Incidence of seropositive myasthenia gravis in Cape Town and South Africa

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Background. Myasthenia gravis (MG) is a treatable autoimmune disease characterised by fatiguable weakness of skeletal muscles. More than 85% of MG patients have antibodies to the acetylcholine receptor (AChR) at the neuromuscular junction or are seropositive for MG (SPMG). In the developed world the incidence of MG has increased, particularly among older individuals, but no epidemiological studies have been done on SPMG in Africa.

Objectives. To determine the annual incidence rate (IR) of SPMG in the Cape Town (CT) municipality, and the crude annual IR of SPMG for the whole of South Africa (SA).

Methods. Positive AChR antibody tests were identified between 1 January 2003 and 1 January 2005 for patients living in CT, and the age- and sex-specific incidences were calculated. To determine the national crude annual IR over the same period, positive assays were identified from the laboratories that process AChR assays for SA. National Census 2001 population statistics formed the denominators.

Results. There were 65 positive assays in CT, and 230 nationwide. Based on these figures the annual IR for CT was 11.2 per million per year (95% confidence interval (CI) 8.7 - 14.3), and for South Africa 2.6 per million/year (95% CI 2.2 - 2.9). After a questionnaire response from CT neurologists regarding the routine use of the AChR antibody assay, the annual IR for CT was adjusted to 12.6 per million (95% CI 9.9 - 15.9) to incorporate those presumed to have SPMG without a confirmatory test. In CT, the IR in females was 15.3 per million/year (95% CI 11.2 - 20.4), and in males, 6.8 per million/year (95% CI 4.1 - 10.7). The CT IRs for blacks, coloureds and whites were not statistically different after adjusting for age and gender. The IR of SPMG in CT was 6 times greater in those presenting after the age of 50 years than in those with earlier disease onset (95% CI 3.7 - 9.7).

Conclusions. The annual IR of SPMG in CT is much the same as rates recorded recently in other developed countries, but the rest of SA has a much lower IR. A preponderance of MG starting after the age of 50 years reflects a worldwide trend, although the CT data showed a relatively lower-than-expected incidence for older males. IRs for SPMG vary widely in different regions in SA; this is likely to be related to differences in regional health care delivery, and underdiagnosis.

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Myasthenia gravis (MG) is a treatable autoimmune disease in which the autoantibody is directed at the acetylcholine receptor (AChR) on the postsynaptic neuromuscular junction. AChR antibodies are identifiable in 85 - 90% of patients with generalised myasthenia, and are highly specific for MG.[1,2] Traditionally MG was viewed as a disease of young women, in whom it may be associated with other autoimmune diseases, specific HLA subtypes (HLA-B8, DR3), and the presence of thymic enlargement (reviewed elsewhere[3,4]). In recent years the incidence and prevalence of MG in the middle-aged and older population have been found to be higher than expected,[4-7] and there is literature to suggest that the true incidence in the elderly is still underestimated.[8] In late-onset MG, with presentation after the age of 50 years,[9] the thymus is usually normal and there is a weak and different HLA association.[9,10] Moreover, there is a near-equal sex incidence in the older age group.[9,10]

Current estimates from North America suggest the prevalence of MG to be about 19 - 21 per 100 000 population.[5] There has been a substantial increase in diagnosis in older age groups,[4] with those over the age of 50 years constituting up to 60% of newly diagnosed seropositive MG (SPMG) cases.[3] The incidence of MG has been found to be similar across racial groups, although one study[11] found a trend towards a higher incidence in young African-Americans from Virginia. No epidemiological data on SPMG are available for Africa. The aims of this study were therefore to determine the incidence rates (IRs) of SPMG in Cape Town (CT) and an overall crude IR for the whole of South Africa (SA), and to compare these findings with IRs in other countries.

Patients and methods

Only two laboratories in SA perform the AChR assay, namely the state-run Allergology Laboratory at the University of

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Cape Town (UCT), and a private laboratory (Drs Du Buisson, Bruinette & Kramer Laboratories Inc.) in Pretoria. To calculate the IR for CT, all positive AChR assays processed by these two laboratories from 1 January 2003 to 1 January 2005 were included; all positive AChR assays from UCT were included if the patients concerned lived within the CT municipality as defined by the national Census 2001 demarcations, and positive assays from the private laboratory were included only if the requesting doctor practised in CT. Age and sex were obtained from the laboratory records. A positive AChR assay included values >0.2 nmol/l for assays done at the UCT laboratory, and values >0.5 nmol/l for assays done at the private laboratory, according to the assay conditions of the different commercial kits used by the two laboratories.

Records of state patients attending the UCT myasthenia gravis clinic (UCT-MG) at Groote Schuur Hospital (GSH) were reviewed to ascertain residential address, age at diagnosis, sex, and race. Data on race were derived from the records in accordance with Statistics South Africa Census categories, viz. black, white, coloured, and Indian/Asian, and were available for the UCT-MG cohort. Demographic data were incomplete for the patients assayed at the private laboratory. A small number of assays of subjects resident in KwaZulu-Natal and Gauteng were tested in a third laboratory, the Neurosciences Laboratory in Oxford, UK. Results were obtained for this subset, but no age, sex or race data. A crude annual IR was calculated for the whole country based on the positive assays from all three laboratories between 1 January 2003 and 1 January 2005.

A questionnaire (not shown) was sent to all private neurologists in CT. This was used to ascertain the number of patients they had diagnosed with MG over the 2-year study period and how often the AChR test was requested when MG was clinically suspected. The results of the questionnaire were used to adjust the calculated IR for CT in an attempt to correct for underdiagnosis.

Data were collected over 2 years and the results were averaged to reduce the possible bias of a small sample. Permission to perform this study was obtained from the UCT Research Ethics Committee (REC REF: 418/2004).

Statistical analysis

IRs were calculated using denominators derived from the Statistics South Africa Census (2001).[12] Confidence intervals (CIs) for IR were estimated using the Poisson distribution. IR ratios (IRRs) between different subgroups were calculated using the Poisson regression analysis.

Results

The two SA laboratories processed a total of 1 024 specimens over the 2-year study period; 120 of the 774 assays performed by the private laboratory were positive (range 0.61 - 15.49 nmol/l) and 69 of 250 assays from the UCT laboratory were positive (0.29 - 16.64 nmol/l). There were 65 recorded positive assays from within the CT municipality in the 2-year study period. Since the total population in the CT municipality in 2001 was 2 893 251 (national Census figures),[12] the overall IR in CT was 11.2 cases per million per year (95% CI 8.7 - 14.3).

Eleven of 13 private neurologists in CT completed the questionnaire. Of these, 1 never used the assay and 5 routinely performed the AChR assay; the remaining 5 estimated that they used the assay in 50% of cases of suspected MG (N = 1), 66% of cases (N = 1), and 80% of cases (N = 3). We estimated that an additional 8 patients would have been diagnosed with SPMG by these doctors if the assay had been performed in all patients. Hence the adjusted total number of SPMG subjects in the study period from CT was 73, with an adjusted overall IR of 12.6 cases per million/year (95% CI 9.9 - 15.9).

The non-adjusted IR among females in CT was 15.3 per million/year (95% CI 11.2 - 20.4) compared with 6.84 per million/year (95% CI 4.12 - 10.7) among males. Among CT patients younger than 50 years, the IR was 6.5 per million/year (95% CI 4.4 - 9.2), whereas among patients older than 50, the IR was 38.7 per million/year (95% CI 26.6 - 54.3), with an IRR of 6.0 (95% CI 3.7 - 9.7). Fig. 1 shows the CT cohort age-specific IRs by gender. Among those with disease onset before 40 years there is a consistent, albeit modest, higher IR for females, with a larger peak between 65 and 74 years. Annual IRs for CT males peaked from 65 to 74 years, and then again over age 85 years; the latter has a very wide CI (IR = 39.2, 95% CI 1.0 - 218.5) owing to the small sample size. However, in the CT cohort there was no statistically significant gender difference in the IRR comparing males with females in either those under 50 years or those over 50 years at disease onset. Although most of the CT males (63%) developed SPMG after the age of 50, the majority (62%) of the late-onset group were female.

Most of the CT data originated from the teaching hospitals (N = 44) and the race of these patients was known. Analysis of race after adjusting for age and gender showed an IR of 9.1 per million/year (95% CI 5.7 - 12.6) for coloured subjects, 4.2 per

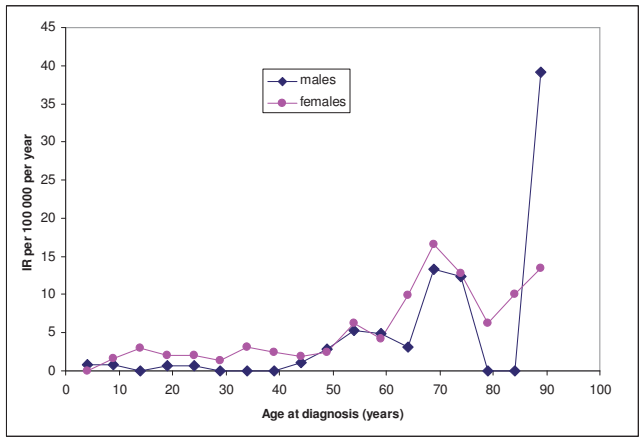

Fig. 1. Age- and sex-specific annual incidence rates (IRs) for subjects with seropositive myasthenia gravis in Cape Town (2003 - 2004).

million/year (95% CI 1.0 - 7.0) for blacks, and 5.0 per million/year (95% CI 0.9 - 9.2) for whites. No statistically significant IR differences were found within race ($p \geq 0.14$). Four thymomas (9%) were diagnosed during the study period.

The number of positive assays nationally was 230. This included 41 positive assays, out of a total of 138 samples, performed by the Oxford laboratory. The crude annual IR for SA nationally was 2.6 per million (95% CI 2.2 - 2.9), using a denominator for the population of South Africa of 44 819 770.[12] The age at which AChR testing was requested nationally (Fig. 2) shows mostly females in the early-onset MG group and slightly more males in the late-onset group.

Discussion

The annual IR for SPMG in the CT municipal area, as averaged for the period 2003 - 2004, is comparable with recent incidence rates reported from Greece[13] but lower than the IRs for SPMG in Spain and the UK[6,8] (Table I). The worldwide trend of increasing diagnosis of late-onset SPMG was also reflected in the CT cohort, with a 6 times greater annual IR among those with onset after the age of 50 years compared with earlier onset. However, the CT results do not reflect the relatively

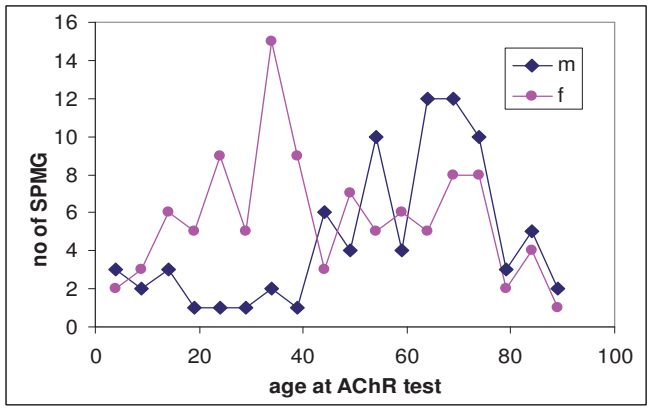

Fig. 2. Age at which AChR-positive tests were requested in SA nationally (2003 - 2004) (46 cases were not plotted as ages were not known).

greater annual IR for older men, seen elsewhere.[8,9] The IRs for older CT females (Fig. 1) are similar to those reported from the UK (75 - 79-year-old IR = 4.8/100 000/year).[8] However, the inconsistent and lower-than-expected IRs for older CT males (Fig. 1) are probably due to bias resulting from a smaller cohort, which is supported by the very wide 95% CIs for older males. Also, in the larger national SA sample (Fig. 2), late-onset SPMG case numbers peak over those of earlier onset, with slightly more males than females among late-onset subjects, consistent with findings in other populations.[6,8]

It has been postulated that the differences in IR between European countries do not reflect secular trend of disease but are due to differences in the accessibility of specialist health services.[7,13] Regional health care delivery is likely to be a major contributing factor in the difference between the crude annual IR of SPMG in SA, and that in CT; the latter is more than 4 times higher than the IR of the country overall. The IR for SA overall was similar to the rate reported from a developing country, viz. Estonia,[7] and far lower than the IRs of developed countries (Table I). The rural population in SA has limited access to secondary and tertiary health care, and we would predict significant underdiagnosis of MG in this sector. In a report from Kalafong Hospital, Pretoria, only 26 patients were consecutively diagnosed with MG over a 12-year period (1986 - 1998), and of the 9 patients tested for AChR antibodies, only 5 were positive.[14] Unfortunately, racial data were available only for patients attending the CT tertiary academic hospitals, comprising about half of all the CT patients; there were no significant differences between age- and sex-adjusted incidence rates among racial groups. However, not only were the subgroups too small to provide meaningful data, but race-related referral patterns would be likely to introduce bias.

SA has been recognised as having one of the most inequitable health services in the world[15] and so it is not surprising to find significant regional variation in the reported incidence of an uncommon disease. In 2003, the number of public-sector medical practitioners per 100 000 population in the Western Cape was the highest in the country at 31.9, with a national average of 19.7. In contrast, the North West

Table I. Comparison of the annual incidence rates (IR) of myasthenia gravis in different countries

Country (year)	IR/million/year (95% CI)	Method of diagnosis
Estonia (1970 - 1996)[7]	4.0 (3.4 - 4.7)	Clin/pharm*
Greece (1992 - 1997)[13]	7.4 (6.5 - 8.3)	Clin/pharm/RNS*
Spain (1991 - 2000)[6]	21.3 (18.9 - 31.2)	Clin/pharm/RNS/AChR*
UK (1997 - 1999)[8]	18.0 (UK)	AChR antibody test – no confirmation of clinical status
Cape Town		AChR
South Africa overall (2003 - 2004)	11.2† (8.7 - 14.3) 2.6 (2.2 - 2.9)	AChR antibody test – no confirmation of clinical status

*Includes seronegative cases.
†Unadjusted IR for Cape Town.
Clin = diagnosis based only on fatiguable muscle weakness; pharm = positive Tensilon test; AChR = positive acetylcholine receptor antibody assay; RNS = >10% decremental response on repetitive nerve stimulation.

province had 11.5 public-sector medical practitioners per 100 000 population.[15] It is perhaps not surprising that a high concentration of public health care professionals influences the trend for diagnosis of this treatable disorder.

In addition, there may be regional differences in diagnostic practice, perhaps partly due to the emphasis placed on the role of the AChR antibody test by the CT region academic centres and private neurologists. In the absence of a standardised diagnostic protocol, some physicians and neurologists may rely predominantly on clinical or pharmacological diagnostic methods, and may not measure AChR antibodies routinely. The morbidity and mortality of untreated MG is significant, and in many instances treatment will necessitate protracted immunosuppressive therapy. The clinical diagnosis is often not clear-cut, especially without access to specialised pharmacological or electrophysiological testing. In our hands, a number of patients initially presumed to have MG were later diagnosed with motor neurone disease, oculopharyngeal muscular dystrophy, or mitochondrial or thyroid myopathy (J Heckmann – personal observation). Senile ptosis or dehiscence of the tarsal plate may be asymmetrical, and can be confused with an ocular MG presentation. This may be the reason why some neurologists (we presume) tend to have a low threshold for requesting the AChR antibody assay, resulting in a large proportion of negative assay results.

Diagnostic tests available for MG include the ice test, pharmacological tests (Tensilon/neostigmine), AChR assay, repetitive nerve stimulation (RNS), and single-fibre electromyography (SFEMG). The ice test may be useful in the diagnosis of ocular MG, but is not specific.[2] Tensilon (edrophonium) has not been available in SA for some time, and neostigmine (intramuscular delivery) may be used instead. However, as this has a longer duration of action, the patient must be monitored for at least an hour, which may not be possible in many settings. RNS and SFEMG are not readily available at most health centres in SA, and moreover are time-consuming and can involve considerable technical difficulties. The AChR is a relatively expensive radio-isotope immunoassay, but the major benefits would be to confirm the diagnosis, as it is highly specific for MG,[1,2] and to indicate that a thymoma may be present. Approximately 10 - 15% of SPMG patients have a thymoma, as was found in the CT cohort, and almost all these will need to be removed surgically. A positive assay therefore underscores the need to exclude the possibility of thymoma using computed tomography of the chest, particularly in the older patient in whom thymectomy is not routinely considered as a treatment option for the myasthenic syndrome itself.[16]

It is a limitation of this study that we do not know the proportion of SA patients outside the Cape Town municipality who may have SPMG but who have not had a confirmatory test, either because of diagnostic practice or financial constraints in the public or private sector. Furthermore, we do not know the extent of underdiagnosis, or the lack of access to specialist health care. Another potential drawback, albeit probably not significant, is the degree of inaccuracy introduced by using population statistics from 2001, before the study period (2003 - 2004). If we assume positive growth and an increase in the denominator, the bias may increase the incidence of MG slightly.

A preponderance of late-onset MG is noted in SA, and CT in particular shows approximately 6 times the number of late-onset cases as those presenting earlier. This is in agreement with the outcome of epidemiological studies conducted in countries such as Denmark, Spain and the UK.[4,6,8] The reason for the higher incidence of target-organ autoimmune disease (such as MG) among the elderly is unknown, but Somnier[4] postulated that it may be due to environmental triggers such as chemical, infectious or tumour antigens.

In conclusion, the IR of SPMG in CT is somewhat lower than rates in recent reports from developed countries such as Spain and the UK, but is significantly higher than in the rest of SA. These differences are likely to reflect inadequate and unevenly distributed specialist health care and laboratory services in SA, and possibly lower numbers of elderly individuals in the disadvantaged socio-economic groups. MG is a potentially fatal yet treatable disease. Our report suggests that this disease may be under-recognised in this country. In addition, the CT data confirm a similar trend to that in the rest of the world, and underscore the need for health practitioners to consider MG as a treatable disease in the elderly.

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