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Hospitalization is associated with subsequent disability in multiple sclerosis

Allan Garland[a,b,c], Luanne M. Metz[d,e], Charles N. Bernstein[a,f], Christine A. Peschken[a,b], Carol A. Hitchon[a], Ruth Ann Marrie[a,b,*]

[a] Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Canada
[b] Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Canada
[c] Manitoba Centre for Health Policy, Winnipeg, Canada
[d] Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada
[e] Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
[f] IBD Clinical and Research Centre, University of Manitoba, Winnipeg, Canada

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ABSTRACT

Background: Although an increasing amount of research has evaluated interactions between MS and comorbid chronic disease, few data exist regarding the interactions between MS and acute illness. As compared to age and sex-matched persons without MS, persons with MS experience higher rates of hospitalization and critical illness, and higher mortality rates and health care utilization following critical illness. We aimed to determine whether acute illness requiring hospitalization is associated with progression of multiple sclerosis (MS).

Methods: We conducted this population-based, retrospective cohort study by linking data from the regional MS Clinic in Calgary, Canada with the Canadian Discharge Abstract Database to identify non-obstetric hospitalizations. We included individuals with a confirmed diagnosis of MS, at least one recorded Expanded Disability Status Scale (EDSS) measurement, and known age of symptom onset of age 10 years or older. Using data from 2009 to 2014, we used generalized linear models with generalized estimating equations to establish the association within individuals between hospitalization and the time course of MS-related disability (as measured by the EDSS), adjusting for sex, age, disease course at onset, and use of disease-modifying therapies.

Results: We included 2104 individuals with MS in the analysis, who had a median of 4 EDSS measurements each. Of these 491 (23.3%) had at least one hospitalization. Most subjects were female, with a relapsing disease course at onset, and a mean (SD) age at symptom onset of 33.0 (10.0) years. The underlying rate of disability progression averaged 0.9 EDSS points per decade. Following hospitalization, there was a step increase in EDSS, averaging 0.23 points, equivalent to 2.5 years of time-related disease progression. Hospitalization did not alter the subsequent temporal rate of disability progression. The findings did not differ in those hospitalized for MS versus other reasons.

Conclusions: Acute illness requiring hospitalization is associated with a worsening of MS-related disability.

1. Introduction

Many people with a given chronic illness have comorbid chronic conditions (van den Akker et al., 1998; Broemeling et al., 2008). In multiple sclerosis (MS), comorbidities are now recognized to influence the length of the delay between MS onset and diagnosis, disability progression, use of disease-modifying therapy, health care utilization and mortality (Marrie et al., 2016; Zhang et al., 2016). Although an increasing amount of research has evaluated interactions between MS and comorbid chronic disease few data exist regarding the interactions between MS and acute illness. As compared to age and sex-matched persons without MS, persons with MS experience higher rates of hospitalization and critical illness, and higher mortality rates and health care utilization following critical illness (Marrie et al., 2014a, 2014b, 2015a, 2015b; Karamyan et al., 2016).

However, the interactions between chronic and acute illness are likely to be bidirectional. For example, in older adults cognitive impairment increases the risk of pneumonia, and pneumonia accelerates the progression to dementia (Shah et al., 2013). The effects of intercurrent acute illness on MS are poorly understood. Therefore, we aimed to evaluate the association between acute illnesses requiring hospitalization and the subsequent progression of MS-related disability. We hypothesized that such acute illnesses would result in both acquisition of disability following hospitalization, and that the subse-

* Correspondence to: Health Sciences Centre, GF 543- 820 Sherbrook Street, Winnipeg, MB, Canada R3A 1R9.
E-mail address: rmarrie@hsc.mb.ca (R.A. Marrie).

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quent progression of disability would be greater than before hospitalization.

2. Materials and methods

This was a retrospective cohort study conducted using two population-based data sources from the Calgary Health Region of the Canadian province of Alberta, population 1.54 million. We linked two existing databases, both obtained from the Canadian Institute for Health Information (CIHI), the Calgary MS Clinic Database (CMSD) and the Canadian Discharge Abstract Database (DAD). The University of Manitoba Health Research Ethics Board approved the study.

2.1. Calgary MS clinic database

The Calgary MS Clinic provides care to 98% of persons with MS in the surrounding region. Diagnoses of MS are confirmed by the treating neurologist based on the prevailing diagnostic criteria at the time of diagnosis (Poser et al., 1983; McDonald et al., 2001; Polman et al., 200, 2011). The Calgary MS Clinic Database (CMSD) captures standardized demographic and clinical information regarding all persons with MS seen in the clinic including a unique patient identifier, date of birth, sex, date of MS symptom onset, and disease course at onset (relapsing, progressive or unknown). The date of each clinic visit is recorded as well as disability status as measured using the Expanded Disability Status Scale (EDSS), and the use of disease-modifying therapies. The EDSS is a physician-scored measure used as the gold standard for disability progression in MS clinical trials. It is scored from 0 (no disability) to 10 (death due to MS). A score of 6 indicates the need for unilateral assistance (e.g. cane), while a score of 6.5 indicates the need for bilateral assistance (e.g. crutches), and a score of 7.0 indicates wheelchair use (Kurtzke, 1983). The EDSS scores are recorded by experienced MS physicians and trainees using a standardized scoring form. The MS physicians are formally trained to do the EDSS and certified. If a trainee is involved in assessing the individual with MS, this is verified by the attending neurologist. Data were available for clinic visits from September 21, 2009 to March 31, 2014.

2.2. Discharge abstract database

The DAD contains information about every hospitalization in Canada, excluding those in Quebec (Canadian Institute for Health Information, 2014a; Canadian Institute for Health Information, 2014b). Data are collected by rigorously trained personnel in each hospital, using uniform definitions and collection methods, regardless of the site of care or reason for admission. Further validation and data cleaning are performed by the provincial health departments, and subsequently by CIHI. We obtained DAD records of all discharges from acute care hospitals for the period April 1, 2005, to March 31, 2015, for all the individuals in the CMSD. This allowed us to identify hospitalizations among participants in the CMSD even if they occurred outside Alberta. Variables include a unique patient identifier, sex, date of birth, postal code, dates of admission and discharge, whether the admission was elective vs. emergent/urgent, up to 25 hospital diagnoses in International Classification of Disease (ICD)-10-CA format, whether the hospitalization included any time in an intensive care unit (ICU), and post-hospital disposition. The DAD includes separate records when an individual is directly transferred between hospitals, therefore we combined such records into episodes of hospital care as described elsewhere, allowing a maximum difference in admission dates of 24 h (Fransoo et al., 2012).

2.3. Study population and period

We merged the two datasets deterministically using the scrambled unique identifier provided by CIHI for this project. Inclusion criteria included: (i) a confirmed diagnosis of MS, and (ii) at least one recorded EDSS measurement (n = 3532). Subjects were excluded if their date of symptom onset was missing because this was used to calculate disease duration, or if age at symptom onset was < 10 years (Fig. e-1). Exclusion criteria for individual EDSS measurements were: values predating the listed date of symptom onset, or within 120 days of the end of the DAD data because hospitalization records were dated by discharge dates, and the 99th percentile of hospital length of stay in this dataset was 120 days. Finally, to minimize confounding due to effects of prior hospitalizations, we required that the first EDSS measurement used was not predated by a hospitalization within five prior years, which also excluded all measurements before April 1, 2010.

2.4. Variables

The primary outcome was the EDSS, while the primary exposure of interest was an inpatient, non-obstetric, hospitalization. Obstetric admissions were removed from the DAD dataset by CIHI using obstetric-related diagnosis and procedure codes (Table e-1). Covariates included in this analysis were age at symptom onset (continuous), sex (male as reference group), whether the reason for admission was for MS or not based on whether MS was listed as the most responsible hospital diagnosis (ICD-10-CA diagnosis code G35), clinical course at onset (relapsing [reference group], progressive, unknown/not recorded), whether a disease-modifying therapy was being used at the time of each EDSS assessment, and socioeconomic status (SES, continuous). We linked the first three digits of the postal code to the 2011 Canadian census to derive area-level median household income as a measure of SES.

2.5. Statistical analysis

Clinical and demographic characteristics were summarized using frequency (percent), mean (standard deviation) or median (interquartile range [IQR]) as appropriate. We conducted the multivariable analysis using a generalized linear model with generalized estimating equations (GEE) to account for clustering of the repeated EDSS measures within individuals (Hardin and Hilbe, 2003). The model was parameterized to estimate three key aspects of the trajectory of EDSS over time, starting from MS symptom onset. First was a slope representing the rate of change of EDSS during the whole study interval for those who had no hospitalizations; this same slope also applied to the time from MS onset until right before the first hospitalization for those who had any hospitalizations during the study interval. Second, for those who had any hospitalizations during the study interval, we allowed for a possible step change in EDSS from before to after the hospitalization. Finally, for those who had any hospitalizations during the study interval, we estimated a slope representing the change in EDSS over time after the hospitalization, which was allowed to differ from that before hospitalization. The core of the analysis was to assess whether the pre-hospital to post-hospital EDSS step change and slope change were statistically and clinically significant.

We utilized an identity link and an exchangeable correlation matrix based on observed pairwise correlations of EDSS values that all ranged from 0.71 to 0.89. GEE models generate effect estimates that are population averages of within-subject and between-subject effects over time (Neuhaus and Kalbfleisch, 1998). Since we were interested in assessing the change in EDSS related to hospitalization *within* individuals, we created separate “within-patient” and “between-patient” components of: (a) time from symptom onset (TIME), and (b) an indicator variable identifying whether the EDSS was measured pre- or post-hospitalization (PREPOST) (Neuhaus and Kalbfleisch, 1998; Begg and Parides, 2003). We also created interaction terms between these components of TIME and PREPOST. For this study, the coefficients of main interest are the within-patient versions, which have the following meanings: (a) $TIME_{within}$ is the slope of the temporal change in EDSS for