INCIDENCE OF ACETYLCHOLINE RECEPTOR-ANTIBODY–POSITIVE MYASTHENIA GRAVIS IN SOUTH AFRICA

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ABSTRACT: Introduction: The aim of this study was to assess age- and gender-specific incidence rates (IRs) of acetylcholine receptor (AChR)–antibody–positive myasthenia gravis (MG) in South Africa, and geographical variations in incidence. Methods: IRs were calculated from positive AChR–antibody laboratory data between 2011 and 2012, using 2011 population census data. Results: 890 individuals were seropositive, for an annual IR of 8.5 per million. Age-standardized IR for early-onset (<50) and late-onset (≥50) MG were 4.1 and 24 per million, respectively, and 4.3 per million for juveniles. The IR between provinces ranged from 1 to 19 per million. Conclusions: In this Southern Hemisphere African population, the overall IR and peak IR (in older men) for seropositive MG is comparable to that in Europe and North America, arguing against environmental factors. However, IRs may be higher among children with African genetic ancestry. Geographical variation in incidence underscores the importance of outreach programs for regions with limited resources.

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Myasthenia gravis (MG) is a treatable condition, but has significant morbidity and mortality if unrecognized. Acetylcholine receptor (AChR) antibodies are detected in the sera of 85–90% of patients with MG, and their presence is highly specific.1 We previously found similar frequencies of AChR-antibody–positive (seropositive) MG in different subpopulations in South Africa.2,3 In addition, Vincent et al. found that AChR-antibody titers did not differ across ages or genders.1

Over the past 2 decades, there has been increasing recognition of MG manifesting in individuals >50 years of age. Data from Denmark, Norway, and the UK suggest this was previously underappreciated.1,4,5 However, the finding of a very sharp peak in incidence rates (IRs) in those aged 75–79 years living in the UK has raised the possibility of a “cohort effect” and that an environmental exposure may increase the risk for developing seropositive MG.1 Data from Africa are limited, but they may prove informative to counter or support this argument.

A systematic review of MG incidence studies showed substantial variation in frequencies in different populations, which may have been due to methodological differences.6 In South Africa, 1 study performed between 2003 and 2004 showed marked variation in the MG IRs between different provinces, most likely due to poor access to healthcare and the limited availability of the AChR-antibody assay at that time.7 Here we review the incidence of MG in South Africa between 2011 and 2012 and use the national population census data collected in 2011. Our aim was to assess the incidence of MG in older subjects from Africa, as well as the incidence of juvenile MG, a group with a high frequency of treatment-resistant ophthalmoplegia, a complication unique to populations with African genetic ancestry.2,3

METHODS

We analyzed the results of all AChR-antibody assays performed on sera by the only 2 laboratories that offer this assay in South Africa: the National Health Laboratory Service and the private laboratory of Drs. du Buisson, Kramer, Swart, & Bouwer, Inc. Demographic data obtained from these laboratories included the hospital of origin of the sample and the age and gender of each subject. The age at which the antibody test was performed was presumed to be the age of MG symptom onset. The province of sample origin was used as a proxy for the geographical location of the individual. A crude annual IR was calculated for the whole country based on positive assays between January 1, 2011 and December 31, 2012. Both laboratories used standard radioimmunoassay kits [RiaRSR AChR Kit (RSR, Ltd., Cardiff, UK) and ARA RRA Kit (IBL International GmbH, Germany)]; each assay included positive and negative control titers to be
matched for quality control verification. Both kits categorize antibody titers <0.25 nmol/L as negative, whereas titers between 0.25 and 0.39 nmol/L are equivocal. For this analysis, tests with antibody titers ≥0.25 nmol/L were considered to be positive.

Incidence was defined as the number of new cases of AChR-antibody–positive MG per year calculated as an average of the population data. Missing ages were imputed by multiple imputation using Gibbs sampling.8 IRs were calculated using denominators derived from the 2011 census results (Statistics South Africa, www.statssa.gov.za). Population estimates for 2011 were used as given, and estimates for 2012 were adjusted by an estimated annual growth rate of 1.34% overall (1.24% for women, 1.44% for men).

Confidence intervals (CIs) for the IRs were estimated using exact Poisson intervals, and bootstrap intervals were calculated for the men-to-women IR ratio estimates. Standardized IRs were calculated from the crude IRs by direct age standardization to the World Health Organization (WHO) world population.9 Differences in proportions were assessed using the chi-square test (alpha = 0.05, 2-tailed). Data not normally distributed are presented as median with interquartile range (IQR). Stata (version 13.0) and R (version 3.0) software were used for all statistical analyses.

The study was approved by the University of Cape Town Health Sciences Faculty Research Ethics Committee (REC: 471/2012).

RESULTS

The final study population comprised 3433 specimens, of which 890 were positive for AChR antibodies (Table 1). The assay titers ranged from 0.25 to 0.39 nmol/L in 17% of cases and were ≥0.4 nmol/L in 83% of cases. Approximately 2% of the 3433 specimens had missing ages, and these were imputed as described above. Of the positive assays, 498 (56%) were women, 364 (41%) were men, and in 28 (3%) the gender was unknown. The median age was 49 years (IQR 33–64 years).

The proportions of positive assays in 2011 and 2012 were different [odds ratio (OR) = 1.27, 95% confidence interval (CI) 1.12–1.46, P = 0.0004]. The total population in South Africa, as measured in the 2011 census, was 51,770,559 (51% women, 49% men). The annual crude IR of seropositive MG was estimated to be 9.6 per million for 2011 and 7.5 per million for 2012. The pooled crude annual IR was 8.5 per million (95% CI 8.0–9.2). Positive assays in different provinces ranged from 2 to 155, resulting in the annual crude IR varying between 1.3 and 18.8 per million (Fig. 1).

The number of patients with onset of seropositive MG before age 50 years (early onset) was 334 (38%), whereas 556 (62%) had onset after age 50 (late onset). Age-standardized IR for early-onset MG was 4.1 (95% CI 3.5–4.7), and for late-onset MG it was 24 (95% CI 21–28). For juveniles (age <20 years), the age-standardized IR was 4.3 per million (95% CI 3.2–5.0), although the crude IR was 3.8 per million. The annual IRs in children (<15 years) were, on average, 3 per million and were similar in the 5-year epochs for those <15 years of age. There were no IR differences for gender in those <10 years of age (Fig. 2). After
puberty the IR doubles, mainly due to the increased incidence in women; at between 15 and 20 years, the IR in women is almost 5-fold higher than that of men (see Fig. S1 in Supplementary Material, available online). Gender differences between early- and late-onset MG were significant (OR $= 0.32$, 95% CI 0.23–0.42, $P < 0.0001$). They remain higher in women until age 45 years, but become higher in men after age 55. The highest IR was seen in men aged 70–80 years (unadjusted average: 36 per million).

**DISCUSSION**

The average annual incidence of AChR-antibody positive MG in South Africa for 2011–2012 was 8.5 per million. This is comparable to the worldwide estimated pooled IR of 7.3 per million based on a meta-analysis of several observational studies and to a recent study from Norway using similar methodology. Our data from adults with seropositive MG show similar age and gender distributions when compared with reports from Norway, Greece, Canada, and the UK, although the IRs in the latter 2 studies were higher.

Over the last 2 decades there has been increasing recognition of MG manifesting in those >65 years of age, and in men more than women. Almost two-thirds of our incident seropositive cases were >50 years of age, similar to the proportions from Norway. Several studies in seropositive MG, including ours, reported a sharp decline in MG IRs after age 80 years (crude IRs; Table 1).

In this cohort from a developing country, where the average age of the population is lower than in developed countries, the slope of the IR peak smoothed substantially after age standardization to the WHO population (see standardized IR; Table 1). Nevertheless, IRs have remained highest among 70–80-year-old men in this cohort from the Southern Hemisphere and African continent, similar to comparable observations from Canada, Denmark, and the UK. Reports from Denmark and Australia, based on population-wide prescriptions of pyridostigmine, and from Japan and Taiwan, derived from hospital records, used different methodologies and included seronegative MG patients, thereby complicating direct comparison with our results; however, the highest incidence rates remain in those >60 years. These observations argue against environmental factors and support biological factors; intriguingly, few immune diseases, apart from the inflammatory myopathies, show a propensity for presenting in late life and in men.

Epidemiological studies of childhood and juvenile MG are limited, and none have been performed in Africa. We found a higher incidence of seropositive MG among African children (<15 years and ≤10 years, both 5 per million, respectively) compared with the UK (≤18 years, 1.5 per million) and Denmark (≤10 years, 0.3 per million). Although the IR for juveniles from Canada (British Columbia, ≤19 years, 3.6 per million) was similar to ours (<20 years, 4.3 per million), the racial composition of that population was not reported. Of the South African children with seropositive MG <15 years of age, 69% were <10 years of age, a proportion substantially higher than the 20% from the UK. In addition, in contrast to the findings from the UK, but similar to a report from Turkey, no gender differences were found among our prepubertal children with seropositive MG. However, between age 15 and 20 years, the
incidence was 5-fold higher in women than in men, similar to the results in young adults. In this study demographic information did not include race, although 89% of the South African population has African genetic ancestry (predominantly indigenous black and a smaller proportion with mixed ancestry), with only 9% of European and 2% of Indian/Asian ancestry (Statistics South Africa, www.statssa.gov.za). Andrews et al. observed that MG onset before puberty may be less frequent in American children with European genetic ancestry compared with African Americans.20 As juveniles with African genetic ancestry and AChR-antibody–positive MG are at risk of developing ophthalmoplegia as a treatment-resistant complication,3 recognition of seropositive MG in children may be important. One study reported that MG was relatively frequent among Asian children in a hospital-based cohort,21 but more recent reports from both Japan and Taiwan, also using hospital-based cohorts including seronegative cases, did not find a childhood-onset peak.14,15 Due to differing methodologies, comparisons with our results are not possible.

We found a wide variation in IR (1–19 per million) among the different provinces. It is worth noting that there was no north–south variation, but rather lower IRs in less populated provinces with fewer resources. South Africa has substantial health inequities that likely result in significant underdiagnoses of disorders that require specialist care. However, there have been recent improvements in healthcare delivery, as illustrated by an apparent overall increase in the IR of seropositive MG from 2.6 to 8.5 per million since the previous study in 2003–2004.7 Factors likely to have contributed include increased availability of the AChR-antibody test, which resulted in an almost 4-fold increase in the number of positive assays compared with the previous study, and improved access to neurological services related to establishment of outreach programs in some regions.

This study has several limitations. Although the antibody test has been widely available for at least 5 years, it is likely that many clinicians rely on clinical diagnosis because of cost considerations. The MG incidence is therefore probably underestimated. Second, the province of origin of the test sample may not reflect the patient’s home region, as patients in resource-limited areas may seek care in other provinces. Indeed, the extremely low MG incidence in some provinces and high incidence in more affluent regions most likely results from migration to regions with better access to healthcare. The assumption that age at test positivity is a proxy for symptom onset may be incorrect. Importantly, there was a significant difference in the number of tests requested in the 2-year period; although we averaged the data, longer observation periods would have produced more robust data. In addition, we found instances of duplicated positive test results; we were unable to adjust for these, as the proportions with duplicated negative tests were unknown. It may be relevant that some studies found lower AChR-antibody titers among elderly MG subjects,13,14 although this finding has been inconsistent.1 We included AChR-antibody titers in the equivocal range and only excluded those in the negative range.

We did not have clinical data available for this cohort, as it comprised a national laboratory-based study. However, we reported previously on a hospital-based cohort (n = 205) and found that 19% had AChR-antibody–negative MG, 10% each had either thymoma-associated MG or ocular MG, respectively, and 24% had MG symptom onset before 20 years of age.2 Subsequently, a national multicenter report on South African juveniles with MG found that 105 of 140 (75%) were seropositive, and 34% had ocular MG. Although 44% of the juveniles achieved remission on treatment, 23% developed treatment-resistant partial or complete ophthalmoplegia, predominantly in the context of seropositive generalized MG.3 We are unaware of data regarding the prevalence of anti-MuSK or anti-LRP4-antibody–associated MG in Africa.

In conclusion, this study of AChR-antibody–positive MG in an African cohort shows a similar tendency to other regions with a high incidence of MG in elderly men. In addition, our data suggest there may be a higher incidence of seropositive MG among children with African genetic ancestry.


