A population based epidemiological study on myasthenia gravis in Estonia

M Ööpik, A-E Kaasik, J Jakobsen

Objective: To describe the occurrence of myasthenia gravis in the Baltic area.

Methods: Data were obtained from hospital files recorded during the period 1942 to 1996 from neurologists and the patient organisation. Survival data were checked with the Estonian Citizenship and Migration Board. Prevalence was determined on 1 January 1997. A questionnaire on the course of myasthenia gravis was sent to all the prevalent patients.

Results: The size of the population surveyed was 1,462,130. The average annual incidence from 1970 to 1996 was 4.0 per million (women, 5.2; men, 2.6). The point prevalence was 99 per million (women, 133; men 59). The incidence in the younger age group (<50 years) was 3.4 per million (women, 4.8; men, 1.9) and in the older age group (≥50 years), 5.5 (women, 5.9; men, 4.9). The prevalence ratio was twofold higher in the older age group (p < 0.0001) for men (p = 0.034) as well as for women (p < 0.001).

Conclusions: Prevalence and incidence values of myasthenia gravis from Estonia are similar to those reported in most studies from Europe and north America. However, there seems to be a higher frequency in the elderly (≥50 years) in Estonia.

There are only a few studies on the epidemiology of myasthenia gravis based on complete populations. There is also a paucity of information on the occurrence of myasthenia gravis in eastern Europe, though recently, regional studies were published from part of Croatia and from Belgrade, Yugoslavia. Estonia was a part of the former Soviet Union during the period 1940 to 1991. A thorough search of published reports on the occurrence of myasthenia gravis in the former Soviet Union revealed only one study, from the Krasnodar territory in south Russia on the Black Sea. There have been no studies on myasthenia gravis in the Baltic countries. We now report epidemiological and clinical data of the first east European, population based study on myasthenia gravis, carried out in Estonia in the Baltic region.

METHODS

Study area

Estonia (45,227 km²) is situated in the northeastern part of Europe, on the southern coast of the Gulf of Finland. On 1 January 1997 the population of Estonia was 1,462,130 inhabitants (781,416 women and 680,714 men).

Estonia has a relatively long tradition of qualified and available neurological services. There were 153 neurologists (1.0 per 10,000 inhabitants) at the end of 1996. All patients with suspected neurological diseases are seen by a neurologist, either following self-referral or after referral by general practitioners or other specialists. Patients with suspected neuromuscular disorders are referred for a final diagnosis to the department of neurology, Tartu University Hospital, serving as a diagnostic centre for south Estonia, or to the department of neurology, Hospital of Neurology and Psychiatry, Tallinn, for north Estonia. Tartu University Hospital is the only university hospital in Estonia and serves as the national competence centre for complicated cases.

Case finding methods

All patients included had an established diagnosis of myasthenia gravis. The diagnostic criteria were: muscle weakness and rapid fatigue aggravated by exercise and relieved by rest in one or more muscle groups; and a positive response to anticholinergic drugs.

The data on discharged patients with myasthenia gravis were obtained from the files recorded during the period 1 January 1942 to 31 December 1996 at the department of neurology, Tartu University Hospital and the department of neurology, Hospital of Neurology and Psychiatry, Tallinn. The other departments of neurology, practising neurologists, and the Estonian Association for Patients with Muscular Disorders were contacted to find other patients with the disease who had not been admitted to the two centres.

Since 1942 complete data on admission and discharge of patients have been preserved in the archives of the department of neurology, Tartu University Hospital, including the case histories since 1945. The data from the department of neurology, Hospital of Neurology and Psychiatry, Tallinn have been available since its establishment in 1955. A computer database with a diagnostic index was established at the Tartu University Hospital in 1978. The International Classification of Diseases (ICD), eighth revision, with the code for myasthenia gravis (733.0) was used to retrieve records of the Tartu University Hospital from the period 1978 to 1985, and the ICD, ninth revision, with the code for myasthenia gravis (358.0), to retrieve the records from 1986 to 1996. Earlier records and the records from the Department of Neurology, Hospital of Neurology and Psychiatry, Tallinn, were retrieved manually.

The medical records were examined according to the diagnostic criteria by one of us (MÖ). In case of doubt the diagnosis was discussed with the other authors. Twenty-six patients with a diagnosis of myasthenic syndrome, myasthenic-myopathic syndrome, and pseudomyasthenia were excluded.

We selected 1 January 1997 as a prevalence day. Survival data were checked by the Estonian Citizenship and Migration Board. Complete population data are available in the Statistical Office of Estonia since 1970. Thus incidence rates for the period 1970 to 1996 were calculated, including cases diagnosed in Estonia or abroad in residents of Estonia.
A questionnaire about the onset and course of the disease, comorbidity, and treatment was sent to all the prevalent patients a maximum of three times.

**Statistical analysis**

All incidence rates and prevalence ratios were calculated per one million inhabitants. The 95% confidence intervals (95% CI) were calculated from the Poisson distribution. Incidence rates and prevalence ratios were age and sex adjusted by the direct method to the European and world standard populations and prevalence ratios were age and sex adjusted by the direct method to the European and world standard populations for cross national comparisons. For group comparison, the Mann-Whitney U test, the $\chi^2$ test, and Fischer's exact test were used. Probability (p) values of <0.05 were considered significant. Statistical analysis was done with the STATISTICA program.

**RESULTS**

During the period 1 January 1942 to 31 December 1996, the diagnosis of myasthenia gravis was established in 208 patients (113 women and 60 men). Figure 1 shows the case identification from the various sources of information. Two hundred and two patients were inhabitants of Estonia at the time of diagnosis. In six patients, myasthenia gravis was diagnosed before immigration to Estonia.

**Incidence**

During the period 1 January 1970 to 31 December 1996, myasthenia gravis was diagnosed in 162 patients (113 women, 49 men). The total crude incidence was 4.0 (95% CI, 3.4 to 4.7) per million per year. After adjustment by age to the European standard population, the incidence was still 4.0 (3.4 to 4.7), while adjustment to the world standard population gave a rate of 3.7 (3.2 to 4.3). The crude incidence was higher for women (5.2 (4.3 to 6.3)) than for men (2.6 (1.9 to 3.4)) (|$z$ = 4.13, $p$ < 0.001).

The age and sex specific incidence rates are shown in table 1. In most age specific groups the rates for women were higher than for men. The difference was approximately fourfold in age groups 40 to 49 ($z = 3.01, p < 0.01$) and 50 to 59 ($z = 3.01, p < 0.01$). In older age group ($\geqslant$50 years) the prevalence ratio was twofold higher ($z = 4.50, p < 0.0001$) than in the younger age group (<50 years), both for men ($z = 2.12, p = 0.034$) and for women ($z = 3.37, p < 0.001$). The prevalence ratio in south Estonia (146 (110 to 190)) was higher than in north Estonia (82 (65 to 101)) ($z = 3.42, p < 0.001$). In south Estonia the prevalence ratio was higher both for women ($z = 2.75, p < 0.01$) and men ($z = 2.06, p < 0.05$).

**Prevalence**

On 1 January 1997, there were 144 patients (104 women, 40 men) with a diagnosis of myasthenia gravis in Estonia (fig 1). The female to male ratio was 2.6 to 1. The median age for both sexes was 49.5 years (range 4.1 to 82.4)—44.0 years (range 4.1 to 76.8) for men and 50.1 years (range 7.8 to 82.4) for women.

The prevalence ratio on 1 January 1997 was 99 (95% CI 83 to 116) per million. After adjustment by age to the European standard population the ratio was 96 (81 to 113), and after adjustment to the world standard population, 82 (70 to 97). The prevalence ratio was higher for women (133 (109 to 162)) than for men (59 (42 to 80)) ($z = 4.52, p < 0.001$).

Age and sex specific prevalence ratios are shown in table 2. In all age specific groups the ratios for women were higher than for men. The difference was approximately fourfold in age groups 40 to 49 ($z = 3.01, p < 0.01$) and 50 to 59 ($z = 3.01, p < 0.01$). In older age group ($\geqslant$50 years) the prevalence ratio was twofold higher ($z = 4.50, p < 0.0001$) than in the younger age group (<50 years), both for men ($z = 2.12, p = 0.034$) and for women ($z = 3.37, p < 0.001$). The prevalence ratio in south Estonia (146 (110 to 190)) was higher than in north Estonia (82 (65 to 101)) ($z = 3.42, p < 0.001$). In south Estonia the prevalence ratio was higher both for women ($z = 2.75, p < 0.01$) and men ($z = 2.06, p < 0.05$).

**Clinical data**

One hundred and eighteen patients (82%; 30 men, 88 women) responded to the questionnaire, while 26 failed to reply to three requests. The median age for responders was 50.7 years (range 4.1 to 76.8) for men (n = 10); and 43.1 years (range 22.4 to 74.8) for the whole group (n = 26); 33.0 years (range 5.0 to 50.7 years) with a diagnosis of myasthenia gravis in Estonia (fig 1).

Figure 2 shows the annual incidence rates from 1970 to 1996. The average annual incidence increased as follows: 1970 to 1978: 1.4 (95% CI 0.8 to 2.2); 1979 to 1987: 4.8 (3.7 to 6.1); 1988 to 1996: 5.7 (4.5 to 7.1). There was a significant increase in the incidence in the period 1979 to 1987 compared with the period 1970 to 1978 ($z = 4.88, p < 0.001$). The increase was significant for women ($z = 4.28, p < 0.001$) as well as for men ($z = 2.38, p < 0.05$). Comparison of the periods 1988 to 1996 and 1979 to 1987 showed an increased incidence in men only ($z = 2.13, p < 0.05$).

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**Figure 1** Case identification. *Missing data represent the cases not registered by the Estonian Citizenship and Migration Board on 1 January 1997."
more specific clinical data about age at onset, onset symptoms, age of the patient at first visit to the doctor for specific myasthenic symptoms, and age at diagnosis were available in 108 patients (81 women, 27 men). The median age for the whole group was 49.9 years (range 7.8 to 82.4): 49.2 years (range 10.7 to 76.8) for men and 50.2 years (range 7.8 to 82.4) for women. There was no significant difference in age (z = 1.15, p = 0.251); men (z = 1.03, p = 0.305); women (z = 0.40, p = 0.687)) or sex (x² = 1.7, df = 1, p = 0.197) between the groups.

The median age at onset of the disease was 34.0 years (range 6.4 to 70.5). The median age at first visit to a doctor for myasthenic symptoms was 35.0 years (range 6.7 to 70.5), and the median age at diagnosis was 35.3 years (range 7.0 to 73.0). Myasthenia gravis was diagnosed within three months in 34 patients (32%), within one year in 71 (66%), within two years in 84 (78%), and within three years in 93 (86%). Figure 3 shows the delay in diagnosis. The median period from onset of disease to first visit to the doctor was 1.0 month (range one day to 23 years) and from first visit to the doctor to establishment of the diagnosis, 3.1 months. There were no differences between men and women.

Initially, 43 patients (40%) consulted a general practitioner, 36 (33%) a neurologist, 23 (21%) an ophthalmologist, and four another specialist. Five patients could not provide information about referral.

Ocular symptoms were present in 64 patients (59%) at disease onset. In 30 patients (28%) the only presenting symptom was weakness of ocular muscles; in seven patients (6%) it was weakness of bulbar muscles; and in 21 patients (19%) it was weakness of girdle and extremity muscles. Generalised weakness was present in 40 patients (37%) and difficulty in breathing in 10 (9%) at the onset.

Myasthenia gravis was diagnosed by the primary physician in eight patients and was the suspected diagnosis in an additional seven. Disorders of eye muscles or nerves were diagnosed in seven patients. The suspected disorders included generalised muscle disorders (3), multiple sclerosis (2), brain tumour (2), brain infarction or transitory ischaemia of the brain (3), psychiatric disorders (6), tiredness (3), and others. In 24 cases no diagnosis was made at the first consultation.

Thyroid disorders were diagnosed in six patients with myasthenia gravis and rheumatoid arthritis in 10.
In two cases, a mother and her daughter, the disease was familial.

**DISCUSSION**

The reliability of epidemiological studies depends on complete case identification. 1,2 The case finding method used in this study should allow identification of most patients in Estonia with a diagnosis of myasthenia gravis. It is likely, however, that there are a few patients with a mild undiagnosed disorder who are relatively free of symptoms.

As expected, a majority of patients (69%) were diagnosed at Tartu University Hospital. The four patients diagnosed in outpatient clinics were recognised by practising neurologists.

The average annual incidence in our study is comparable with most other reports 1,2,4-16 and is also in accordance with Kurtzke’s estimation that incidence of myasthenia gravis is between two and six per million. 17 Some of the later studies have observed rates between 7.1 and 11.1 per million. 18-21 The highest average annual incidences reported so far are 15 per million in Cyprus 22 and 14.7 in Italy. 23 The latter report is comparable to those in countries around the Baltic sea. 3,4,12-14,20,25 Kurtzke estimated the likely prevalence of myasthenia gravis to be about 40 per million population, 16 but recent studies report more than threefold higher ratios. 61,82,1 The highest prevalence ratio reported so far is 175 per million. 22 The prevalence ratios in various countries have been compared on the basis of reported ratios. 13,41,21,31,52,1 One study reported an equal female to male ratio. 22 The relatively high female to male ratio in our study (2.6:1) could be explained by the higher proportion of women in the Estonian population, especially among the elderly. In 1995 the mean life expectancy at birth was 67.9 years in Estonia, being 61.7 years for men and 74.3 years for women. 4

Higher incidences and prevalence ratios in the older age group could be the result of improved diagnosis and treatment during recent years. 18,19,24,26 This suggests that myasthenia gravis is predominantly a disorder of elderly people, and the number of patients with the disease will increase as the population ages. 18

Some investigators have found a higher prevalence of myasthenia gravis in areas with higher population densities, 4,13 better availability of neurological services,

<table>
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<th>Table 2</th>
<th>Age and sex specific prevalence ratios (per million) of myasthenia gravis in Estonia on 1 January 1997</th>
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<td>Age group (years)</td>
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<tr>
<td></td>
<td>Men</td>
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<tr>
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*Statistical differences between the ratios for men vs women.

Figure 3 Delay in diagnosis. The median period from onset of disease to first visit to the doctor was 1.0 months, from first visit to the doctor to establishment of the diagnosis, 3.1 months, and from onset of disease to diagnosis, 6.1 months. Black diamonds, period from onset of the disease to first visit to the doctor; white squares, period from first visit to the doctor to establishment of the diagnosis; black triangles, period from onset of the disease to diagnosis.
and a longer tradition of epidemiological surveys. Consequently, population, territory size, different behaviour of the patients in various areas, and different power of information sources may bias prevalence studies on the disease. 27 We observed a higher prevalence ratio in south Estonia. In comparison with other countries there is a relatively large number of neurologists in Estonia, but there is no difference in the relative number of neurologists in the north and the south, neither were there any differences in age and sex. The population density is 38.9/km² in north Estonia and 24.2/km² in south Estonia. The north–south gradient of the prevalence ratio might indicate differences in case finding in the two regions but might equally reflect regional differences in disease occurrence. In addition, epidemiological studies of rare diseases in smaller populations will lead to increased variation in estimates, emphasising the importance of studies involving entire populations. The median age at onset has been reported to be in the range of 31 to 40 years. Our results are in accordance with previous reports.61 6 The most common associated conditions were thyroid diseases and rheumatoid disorders, but thyroid diseases were diagnosed less often in the present study than in previous reports.15 25 26

**Conclusions**

These data from the first population based study of myasthenia gravis in the Baltic region suggest that this is predominantly a disorder of the elderly, and that younger women are more susceptible than younger men. Prevalence and incidence values from Estonia are similar to those reported in most studies from Europe and north America.

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Competing interests: none declared

**REFERENCES**


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**Table 3**

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<th>Country</th>
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<td></td>
<td>Observed</td>
<td>Adjusted</td>
<td>Observed</td>
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<td>Estonia</td>
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<td>Norway</td>
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<td>Denmark</td>
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<td>England</td>
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<td>98.3 (64.9)</td>
<td>195.2</td>
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<tr>
<td>Yugoslavia</td>
<td>98.8</td>
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<td>Virginia</td>
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*Ratios are adjusted to the European and world (in parentheses) standard populations.*
NEUROLOGICAL PICTURE

Ulcus terebrans: an unusual cause of paraparesis

A rare case of progressive paraplegia is described. A 55 year old man was admitted on 18 February 2002, because of gradually increasing weakness in both legs, sensory disturbance below the level of T7, and a significant loss of body weight.

A physical examination revealed an oval giant ulcerating tumour of the back, measuring 30 cm × 20 cm, which destroyed the skin of the entire thoracic area, the subcutaneous tissue, and the thoracolumbar fascia, and invaded the muscles. The spinous processes of the T5–T8 thoracic vertebrae were exposed centrally (fig 1). The lesion has been growing over a 10 year period and finally developed into an ulcus terebrans. The patient had not received any previous treatment because of his attitude of neglect.

MRI of the spine showed an advanced ulcerating tumour, which had deeply destroyed larger parts of the back, infiltrating the thoracic spine at T5–T8 vertebral level (fig 2A). Axial T1-weighted MRI of the T7 vertebrae demonstrated a tumour mass that extended into the spinal canal, compressed the cord, and involved the vertebral body (fig 2B). The lesion was biopsied and histopathologically diagnosed as an ulcerating basal cell carcinoma. Tumour nests with peripheral palisading invaded deeply into the subcutaneous tissue and were accompanied by vascular invasion. The man refused complete surgical removal. He received palliative irradiation and he was alive at last follow up.

Basal cell carcinoma, the most common skin cancer, is locally invasive but rarely metastasises. Only 10% of all basal cell carcinomas are located on the trunk.

Small basal cell carcinomas of the trunk are usually regarded as relatively harmless. In contrast, large and ulcerating basal cell carcinomas may become a therapeutic challenge with a less favourable prognosis and high risk of recurrence. The development of mutilating giant basal cell carcinomas appears less due to the biological aggressive character of the tumours, but rather to the patients’ attitude of neglect.

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References