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ORIGINAL ARTICLE

Adult hospital admissions associated with multiple sclerosis in Finland in 2004–2014

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ABSTRACT

Introduction: Treatment of multiple sclerosis (MS) has developed significantly and several new immunotherapeutic drugs have become available in Finland since 2004. We studied whether this is associated with changes in hospital admission frequencies and healthcare costs and whether admission rates due to infection have increased.

Methods: The national Care Register for Health Care was searched for all discharges from neurological, medical, surgical, neurosurgical and intensive care units with MS as a primary diagnosis or an auxiliary diagnosis for primary infection diagnosis in 2004–2014. Only patients ≥16 years of age were included.

Results: We identified 12,276 hospital admissions for 4296 individuals. The number of admissions declined by 4.6% annually ($p = .0024$) in both genders. Proportion of admissions with an infection as the primary diagnosis increased but no change in their frequency was found. They were longer than admissions with MS as the primary diagnosis and were associated with increased in-hospital mortality. The annual aggregate cost of hospital admissions declined by 51% during the study period.

Conclusions: This study shows that hospital admission rates and costs related to MS hospital admissions have markedly declined from 2004 to 2014 in Finland, which coincides with an increase in the use of disease-modifying therapies.

KEY MESSAGE

- Hospital admission rates and costs related to MS hospital admissions have markedly declined from 2004 to 2014 in Finland.
- Proportion of admission related to infection has increased and they are associated with longer hospitalizations and increased in-hospital mortality pointing out the importance of infection prevention.

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Cost; hospital admission; infection; multiple sclerosis; treatment

Introduction

Multiple sclerosis (MS) is the most common neurological disorder which causes disability in young adults. It is a chronic autoimmune disease in which immune cells destroy central nervous system (CNS) myelin. In most patients, MS is at first relapsing-remitting but becomes progressive over time. There is no cure for MS, but therapies affecting the immune system can reduce disease activity and progression of disease in relapsing forms of MS. Like the other Nordic countries Finland belongs to a high-risk area of MS. Incidence and prevalence are increasing and there are marked regional differences such that the disease is most common both in western and southwestern Finland [1–4].

Treatment of MS has developed significantly since the era of the first injectable therapies became available more than 20 years ago. Several new disease-modifying therapies (DMT's) have been introduced since 2004: natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon β-1a, daclizumab, cladribine and ocrelizumab [5–12]. The superior therapeutic efficacy of the monoclonal antibody therapies and daclizumab has been demonstrated in phase 3 trials by comparing them against the older platform injectable therapies, or by large-scale

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real-world data bases [6,8,10,11]. It has been established that the earlier the DMT's are used, the better their efficacy is in reducing relapses [11]. However, there is less evidence of DMT's preventing disease progression. Prevention of progression to severe disability could lead to reduced need for e.g. intrathecal baclofen pumps for severe spasticity. On the other hand, the most potent immunosuppressive therapies bear higher risk for adverse events such as opportunistic infections [12]. Emergence of secondary autoimmune diseases has also been observed in patients treated with alemtuzumab, and fingolimod therapy has been associated with an increased risk of cardiac and eye complications [6,13].

Hospital admissions use a significant amount of healthcare resources. Hospital admission rates in MS patients are higher than in the general population despite a dramatic decrease observed over the past 25 years [14]. In addition to MS relapses severe enough to necessitate hospital admission, a proportion of this raised risk of hospitalization may be due to surveillance bias as patients are being monitored regularly by outpatient clinic. MS patients have been shown to be at an increased hospital admission risk for infections [15].

The purpose of this study was to evaluate recent trends in MS hospital admission rates and the role of infections in MS-related hospital admissions in all Finnish hospitals. We wanted to find out whether disease-modifying drugs have affected hospital admission rates and whether admission rates due to infection have increased. Our hypothesis was that admission rates would have decreased but admissions related to infections could have increased. To answer these questions, we did a retrospective database search to investigate hospital admissions related to MS, and admissions with an infection as a primary diagnosis and MS as an auxiliary diagnosis, from 2004 to 2014 using administrative public health care hospital discharge data. We will discuss hospitalization trends and costs in relation to the changes in the use and costs of MS DMTs during the same time in Finland.

Material and methods

Data collection

The Care Register for Health Care (CRHC), a mandatory database maintained by National Institute for Health and Welfare (THL) for all public health care hospital discharges in Finland, was searched for all discharges from neurological, medical, surgical, neurosurgical and intensive care units with MS (ICD-10 code G35) as a primary diagnosis or an auxiliary diagnosis for primary infection diagnosis between 1 January 2004 and 31 December 2014. The search included all five university hospitals and 39 other hospitals on mainland Finland. Only patients $\geq$16 years of age were included. The data on intensive care admission counts proved insufficient for analysis. The Diagnosis Related Group (NordDRG categorization) daily cost of MS hospital care was extracted from THL statistical reports for 2006 (343.35 €/day) and 2011 (473.91 €/day) [16,17]. The mean of these figures (408.63 €/day) was used for economic calculations in this study. Drug reimbursement data was obtained from the statistics of the Social Insurance Institution of Finland (KELA). The study was approved by the Turku University Hospital Clinical Research Center (Turku CRC) and the National Institute for Health and Welfare of Finland (permissions no.: THL/143/5.05.00/2015 and THL/1349/5.05.00/2015).

Statistical methods

Shapiro–Wilk and Kolmogorov–Smirnov tests were used to assess the distribution of continuous variables and, subsequently, the Mann–Whitney *U*-test or independent samples of the Kruskall–Wallis test were used as appropriate to analyze patient characteristics. Poisson regression was used for analysis of count data, Cox regression was used for in-hospital mortality analysis and linear regression was used for analysis of length of stay (LOS) (log transformed due to skewness) and admission costs. Trend analysis were age and sex adjusted except for admission cost analysis (sex- and age-specific data was not available). Results of univariate analyses were comparable to multivariate models. When analysing differences in LOS, generalized estimating equations (GEE) to accompany repeated admissions from individual subjects were used. 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) or IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY).

Ethical standards

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.

Results

Altogether 12,276 hospital admissions for 4296 individuals were identified (median frequency of admissions

per patient: 1; interquartile range 2; range 1–78). In over two-thirds of admissions (69.1%), the patient was a woman. Admitted men were older [median 44 years, interquartile range (IQR) 19] than women (median 43 years, IQR 20; $p < .001$) (Table 1). The number of admissions declined by estimated 4.6% annually ($p = .0024$) and the trend was evident in both genders (interaction $p = .93$ between genders, Figure 1). Most of the admissions occurred in neurology wards (79.9%) with internal medicine services (13.4%) and surgical services (5.0% with an additional 1.8% admitted to neurosurgical services) coming next.

Mean LOS was 4.2 and standard deviation (STD) 5.2 days (median 3 days, range 1–127 days) with a declining trend of admission duration during the study period ($\beta = -0.05$, $p < .0001$; Figure 2). LOS was longer in men (mean 4.5, STD 5.7) compared to women (mean 4.1, STD 4.9; age and study-year adjusted

Table 1. Characteristics of hospital admissions associated with multiple sclerosis in Finland in 2004–2014.

Characteristic	Admissions, *n* (%)	Median age at admission (25th, 75th percentile), years
Total	12276	44.0 (34, 54)
Male	3788 (30.9)	44.0 (36, 55)
Female	8488 (69.1)	43.0 (33, 53)

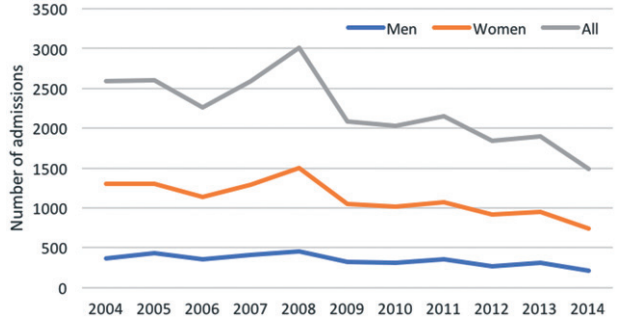

Figure 1. The annual number of hospital admissions associated with multiple sclerosis in Finland in 2004–2014.

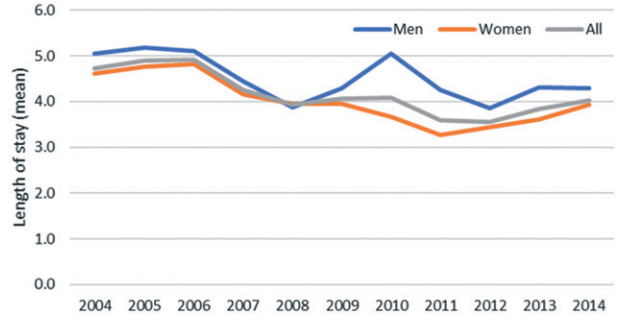

Figure 2. The mean length of stay of hospital admissions associated with multiple sclerosis in Finland in 2004–2014.

$p < .0001$). Patients were discharged to home in 72.6% of admissions. In-hospital mortality rate was 0.59% (0.29–0.94% or 4–11 deaths per year) with no difference between genders ($p = .318$) or evidence of a trend ($p = .212$).

An infection was the primary diagnosis in 11.7% of admissions and the proportion increased ($\beta = 0.87$, $p = .001$, linear regression) during the study period with; however, no change in their frequency ($p = .68$, Poisson regression; Figure 3). The most common infections, auxiliary diagnoses included, were pyelonephritis and pneumonia non ultra descriptus (NUD) (Table 2). Admission primarily for infectious cause lasted longer than non-infectious admission (mean 6.6 STD 6.2 versus mean 3.8 STD 4.9 days, $p < .0001$, independent samples *t*-test). MS admission with infection as primary cause was associated with increased in-hospital mortality (HR 9.39; CI 5.25–16.77; $p < .0001$, adjusted for age, gender and study-year) compared to non-infectious admissions.

The annual numbers of procedures of interest were modest during the study period (Table 3). Poisson regression analysis was performed only on intrathecal baclofen implantations with no evidence of a trend ($p = .059$). The annual aggregate NordDRG-based cost of hospital admissions declined from 2,515,118 € in 2004 to 1,234,471 € in 2014 ($\beta = -0.95$, $p < .001$, linear regression; Figure 4).

Discussion

In this article, we showed that MS-associated hospital admissions in Finland have steadily decreased at a rate of 4.6% a year over a decade from 2004 to 2014. At the same time, the LOS has shortened. The proportion of admissions related to infections increased and admissions with an infection as the primary diagnosis were longer and associated with increased in-hospital mortality.

Relapses are a frequent cause of hospitalizations in MS. The use of more effective therapies may have decreased the rate and severity of relapses and thus reduced the need for inpatient care of relapses, but the infectious complications of MS or its therapies may not have decreased at the same pace.

MS patients are at increased infection risk and functional limitations associated with MS may increase this risk. In a previous study from the Hospital district of Southwest Finland, we observed that the risk of infections in MS patients was more than two-fold compared with a matched control population, and that infections were the major cause of death among MS patients in Southwest Finland [18]. The most common infections associated with MS admissions in the

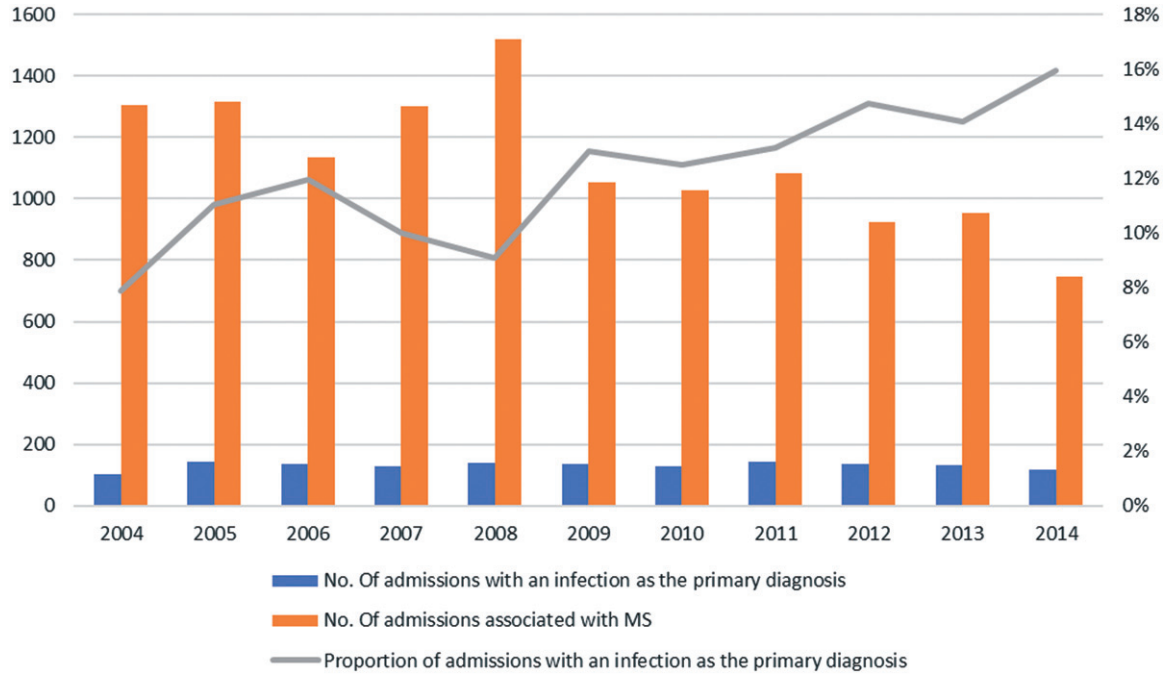

Figure 3. Infections as the primary diagnosis of hospital admissions associated with multiple sclerosis in Finland in 2004–2014. MS: multiple sclerosis.

Table 2. Frequencies of the most common infection diagnoses among the 12,276 admissions.

ICD-10 code	Disease	Frequency (*n*)	%
N10	Acute pyelonephritis	468	29.1
J15.9/J18.9	Bacterial pneumonia/pneumonia NUD	393	24.4
N30.0/N30.9	Cystitis	143	8.9
N39.0	Urinary tract infection	96	6.0
A46	Erysipelas	76	4.7
A49.9	Bacterial infection, NUD	73	4.5
A09	Gastroenteritis	63	3.9
J06.9	Acute upper respiratory infection	60	3.7
J20.9	Acute bronchitis	56	3.5
J69.0	Aspiration pneumonia	54	3.4
A41.5	Sepsis due to other Gram-negative organisms	45	2.8
A04.7	Enterocolitis due to Clostridium difficile	44	2.7
A41.9	Sepsis, unspecified organism	37	2.3

Table 3. Annual numbers of recorded procedures of interest in hospital admissions associated with multiple sclerosis.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
ITB	7	10	8	9	10	8	9	12	10	13	15	111
PEG	4	5	5	6	4	7	5	6	6	7	3	58
PF	0	0	1	0	4	3	6	1	0	4	1	20

ITB: intrathecal baclofen delivery device implantation; PEG: percutaneous gastrostomy implantation; PF: plasmaferesis.

present paper were pyelonephritis (N10), pneumonia (J18.9) and cystitis (N30.0). Bladder and bowel dysfunction may raise the risk of urinary tract and gastrointestinal infections [19]. Swallowing impairment and inability to cough and clear the lungs may increase respiratory tract infection risk [20]. Infections may increase the risk of MS relapses and thence increase relapse-related admissions. The absolute number of hospital admissions associated with infections in patients with MS remained unchanged in our study. However, since the total number of hospital admissions decreased, the proportion of infection-related admissions increased. This is disconcerting because admissions due primarily to infection were longer and displayed increased in-hospital mortality compared to admissions with MS as the primary diagnosis. It appears that measures to prevent infections in MS patients are very much needed.

Marrie et al. [14] has studied hospital admission rate changes in 5797 MS patients from 1984 to 2011

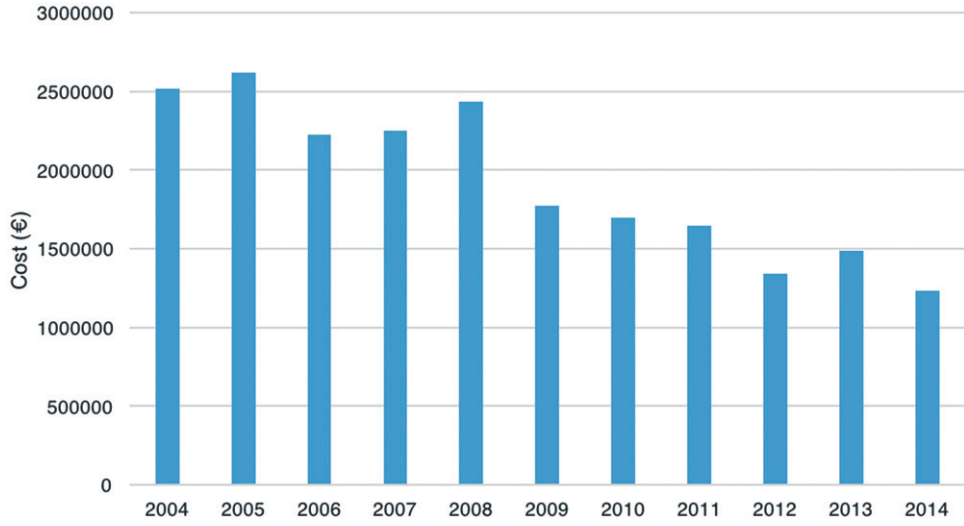

Figure 4. Annual aggregate cost (€) of hospitalizations related to MS.

compared with a matched large general population cohort. They observed a decrease by 75% in 27 years in MS admissions, while in the general population the admission rates decreased in the same time span by 41%. We did not have a control population comparison in our study, but we have previously studied the hospital admission rates for stroke and Guillain-Barré syndrome (GBS) in Finland during the same study period. In these studies, we showed increasing admission rates for ischemic stroke, and relatively stable for GBS and intracerebral hemorrhage (ICH) [21,22]. It is possible that altered treatment practices during the study period with reduced number of hospital beds and preferring of outpatient to inpatient care have affected our results. However, annual reports of somatic health care by National Institute for Health and Welfare of Finland suggest increasing admission rates but shortening length of hospitalizations in neurology wards in general during our study [23].

In Norway and British Columbia, Canada, the prevalence of MS and median age of the MS population has increased during the past decades [24,25]. Improved survival that has been found during the same period is a likely explanation for the increased prevalence, since incidence changes do not explain the rise in prevalence [26]. A country wide prevalence of MS in Finland from the period of the study 2004–2014 has not been published. Regional studies of MS epidemiology in Finland from the time period of our study have pointed towards increasing incidence and prevalence [1–4]. Hence, it seems evident that decreased hospital admissions cannot be explained by a decline in prevalence.

Earlier initiation and wider use of MS therapies as well as use of more potent therapies may slow the progression of MS to severe disability, although confirmation of this needs long-term real-world registry-based data and remains to be proven [11]. We hypothesized that in case that MS progression to severe disability would had decreased in Finland during the observation period, the need for some procedures used for advanced MS, such as intrathecal baclofen delivery device implantation, PEG implantation and plasmapheresis for severe relapses, could have decreased. However, the absolute number of these procedures during the follow-up period remained rather low and no apparent change in the numbers of the procedures was observed. Nevertheless, the proportion of patients needing these procedures could have decreased in case that MS prevalence has increased similarly as has been observed in the regional prevalence studies in Finland and in the other Nordic countries [1–4,24].

During the follow-up period, the total amount of patients eligible for reimbursement of symptomatic MS drugs (not including immunomodulatory agents) from the Social Insurance Institution (KELA) has doubled from 3820 to 7643. In the end 2004, there was only one reimbursement category for immunomodulatory MS drugs (interferon-β, glatiramer acetate) and this was granted to 2447 patients. By the end of 2014, also natalizumab, fingolimod, teriflunomide, dimethylfumarate and alemtuzumab were available. Natalizumab and alemtuzumab are not reimbursed by KELA but from the hospital budgets in Finland. In 2014, a total of 3795 patients were reimbursed by KELA for interferons, glatiramer acetate, teriflunomide or dimethylfumarate (codes 303 or 157) and 524 for fingolimod (code 164) [27]. Although some patients had been granted eligibility for several of the reimbursement codes, almost a doubling in the number of

patients granted a reimbursed DMTs seems to have happened during our study period.

Natalizumab became available in Finland 2006 and its use increased steadily until 2012, when 400 patients were treated with natalizumab. By the end of year 2014, use of natalizumab had decreased to 300 patients. Alemtuzumab did not become available in Finland until December 2013 and our results have not likely been affected by its use. Reimbursement data for MS drugs was available from 2008 and increased comparatively little (from 37,934,080 € in 2008 to 38,361,484 € in 2014; source: KELA) with the nearly 1.3 M€ decrease in hospital costs during the study period appearing more consequential.

Limitations of this study include its retrospective design and reliance on solely data retrieved from an administrative registry. However, Finnish CRHC has been found to be reliable for data collection [28]. The impact of specific comorbidities on the LOS and mortality was not evaluated due to challenges in consistently identifying comorbidities over the entire study period. There was no comparison group in our study making definitive statements limited. We did not have access to death register data and therefore overall mortality trends in MS patients during the time period studied need to be addressed in more detail in the future.

We conclude that hospital admission rates and costs have markedly declined during an 11-year observation period from 2004 to 2014 in Finnish MS patients. Proportion of admission related to infections has increased and they are associated with longer hospitalizations and increased in-hospital mortality pointing out the importance of infection prevention. Intermittent follow-up of these rates is an important component of a comprehensive cost-effectiveness and safety evaluation of developing MS therapies.

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Disclosure statement

A.-L.P.: has received congress fee covering by Sanofi Genzyme. J.O.T.S.: has received travel grants and congress fee covering (Orion Corporation, Abbvie, Lundbeck, Merck Serono, Sanquin) and holds shares (Orion Corporation). M.S.-H.: has received congress fee covering, investigator fees and honoraria for lectures or advisory boards (Biogen, Merck, Novartis, Roche, Sanofi- Genzyme, Teva). P.R.: has received congress fee covering (Roche, The Finnish Innovation Fund Sitra). V.K.: none.

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