease as an underlying or contributing cause of death among patients with MG than among controls; 28.1% for patients with MG compared with 20.9% for controls (p = 0.012; table 1). Men in the age group 30–69 years and women in the age group 50–69 years were responsible for this difference (table 2). Furthermore, the findings for the men were due to increased mortality from respiratory tract disease prior to 1996 (table 3), whereas there was no difference in the period 1996–2001. For women, the occurrence of respiratory tract disease as a cause of death did not differ significantly when stratifying for year of death (table 3). However, there was a tendency towards more women with MG to have died from respiratory tract disease compared with controls before 1985. The majority of respiratory tract disease diagnoses consisted of infections such as pneumonia and influenza (table 4).

For cardiac disease there was a significantly lower occurrence among patients with MG than controls in the age group 50–69 years, for both men (19.4% *v* 52.0%, p = 0.001) and women (14.6% *v* 29.6%, p = 0.036) (table 2). The overall occurrence of cardiac disease was significantly lower among patients with MG than controls (table 1). Similarly, overall data for cerebrovascular disease showed significantly lower occurrence in patients than controls (10.0% *v* 18.2%, p = 0.002). The difference between patients and controls was most pronounced for women with MG aged >70 years (table 2).

Both men and women with MG showed a significantly lower occurrence of malignancy as cause of death compared with controls (11.1% in patients *v* 22.2% in controls for men p = 0.011; 7.4% *v* 30.6% for women, p <0.001). Logistic regression analyses adjusting for year of death (table 2) and age at death (table 3) respectively, did not change these results. Both male and female controls had a higher median age and a wider age range at death than the patients (table 5).

Both patients and controls had an increase in number of diagnoses from the earliest (1951–1968) to the latest (1996–2001) recording period (change in mean number of diagnoses for patients was 1.36 to 3.37, p<0.001; for controls 1.23 to 2.46, p<0.001). For deaths after 1968, patients with MG had a significantly higher mean number of diagnoses than the controls (table 6).

DISCUSSION

Our data show that patients with MG are more likely than controls to die of respiratory tract disease, most likely because of the direct effect of MG on respiratory muscle function. Dysphagia and respiratory failure are factors known to be associated with MG, and several reports have highlighted the importance of dysphagia and aspiration precipitating a myasthenic crisis.[16 17] Respiratory failure can even be a first presentation of MG.[18] Maximum voluntary ventilation has been shown to be only 65–75% of expected value in patients with MG with mild or moderate disease (Osserman grade IIa and IIb),[19] illustrating that many patients with MG have a mild respiratory impairment without respiratory symptoms or clinically diagnosed respiratory insufficiency. Dysphagia

Table 2 Major groups of diseases stratified for sex and age at death, comparison between patients with MG and matched controls

Age at death	Male patients (n = 100)	Male controls (n = 500)	p	Female patients (n = 149)	Female controls (n = 745)	p
Respiratory tract disease						
0–29 years	0/2	0/10		1/4 (25.0)	0/14	0.05
30–49 years	3/6 (50.0)	1/25 (4.0)	0.003*	4/22 (18.2)	4/50 (8.0)	0.21
50–69 years	12/36 (33.3)	14/127 (11.0)	0.001*	14/48 (29.2)	24/179 (13.4)	0.009*
⩾70 years	20/56 (35.7)	89/338 (26.3)	0.15	16/75 (21.3)	128/502 (25.5)	0.44
Total	35/100 (35.0)	104/500 (20.8)	0.002*	35/149 (23.5)	156/745 (20.9)	0.49
Cardiac disease						
0–29 years	0/2	0/10		0/4	1/14 (7.1)	0.58
30–49 years	0/6	8/25 (32.0)	0.11	2/22 (9.1)	6/50 (12.0)	0.72
50–69 years	7/36 (19.4)	66/127 (52.0)	0.001*	7/48 (14.6)	53/179 (29.6)	0.036*
⩾70 years	22/56 (39.3)	179/338 (53.0)	0.06	34/75 (45.3)	227/502 (45.2)	0.99
Total	29/100 (29.0)	253/500 (50.6)	<0.001*	43/149 (28.9)	287/745 (38.5)	0.026*
Malignant disease						
0–29 years	0/2	0/10		0/4	3/14 (21.4)	0.31
30–49 years	0/6	3/25 (12.0)	0.37	1/22 (4.5)	23/50 (46.0)	0.001*
50–69 years	4/36 (11.1)	36/127 (28.3)	0.034*	5/48 (10.4)	93/179 (52.0)	<0.001*
⩾70 years	7/56 (12.5)	72/338 (21.3)	0.13	5/75 (6.7)	109/502 (21.7)	0.002*
Total	11/100 (11.0)	111/500 (22.2)	0.011*	11/149 (7.4)	228/745 (30.6)	<0.001*
Cerebrovascular disease						
0–29 years	0/2	0/10		0/4	1/14 (7.1)	0.58
30–49 years	1/6 (16.7)	2/25 (8.0)	0.52	0/22	5/50 (10.0)	0.12
50–69 years	1/36 (2.8)	15/127 (11.8)	0.11	3/48 (6.3)	17/179 (9.5)	0.48
⩾70 years	10/56 (17.9)	66/338 (19.5)	0.77	10/75 (13.3)	121/502 (24.1)	0.038*
Total	12/100(12.0)	83/500 (16.6)	0.25	13/149 (8.7)	144/745 (19.3)	0.002*

The fraction, as well as the percentage (in brackets), shows the occurrence of the disease compared with all deceased individuals of the same sex who died in the same time period. * Pearson x2 tests were used. Statistical significance.

and weakness of the respiratory muscles increase susceptibility to infections, and an infection can itself increase the pre-existing dysphagia and respiratory weakness. This combination of muscle weakness and infection may cause serious illness and even death in patients with MG. Timely immunotherapy and respiratory support is needed in case of development of myasthenic crisis, and advances in intensive care have reduced mortality from 75% to <5% over the last four decades.[20–23]

Our study shows that these effects of MG have a direct impact on the reported causes of death for patients dying before the age of 70 years. At ages over 70 years, the difference in susceptibility to serious respiratory tract disease between patients with MG and controls disappears, owing to the high rate of such disease in dying individuals irrespective of any coexisting diseases. However, there is evidence that MG is underdiagnosed in elderly people.[24 25] A correct diagnosis of MG in this group could change the results, although not necessarily increasing the occurrence of respiratory tract disease among patients with MG.

The study shows that improved treatment has reduced the deaths due to respiratory tract disease for patients with MG.

Table 3 Major groups of diseases stratified for sex and time of death, comparison between patients with MG and matched controls

Age at death	Male patients (n = 100)	Male controls (n = 500)	p	Female patients (n = 149)	Female controls (n = 745)	p
Respiratory tract disease						
1951–1968	4/19 (21.1)	1/36 (2.8)	0.025*	5/36 (13.9)	5/74 (6.8)	0.22
1969–1985	16/39 (41.0)	39/182 (21.4)	0.010*	13/44 (29.5)	40/193 (20.7)	0.21
1986–1995	10/23 (43.5)	54/258 (20.9)	0.013*	9/42 (21.4)	84/377 (22.3)	0.90
1996–2001	5/19 (26.3)	10/24 (41.7)	0.29	8/27 (29.6)	27/101 (26.7)	0.76
Total	35/100 (35.0)	104/500 (20.8)	0.002*	35/149 (23.5)	156/745 (20.9)	0.49
Cardiac disease						
1951–1968	1/19 (5.3)	13/36 (36.1)	0.013*	2/36 (5.6)	13/74 (17.6)	0.09
1969–1985	8/39 (20.5)	107/182 (58.8)	<0.001*	14/44 (31.8)	81/193 (42.0)	0.22
1986–1995	13/23 (56.5)	120/258 (46.5)	0.36	15/42 (35.7)	149/377 (39.5)	0.63
1996–2001	7/19 (36.8)	13/24 (54.2)	0.26	12/27 (44.4)	44/101 (43.6)	0.94
Total	29/100 (29.0)	253/500 (50.6)	<0.001*	43/149 (28.9)	287/745 (38.5)	0.026*
Malignant disease						
1951–1968	0/19	7/36 (19.4)	0.040*	0/36	32/74 (43.2)	<0.001*
1969–1985	2/39 (5.1)	34/182 (18.7)	0.038*	5/44 (11.4)	62/193 (32.1)	0.006*
1986–1995	5/23 (21.7)	62/258 (46.5)	0.81	0/42	105/377 (27.9)	<0.001*
1996–2001	4/19 (21.1)	8/24 (33.3)	0.37	6/27 (44.4)	29/101 (28.7)	0.50
Total	11/100 (11.0)	111/500 (22.2)	0.011*	11/149 (7.4)	228/745 (30.6)	<0.001*
Cerebrovascular disease						
1951–1968	1/19 (5.3)	2/36 (5.6)	0.96	0/36	6/74 (8.1)	0.08
1969–1985	5/39 (12.8)	32/182 (17.6)	0.47	5/44 (11.4)	36/193 (18.7)	0.25
1986–1995	2/23 (8.7)	47/258 (18.2)	0.25	5/42 (11.9)	82/377 (21.8)	0.14
1996–2001	4/19 (21.1)	2/24 (8.3)	0.23	3/27 (11.1)	20/101 (19.8)	0.30
Total	12/100 (12.0)	83/500 (16.6)	0.25	13/149 (8.7)	144/745 (19.3)	0.002*

The fraction, as well as the percentage (in brackets), shows the occurrence of the disease compared with all deceased individuals of the same sex who died in the same time period. Pearson χ^2 tests were used. *Statistical significance.

Table 4 Subgroups of respiratory tract diseases

Disease	Patients (n = 249)	Controls (n = 1245)	p
Pneumonia	54 (21.7%)	214 (17.2%)	0.09
Influenza	3 (1.2%)	6 (0.5%)	0.18
COPD	11 (4.4%)	52 (4.2%)	0.86
Other	9 (3.6%)	15 (1.2%)	0.006*

*Statistical significance. COPD, chronic obstructive pulmonary disease. Individuals having more than one of the respiratory tract diseases in this table only counted for one in the other tables. Patients and controls were compared with the Pearson χ^2 test.

Deaths among male patients before 1996 were more commonly related to respiratory tract disease than after 1996, reflecting the development in MG therapy. In the early 1950s, pyridostigmine became the drug of choice for symptomatic MG treatment. Two decades later the use of oral prednisone for MG showed beneficial effects. This was later widely combined with the chemotherapeutic drug azathioprine, followed by many alternative immunosuppressive drugs. Plasma exchange has been used for over 30 years, and, from the mid-1980s, the equally effective intravenous immunoglobulin. The role of thymectomy for patients with non-thymoma MG has not been proven by randomised controlled trials, but is regarded as the main reason for the improved prognosis of MG in these patients. Early treatment in intensive care units is necessary in MG exacerbations and threatening crises.[26]

Cardiac involvement in MG has been suggested. Unspecific ECG changes in MG, such as terminal notching of the QRS complex and prolonged QT intervals can occur,[27 28] as well as myocarditis and disorders of rhythm.[29 30] One study has shown impaired diastolic filling in patients with MG, which is normalised by pyridostigmine, indicating a subclinical functional disturbance due to MG.[31] Cardiac involvement in MG has been linked to the presence of a thymoma. Thymomas can produce both neoplastic invasion and infiltration of the heart and its surrounding structures and paraneoplastic myocarditis with disorders of rhythm.[32–34] However, the unselected patients in our present study, representing all deaths from MG in Norway, were less frequently reported to have cardiac disease as an underlying or contributing cause of death than were controls. We find it unlikely that patients with MG should be protected from cardiac disease, and predict that the higher frequency in the controls is the result of competition between causes of death; individuals not having respiratory tract disease as a cause of death must have another cause of death, and in any western population cardiac disease is most likely. If MG related cardiac disease exists, it is probably mild and/or rare. Similarly, the low occurrence of death due to malignant disease in this study is most probably a result of competing risk, an even more likely scenario because paraneoplastic MG due to a thymoma increases the death risk through several mechanisms, especially when RyR antibodies are present.[11 12 35]

Table 5 Age at death (years) for patients with MG and controls

Group	Median age	Range
Male patients (n = 100)	71	21–93
Male controls (n = 500)	75	0–101
Female patients (n = 149)	70	22–94
Female controls (n = 745)	76	0–105

Table 6 Number of diagnoses, underlying or contributing, according to period of death

Time of death	Mean no. of diagnoses: Patients (n = 249)	Mean no. of diagnoses: Controls (n = 1245)	p
1951–1968	1.36	1.23	0.09
1969–1985	2.53	1.90	<0.001*
1986–1995	2.63	1.98	<0.001*
1996–2001	3.37	2.46	<0.001*

Mann-Whitney tests were performed for each time period, comparing the number of diagnoses in patients and controls. *Statistical significance.

The increase in number of diagnoses on the death certificates shows an increased appreciation of the importance of comorbidity. Patients with MG dying later than 1969 had a significantly higher number of diagnoses, underlying and contributing, than did the controls. After 1996, patients with MG and controls had the same number of non-MG diagnoses, indicating that the MG is added to the causes of death found in the general population, and perhaps is less relevant as contributing to death than in previous time periods.

All deaths in Norway over a 50 year time period were examined. Given the specificity of the MG diagnosis in the ICD system, false positive cases are not likely to be present in our material. With a MG prevalence of 9.6 per 100 000, the identification of 249 dead patients in a total population of 1 992 342 (12.5 per 100 000 deaths), indicates a reliable inclusion of patients. If some patients with MG were missed because of incomplete diagnosis on the death certificates, this would not influence the comparison between the patients and the control group as MG is such a rare disease. The design of this study did not allow for identification of individual patients or controls, and it was therefore impossible to validate their diagnoses at time of death. Death certificates represent a standardised document of high medical and legal importance in Norway. Even so, they are sometimes completed in settings where it is inevitable that a complete knowledge of a patient's history or the full appreciation of all underlying medical conditions is missing.

The patients had a lower median age than the controls, and the age range also differed between the groups. This reflects the typical onset of MG in adult life, and therefore necessarily with a narrower spread of age at death. Such an age at death limitation does not apply to the controls. Our data do not provide information about life expectancy of patients with MG as we studied only deceased patients.

This study shows that patients with MG have an increased risk for severe respiratory tract disease. Until recently, such disease was a major cause of death for patients with MG, but new medical treatment seems to have reduced respiratory disease mortality in patients with MG to a near to normal level. Cardiac involvement in MG is not a significant death risk.

ACKNOWLEDGEMENTS

This work was supported by EC grant QL61-CT-2001-01918.

Authors' affiliations

J F Owe, N E Gilhus, Department of Clinical Medicine, Section for Neurology, University of Bergen, Norway, and Department of Neurology, Haukeland University Hospital, Bergen, Norway
A K Daltveit, Section for Epidemiology and Medical Statistics, Department of Public Health and Primary Health Care, University of

Bergen, Norway, and Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen, Norway

Competing interests: none

REFERENCES

1 **Vincent A**, Palace J, Hilton-Jones D. Myasthenia gravis. *Lancet* 2001;**357**:2122–8.
2 **Romi F**, Skeie GO, Aarli JA, *et al*. Muscle autoantibodies in subgroups of myasthenia gravis patients. *J Neurol* 2000;**247**:369–75.
3 **McConville J**, Farrugia ME, Beeson D, *et al*. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. *Ann Neurol* 2004;**55**:580–4.
4 **Lindstrom J**. Is ''seronegative'' MG explained by autoantibodies to MuSK? *Neurology* 2004;**62**:1920–1.
5 **Phillips LH**, Torner JC. Epidemiologic evidence for a changing natural history of myasthenia gravis. *Neurology* 1996;**47**:1233–8.
6 **Storm-Mathisen A**. Epidemiology of myasthenia gravis in Norway. *Acta Neurol Scand* 1984;**70**:274–84.
7 **Thorlacius S**, Aarli JA, Riise T, *et al*. Associated disorders in myasthenia gravis — autoimmune diseases and their relation to thymectomy. *Acta Neurol Scand* 1989;**80**:290–5.
8 **Christensen PB**, Jensen TS, Tsiropoulos I, *et al*. Mortality and survival in myasthenia gravis: a Danish population based study. *J Neurol Neurosurg Psychiatry* 1998;**64**:78–83.
9 **Gronseth GS**, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;**55**:7–15.
10 **Evoli A**, Minisci C, Di Schino C, *et al*. Thymoma in patients with MG: characteristics and long-term outcome. *Neurology* 2002;**59**:1844–50.
11 **Evoli A**, Punzi C, Marsili F, *et al*. Extrathymic malignancies in patients with thymoma. *Ann Oncol* 2004;**15**:692–3.
12 **Pan CC**, Chen PC, Wang LS, *et al*. Thymoma is associated with an increased risk of second malignancy. *Cancer* 2001;**92**:2406–11.
13 **Somnier FE**, Keiding N, Paulson OB. Epidemiology of myasthenia-gravis in Denmark - a longitudinal and comprehensive population Survey. *Arch Neurol* 1991;**48**:733–9.
14 **Gjertsen F**. (The cause of death registry and research.) *Tidsskr Nor Laegeforen* 2000;**120**:723–5.
15 **Gjertsen F**. (Cause of death registry—an important data source for medical research.) *Tidsskr Nor Laegeforen*, 2002;**122**:2551–4.
16 **Cohen MS**, Younger D. Aspects of the natural history of myasthenia gravis: crisis and death. *Ann NY Acad Sci* 1981;**377**:670–7.
17 **Ertekin C**, Yuceyar N, Aydogdu I. Clinical and electrophysiological evaluation of dysphagia in myasthenia gravis. *J Neurol Neurosurg Psychiatry* 1998;**65**:848–56.
18 **Qureshi AI**, Choundry MA, Mohammad Y, *et al*. Respiratory failure as a first presentation of myasthenia gravis. *Med Sci Monit* 2004;**10**:CR684–9.
19 **Heliopoulos I**, Patlakas G, Vadikolias K, *et al*. Maximal voluntary ventilation in myasthenia gravis. *Muscle Nerve* 2003;**27**:715–19.
20 **Ashworth B**, Hunter AR. Respiratory failure in myasthenia gravis. *Proc R Soc Med* 1971;**64**:489–90.
21 **Gracey DR**, Divertie MB, Howard FM Jr. Mechanical ventilation for respiratory failure in myasthenia gravis. Two-year experience with 22 patients. *Mayo Clin Proc* 1983;**58**:597–602.
22 **Tether JE**. Management of myastheni and cholinergic crises. *Am J Med* 1955;**19**:740–2.
23 **Thomas CE**, Mayer SA, Gungor Y, *et al*. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. *Neurology* 1997;**48**:1253–60.
24 **Aragones JM**, Bolibar I, Bonfill X, *et al*. Myasthenia gravis: a higher than expected incidence in the elderly. *Neurology* 2003;**60**:1024–6.
25 **Vincent A**, Clover L, Buckley C, *et al*. Evidence of underdiagnosis of myasthenia gravis in older people. *J Neurol Neurosurg Psychiatry* 2003;**74**:1105–8.
26 **O'Riordan JI**, Miller DH, Mottershead JP, *et al*. The management and outcome of patients with myasthenia gravis treated acutely in a neurological intensive care unit. *Eur J Neurol* 1998;**5**:137–42.
27 **Luomanmaki K**, Hokkanen E, Heikkila J. Electrocardiogram in myasthenia gravis. Analysis of a series of 97 patients. *Ann Clin Res* 1969;**1**:236–45.
28 **Buyukozturk K**, Ozdemir C, Kohen D. Electrocardiographic findings in 24 patients with myasthenia gravis. *Acta Cardiol* 1976;**31**:301–5.
29 **Hofstad H**, Ohm OJ, Mork SJ, *et al*. Heart disease in myasthenia gravis. *Acta Neurol Scand* 1984;**70**:176–84.
30 **Tanahashi N**, Sato H, Nogawa S, *et al*. A case report of giant cell myocarditis and myositis observed during the clinical course of invasive thymoma associated with myasthenia gravis. *Keio J Med* 2004;**53**:30–42.
31 **Johannessen KA**, Mygland A, Gilhus NE, *et al*. Left ventricular function in myasthenia gravis. *Am J Cardiol* 1992;**69**:129–32.
32 **Bolognesi R**, Vasini P, Tsialtas D, *et al*. Acute heart failure due to neoplastic invasion of ventricular myocardium by relapsing thymoma. *Eur J Heart Fail* 2001;**3**:113–16.
33 **Cooper LT Jr**. Giant cell myocarditis: diagnosis and treatment. *Herz* 2000;**25**:291–8.
34 **Pentz WH**. Advanced heart block as a manifestation of a paraneoplastic syndrome from malignant thymoma. *Chest* 1999;**116**:1135–6.
35 **Romi F**, Gilhus NE, Varhaug JE, *et al*. Disease severity and outcome in thymoma myasthenia gravis: a long-term observation study. *Eur J Neurol* 2003;**10**:701–6.