

## **Low testosterone and myasthenia gravis in males: a national record-linkage study**

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## Introduction

A disease of ‘young women and old men’, MG exhibits a bimodal distribution in age with a peak in the second and third decades of life with a female predominance, and a later peak in the sixth to eight decades of life with a male predominance [1]. A role for low testosterone in influencing MG risk in males is suggested by the fact that the age-dependent risk of MG in males coincides with an age-related decline in male testosterone levels [2]. Exploration of a role of testosterone has previously been limited to one case report of hypergonadotropic hypogonadism and MG [3]. We aimed to investigate an association between testicular hypofunction (TH), as a proxy for low testosterone levels, and subsequent MG risk in males.

## Methods

### *Population and data*

A retrospective cohort study was conducted through analysis of linked English Hospital Episode Statistics, which incorporate abstracts of every episode of day-case or inpatient care across all English National Health Service hospitals, and English national death registrations, 1999-2011. More detail about the analytical methodology can be found elsewhere [4].

A cohort of males with TH (ICD10 code E29.1) was constructed by identifying the first record of day-case care or inpatient admission for TH (whether as the principal diagnosis or secondary diagnoses). A reference cohort was constructed of individuals admitted for other various, mainly minor, conditions (footnotes). Individuals with a preceding/concurrent MG admission (ICD 10 G70.0) were excluded. We identified any subsequent episode of care for, or death from, MG in the respective cohorts.

\*Conditions used in reference cohort: cataract, otitis externa/media, varicose veins, haemorrhoids, upper respiratory tract infection, nasal polyp/deflected septum, teeth disorders, inguinal hernia, sebaceous cyst, internal derangement of knee, gall bladder disease, bunion, contraceptive management, limb fractures, hip replacement, knee replacement, tonsillectomy, adenoidectomy, ingrown toenail and other diseases of nail, head injury, appendectomy, superficial injury and contusions, dislocations sprains and strains

### *Statistical methods*

We calculated rates of MG, stratified and then standardized by age (5-year age groups), sex, calendar year of cohort

entry, region of residence, and quintile of patients' Index of Deprivation score. The indirect method of standardization was used, taking the exposed cohort and the reference cohort combined as the standard population. The rate ratio was calculated by taking the standardized rate of occurrence of MG in the TH cohort relative to the reference cohort, mathematically equivalent to  $(O^{TH}/E^{TH})/(O^{REF}/E^{REF})$ , where O and E are the observed and expected numbers of MG in the TH and reference cohorts. The confidence interval and chi-square statistics were calculated as described elsewhere [5]; and the way the analysis works with very small observed and expected numbers (as here) is explained elsewhere [4].

## Results

There were 5031 males in the TH cohort with a mean age of 50 years. There were 4.9 million in the reference cohort. Across the exposure and reference cohort there were 1100 males identified with MG, of whom the majority were first known to be hospitalised with MG between ages 65-84 (age 65-69, n=112, age 70-74, n=201, age 75-79, n=244, age 80-84, n=185). The adjusted rate ratio of MG following TH was 4.25 (95% confidence interval 1.15-10.90),  $p < 0.01$ , based on 4 observed cases and 0.9 expected. All observed cases of TH and subsequent MG were between ages 45-74, with a time interval of 1-4 years between first episode of TH and first episode of MG. Of note, all cases of MG occurred at least one year after first admission with TH.

## Conclusions

We report a significant positive association between TH and subsequent MG. This study utilises a very large dataset and a person-based cohort design to study an association that would otherwise be logistically extremely difficult to investigate epidemiologically. Hence, though numbers of TH-associated MG cases are small, we consider these the “best possible” using routine data from a population of 50 million.

Our findings are supportive of a proposed notion of low testosterone influencing risk of autoimmune diseases in males more generally. We have previously demonstrated a strong positive association (near five-fold elevation of rates) between TH and multiple sclerosis [6], and hypogonadism in males has recently been linked to an increased risk of rheumatoid arthritis [7]. Our observation may also in part be explained by suggested neuroprotective qualities of testosterone supplementation, and its role in increasing muscle mass in men, which may in turn have a role in alleviating early MG [8-9].

Consideration of possible confounding factors is limited by the availability of data in routine statistics. This, and small

numbers, means our findings must be regarded as hypothesis-generating rather than testing.

In conclusion, we show a positive association between low testosterone levels and risk of MG in males. We speculate that low testosterone may contribute to the age-related sex ratio of MG, but highlight a need for further work to more directly investigate the influence of testosterone on males with MG and other autoimmune diseases [6-7].

Characterising the role of sex hormones may be critical in understanding disease aetiology of some cases of MG.

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## Authorship

J.P. proposed the study, conducted the analyses and wrote the first draft of the manuscript. R.G. helped with the analyses. M.J.G. is the guarantor of and designed the study. All authors contributed to the interpretation of the data and revision of the manuscript for important intellectual content.

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