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Hospital admission and prevalence trends of adult myasthenia gravis in Finland in 2004–2014: A retrospective national registry study

Jussi O.T. Sipilä[a,*], Merja Soilu-Hänninen[b], Päivi Rautava[c], Ville Kytö[d]

[a] Department of Neurology, Siun sote, North Karelia Central Hospital, Joensuu, Finland, Division of Clinical Neurosciences, Turku University Hospital, Turku, Finland, Department of Neurology, University of Turku, Turku, Finland
[b] Turku University Hospital, Division of Clinical Neurosciences, Turku, Finland, Department of Neurology, University of Turku, Turku, Finland
[c] Department of Public Health, University of Turku and Turku Clinical Research Centre, Turku University Hospital, Turku, Finland
[d] Heart Center, Turku University Hospital, Turku, Finland, Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland, Center for Population Health Research, Turku University Hospital and University of Turku, Turku, Finland

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ABSTRACT

Hospital admission trends in Myasthenia Gravis are largely unknown, so they were here investigated in Finland between 2004 and 2014 using national mandatory registry data. There were 2989 hospital admissions (59.7% for women) for 861 individuals (median 2 admissions/individual) The annual number of admissions ($p = .56$), the age of admitted patients ($p = .24$) or length of stay ($p = .20$) showed no change during the study period. The proportion of infections as the primary diagnosis increased from 4.5% to 10.4% ($p = .0056$). These admissions lasted longer than admissions with a non-infectious primary diagnosis (median 6 vs. 4 days, $p < .0001$). In-hospital mortality rate was 1.0%, predicted by age over 65 (HR 8.8; $p = .0034$) and infection as the primary diagnosis (HR 6.9; $p < .0001$). Annual frequencies of thymectomies ($p = .66$) or plasmaphereses ($p = .12$) remained unchanged. Myasthenia drug reimbursement data suggested increasing MG prevalence during the study period ($p < .00001$). Considering that the annual hospitalisation frequency remained stable, this would suggest decreased need of hospitalisations per patient. The importance of infections as causes of myasthenia hospitalisations merits further study.

1. Introduction

Treatment options for neuroimmunological disorders have increased considerably during the last decades [1,2] but progress in the treatment of myasthenia gravis (MG) has been modest. Indeed, in 2017 eculizumab was the first drug to receive regulatory approval for treating MG in six decades. New options are much needed since about 10% of MG cases are refractory to conventional immunosuppressive therapy. These patients have recently been treated off label with rituximab or tacrolimus and, in some cases, chronic administration of plasmapheresis (PLEX) or intravenous immunoglobulin (IVIg). Importantly, immunosuppressive medications increase susceptibility to infections, to which acute exacerbations are often linked [3,4]. Long-term PLEX also exposes patients to complications and IVIg has limited availability. Indeed, the recently obtained robust evidence of the effect of thymectomy in treating MG[5] is arguably the most important development in this field even though the procedure has long been suggested for many patients in treatment guidelines [6,7].

Treatment of multiple sclerosis (MS) has advanced more rapidly and we have recently reported that the rates of hospital admissions related to MS have markedly declined from 2004 to 2014 in Finland with halving of the costs related [8] even as MS prevalence has increased in many parts of the country [9–12]. Of note, the proportion of admissions with an infection as the primary diagnosis increased suggesting a possible adverse effect of more efficacious treatments. Also, in the United States the annual number of MS hospital discharges remained quite stable between 2003 and 2013 while in the United States that of MG increased six-fold [13]. We therefore now evaluated recent trends in MG hospital admissions in Finland. Since there are no current data available on MG epidemiology in Finland, we also sought to approximate the prevalence of the disease.

* Corresponding author at: Department of Neurology, Siun sote, North Karelia Central Hospital, Tikkamäentie 16, FI-80210 Joensuu, Finland.
E-mail address: jussi.sipila@utu.fi (J.O.T. Sipilä).

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2. Materials and methods

2.1. Data collection

We searched the Care Register for Health Care (CRHC), a mandatory database maintained by National Institute for Health and Welfare (THL) registering all public health care hospital discharges in Finland, for all discharges from neurological, medical, surgical, neurosurgical and intensive care units with MG (ICD-10 code G70) as a primary diagnosis or an additional diagnosis for primary infection diagnosis between January 1, 2004 and December 31, 2014. All public hospitals (five university hospitals and 39 other hospitals) on mainland Finland were included (MG is not treated in private hospitals in Finland). Patients under 16 years of age were excluded.

Persons with certain health conditions are entitled to drug cost reimbursements from the state. Reimbursement rights are given when a written, detailed statement confirming the condition provided by the treating neurologist has been accepted by the specialist physician of the Social Insurance Institution of Finland (KELA). All MG patients diagnosed by a neurologist are eligible to receive the imbursement and this is routinely obtained at the time of diagnosis. The number of reimbursement entitlements therefore directly reflects the number of MG patients alive in Finland. We obtained the number of persons eligible for drug reimbursement for MG at the end of each year from 2004 to 2014 in Finland from KELA. This data was available only for 5-year age brackets and will therefore be presented for people at least 15 years of age. Population data were obtained from the national authority, Statistics Finland. Seasons were divided as spring (March–May), summer (June–August), fall (September–November) and winter (December–February).

The study was approved by the Turku University Hospital Clinical Research Center (Turku CRC) and THL (permissions no: THL/143/5.05.00/2015 and THL/1349/5.05.00/2015). According to Finnish law, ethical committee approval was not needed since the study was based on administrative register data and included no contact with patients.

2.2. Statistical methods

Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the distribution of continuous variables and, subsequently, results presented as means and standard deviations or medians and interquartile ranges (IQR) as appropriate and the Mann-Whitney *U* test or independent samples of the Kruskall-Wallis test used to analyse patient characteristics.

Poisson regression was used for analysis of count data (scaled due to over dispersion), Cox regression was used for in-hospital mortality analysis and linear regression was used for analysis of length of stay (beginning days, log transformed and standardized due to skewness). In analysis of seasonal and monthly number of admissions, differences in number of days between seasons were accounted for by using the logarithm of day number as an offset parameter in regression model. Statistical significance was considered to be presented by a *P*-value < .05. Analyses were conducted using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA) or IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp).

3. Results

The number of persons > 15 years of age eligible for MG drug reimbursements in Finland increased from 983 persons on December 31, 2004 to 1321 at the end of 2014 ($p < .00001$). The latter suggests a prevalence of 29/100,000 among Finns > 15 years of age (Fig. 1).

We identified 2989 hospital admissions for 861 individuals (median admission frequency per patient: 2; range 1–138) in 2004–2014. In the majority admissions the patient was a woman (59.7%). Admitted men were older (median 66 years, IQR 15) than women (median 63 years, IQR 24; $p < .001$; Fig. 2). There was no change in the age of admitted patients ($p = .24$) or the annual number of admissions during the study period ($p = .56$; mean 272; range 228–312). There was seasonal variation in the number of admissions ($p = .0017$) with a nadir in summer (Table 1). Seasonal variation was not affected by gender ($p = .66$), age over 65 years ($p = .26$), or admission year ($p = .63$).

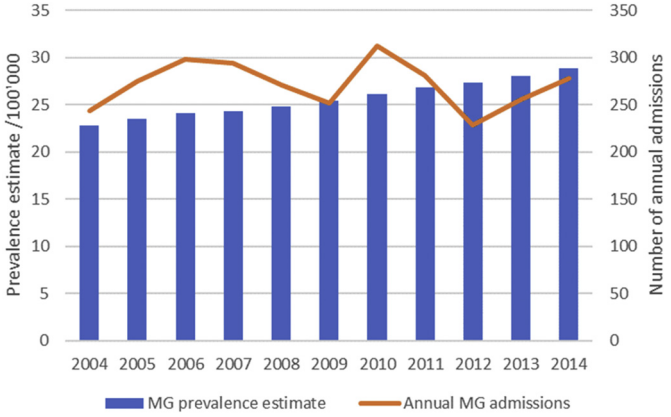

Fig. 1. Annual estimate of Myasthenia Gravis prevalence in Finland with annual MG hospital admissions.

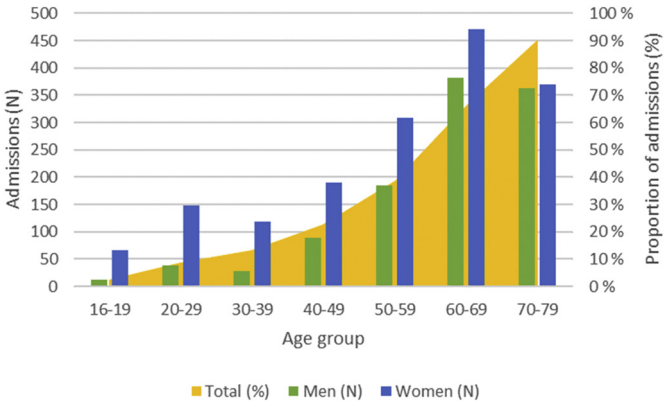

Fig. 2. Myasthenia Gravis hospital admissions in Finland in 2004–2014 by age and gender.

An infection was the primary diagnosis in 8.03% of the 2989 admissions and the annual proportion increased ($\beta = 0.55$, SD 0.15, $p = .0056$, linear regression) from 4.5% to 10.4% during the study period. The most common categories of primary infection diagnoses were lower respiratory tract infections ($N = 65$), septicaemia ($N = 36$) and urinary tract infections ($N = 18$). Admission primarily for an infectious cause lasted longer than admissions with a non-infectious primary diagnosis (median 6, IQR 5 vs. median 4, IQR 4 days, $p < .0001$). There was no seasonality in the proportion of an infection as the primary diagnosis ($p = .79$).

Mean length of stay (LOS) was 6.6 ± 10.2 days (median 5, range

Table 1
Seasonal variation in Myasthenia Gravis admissions in Finland in 2004–2014.

Season	Admissions % (per month*)	RR (vs. summer) (95%CI)	P
Autumn	27.2% (6.1)	1.22 (1.10–1.35)	0.0001
Winter	25.2% (5.7)	1.14 (1.03–1.27)	0.0131
Spring	25.1% (5.6)	1.11 (1.00–1.24)	0.0413
Summer	22.5% (5.0)	–	–

RR, rate ratio compared to summer. RR was estimated using Poisson regression and adjusted for age, sex, study year and number of days (as an offset).

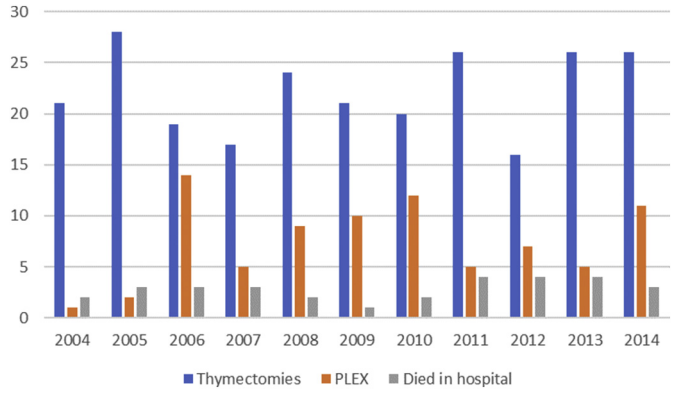

Fig. 3. Annual number of thymectomies, plasmaphereses and in-hospital deaths in hospital admissions related to MG in Finland.

1–406) with no change during the study period (p = .20). LOS was longer in men (median 5, IQR 5) compared to women (median 4, IQR 5; $p < .001$) and in patients over 65 years of age (mean 8.1 ± 7.7 days; median 6 days) compared to those 16–64 years of age (mean 6.9 ± 12.3 days; median 5 days; p = .0004). There was no seasonal (p = .16) or monthly (p = .11) variation in LOS. In multivariate analysis, gender (men vs. women: β = 0.23, SE 0.037, $p < .0001$), infection as the primary diagnosis (β = 0.24, SE 0.067, p = .0003) and age over 65 years (β = 0.13, SE 0.037, p = .0004) independently predicted longer LOS whereas season (p = .16) and year of admission (p = .10) had no effect.

Most of the admissions occurred in neurology wards (77.0%) with surgical and internal medicine services covering the rest. In-hospital mortality rate was 1.0% (1–4 deaths annually and 31 in total, Fig. 3). In multivariate analysis, in-hospital mortality was predicted by age over 65 (HR 8.8; 95% CI 2.1–37.4; p = .0034) and infection as the primary diagnosis (HR 6.9; 95% CI 3.3–14.5; $p < .0001$) but not by year of admission (p = .27), season of admission (p = .43) or gender (p = .40).

There was no trend in annual numbers of either thymectomies (N = 277; p = .66) or plasmaphereses (N = 81; p = .12) (Fig. 3).

4. Discussion

In this nationwide study we observed no change in adult hospitalisation rates, length of hospital stay or in-hospital mortality for MG from 2004 to 2014. However, our results also suggest an increase in the prevalence of MG in Finland during the same period and together these results suggest a decreased need of hospitalisation per patient. Nevertheless, considering that during the same period the prevalence of MS has increased [9–12] and the number of annual MS admissions has decreased [8]. it appears possible that the progress of MG therapy has not matched the impact of MS DMTs.

Published data on MG admission trends are scarce. Recent data exists only for the United States where hospitalisation rates have increased six-fold from 2003 to 2013 [13]. The authors pondered if this might be related to an increasing number of MG patients being elderly. Indeed, some studies have reported increases in MG incidence and prevalence particularly in the elderly [14–17] and it appears logical that with increasing frailty and number of comorbidities, older patients would be more likely to be hospitalised compared to younger ones. However, our observation of no change in the age of admitted patients during the study period contradicts this although our observation of longer LOS in older patients could partly explain the higher costs observed in the United States. Unfortunately, we do not have data on the age distribution of MG patients in Finland. Further studies on MG epidemiology and age-specific hospitalisation rates are needed.

Globally, the prevalence of MG has increased over decades [18]. No recent data of MG epidemiology is available for Finland, but the prevalence increased from 2.3/100,000 in 1964 to 5.6/100,000 in 1976 [19,20]. Our data on drug reimbursement rights suggests this trend has continued and the most recent figure for persons > 15 years of age would be 29/100,000. Compared to some recent studies [15–17,21,22], this appears high. However, it should also be remembered that Finland is a high-risk area of many autoimmune diseases such as MS [12], type 1 diabetes [23], and rheumatoid arthritis [24]. Considering also the global trend of increasing MG prevalence and the recent figures of 24/100,000 from Pavia, Italy [25], 24.8/100,000 from Slovakia [14] and 32.0/100,000 from Ontario, Canada [26] our result appears credible. Therefore, considering the increase in persons eligible for MG drug imbursement during the study period and the stability of annual number of MG hospitalisations, it seems that the annual number of hospitalisations needed per patient has decreased.

This favorable trend, however, seems modest compared to that we recently observed for MS. [8,12] This might be related to the fact that treatment options for MS are considerably more diverse compared to those available for MG, the monoclonal antibody therapies have been shown to be more efficient than the older injectable therapies [27–29] and it has been shown that the rate of relapse reduction and slower accumulation of disability are correlated with earlier introduction of DMTs in the disease course [28,30]. Evidence-base for effectiveness of immunosuppressive treatment of MG is considerably weaker [31].

Immunosuppressive therapies also increase the risk for infections. Similar to our recent results concerning MS admissions, we observed an increase in the proportion of MG admissions that were related to infections. As we do not have data on the drugs used by our patients it remains unclear whether immunosuppression was responsible for this. Interestingly, we observed no seasonality in infection-associated admissions suggesting that they were not dependent on natural seasonal variation of infectious disease occurrence. This, in turn, might implicate a more continuous predisposing factor, such as immunosuppressive therapy. Moreover, admissions with an infection as the primary diagnosis were longer than those with MG as the primary diagnosis. Unfortunately, admission cost data for MG in Finland is not available.

Considering the increasing proportion of admissions associated with an infection and that infections are associated with life-threatening events in MG [4], it is noteworthy that no change in the annual number of PLEX were observed. Should our results on MG prevalence trends in Finland be confirmed, the stable PLEX frequency would indicate a relative decline in the risk of very serious exacerbations. Indeed, life-threatening events appear to be quite rare in MG these days [4]. However, the stable PLEX frequency may also be interpreted as a counter argument to our suggestion of increasing prevalence. It is unfortunate that we do not have IVIg data at our disposal to compare with PLEX frequencies. The annual number of thymectomies also remained stable but, should our prevalence results be confirmed, more would be needed considering the procedure's efficacy [5]. However, these rates may already have increased after our study period.

Our study relies on retrospectively analysed administrative data and has the inherent flaws of all such studies, including possible errors in coding, possible changes in diagnostic and treatment practices during the study period that cannot be discerned from the data, and lack of clinical data such as that of medications (including IVIg use), the usage and results of diagnostic tests, clinical manifestations and disease severity. Indeed, had long-term IVIg usage increased during the study period it could have inflated the number of admissions since it requires regular infusions. However, IVIG infusions can be given also in day hospital setting, which is not recorded as inpatient care. Since actual IVIG usage patterns in Finland are not known, we cannot assess how much this might confound our results. As for the veracity of the data, the registry has been proven reliable for these kinds of studies [32]. Nevertheless, epidemiological figures drawn from mere administrative data tend to be higher than those with patient chart verification [33] and our prevalence figures should therefore be interpreted cautiously. The strengths of the study also include nationwide coverage and its

span over a decade. Considering trends in neurologic hospitalisations in Finland during the same period, we have previously reported not only a decrease in MS hospitalisations but in hospitalisations for subarachnoid hemorrhage, no change in hospitalisation frequencies for intracerebral hemorrhage or Guillain-Barré syndrome and an increase in hospitalisations for ischemic stroke [8,34,35]. Therefore, it appears that changes in hospitalisation rates for neurological disease cannot be explained by any single administrative or other general reason.

In conclusion, no change in annual frequency of hospitalisations associated with MG was observed from 2004 to 2014. The prevalence of MG appears to have increased during the same time, implying a decreased need of hospital admissions per patient.

Disclosure of interest

Jussi O.T. Sipilä: has received honoraria, travel grants and congress fee covering (Orion Corporation, Merck, Pfizer, Abbvie, Sanofi Genzyme) and holds shares (Orion Corporation).

Merja Soilu-Hänninen: has received congress fee covering, investigator fees and honoraria for lectures or advisory boards (Biogen, Merck, Novartis, Roche, Sanofi- Genzyme, Teva).

Päivi Rautava: none.

Ville Kytö: none.

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