ORIGINAL ARTICLE

A population-based study comparing multiple sclerosis clinic users and non-users in British Columbia, Canada

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Keywords:
clinical research, databases, epidemiology, health services, multiple sclerosis

Received 11 December 2015
Accepted 2 February 2016

European Journal of Neurology 2016, **23:** 1093–1100

doi:10.1111/ene.12990

Background and purpose: Much clinical knowledge about multiple sclerosis (MS) has been gained from patients who attend MS specialty clinics. However, there is limited information about whether these patients are representative of the wider MS population. The objective of this study was to compare incident MS cases who were MS clinic users to non-users of the specialty MS clinics in British Columbia, Canada.

Methods: This was a retrospective record-linkage cohort study using prospectively collected data from the British Columbia Multiple Sclerosis database and province-wide health administrative databases.

Results: There were 2841 incident MS cases between 1996 and 2004 including 1648 (58%) that had registered at an MS clinic ('clinic cases') and 1193 (42%) that had not ('non-clinic cases'). Gender and socioeconomic status distributions were similar; however, non-clinic cases were older, accessed health services more frequently and had a higher burden of comorbidity than clinic cases. Only 1% of the non-clinic cases had filled a prescription for an MS-specific disease-modifying therapy, compared to 51% of the clinic cases.

Conclusions: Our findings have several important implications: even within a publicly funded healthcare system, a high proportion of individuals with MS may not access a specialty MS clinic; the needs of MS patients managed in the community may differ from those referred to an MS clinic; findings from studies involving clinic-based MS cohorts may not always be generalizable to the wider MS population; and access to population-based health administrative data offers the opportunity to gain a broader understanding of MS.

Introduction

Multiple sclerosis (MS) is a chronic neurological disorder characterized by inflammation and degeneration of the central nervous system. Much of the medical literature and related knowledge surrounding MS is based on information gained from patients who attend MS specialty clinics affiliated with academic centres, whether through observational studies or enrolment in clinical trials [1–4]. A major advantage of studying these cohorts [5–10] is the confidence in the diagnosis of MS and, often, the availability of detailed MS-specific clinical information. Whether or not these clinic patients are representative of the wider population of people with MS, however, is largely unknown [10,11]. An understanding of the differences and similarities between MS clinic and non-clinic users would be helpful and relevant to clinicians and researchers who recruit from or study clinic-based cohorts as well as healthcare planners and related stakeholders.

Routinely collected population-based health administrative claims data represent a powerful resource for the study of health outcomes and health utilization and these data are being validated and used for research purposes with greater frequency [12–18].

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EUROPEAN JOURNAL OF NEUROLOGY

Using data from the British Columbia Multiple Sclerosis (BCMS) database and province-wide health administrative claims, incident MS cases who attended a specialty MS clinic in British Columbia (BC), Canada, were compared with incident MS cases from the BC general population who did not register at one of the clinics. It was hypothesized that these MS cases may differ with respect to their demographic and clinical features: specifically sex, age at onset, socioeconomic status (SES), use of medications [including disease-modifying therapies (DMTs)] and health services (hospitalizations and physician visits), and comorbidities.

Methods

This was a retrospective record-linkage cohort study based on prospectively collected patient data from the BCMS database and province-wide health administrative databases. Established in 1980, the BCMS database includes information from people who first attended one of the four MS clinics in BC. These four clinics were the only source of specialty MS care (including access to the MS DMTs under the BC government's health-coverage scheme) in the province until 1 January 2005, when a fifth clinic opened. Data for all patients who first visited a BC MS clinic by the end of 2004 were linked via their personal health number, a unique lifelong identifier, to their individual-level information contained within several province-wide health administrative databases. The Medical Service Plan [19] payment information file provided information on physician visits and the Discharge Abstract Database [20] provided data on hospital visits. Both databases included diagnoses coded using the International Classification of Diseases, Ninth or Tenth Revision (ICD-9/10), diagnostic codes. PharmaNet [21], BC's province-wide prescription database, provided data on prescriptions dispensed, coded according to Health Canada's Drug Identification Number (DIN) classification system. The BC Vital Statistics Agency database [22] provided mortality data and, together with the BC Ministry of Health's Registration and Premium Billing Files [23], enabled confirmation that an individual was alive and resident in BC. Finally, Census Geodata provided an area-level measure of SES based on the first three characters of the postal code and aggregated neighbourhood level income data [24]. Data were available in all sources until 31 December 2008; once the data were linked the personal identifiers were removed. The linkages were facilitated by Population Data BC, a pan-provincial comprehensive data platform (http://www.popdata.bc.ca).

Incident cases of MS in the BC general population were identified using a validated algorithm of hospital and physician diagnostic codes [14,25]. The MS case definition was ≥7 hospital or physician claims specifically for MS (ICD 9 code 340 or ICD 10 code G35) for people who were resident in BC for more than 3 years following their first demyelinating disease claim (see Appendix S1, Table S1, for the relevant ICD codes) and ≥3 MS claims for those with 3 years of residency or less [14]. To meet the incident case definition, each case had to be resident in BC for at least 5 years before their first demyelinating disease claim; this first claim date was considered the index date for both the non-BCMS clinic and the BCMS clinic cases. Incident cases between 1996 and 2004 (the last year of registration as a confirmed MS case in the BCMS cohort for this study) were examined.

The incident MS cases that were ever seen at a BCMS clinic ('clinic') were compared with incident cases that had never attended a BCMS clinic ('non-clinic') during the entire study period (1996–2004). Demographic comparisons were made by sex, year, age and quintile of neighbourhood SES at the index date. Dispensation of at least one prescription for a DMT, including interferon β-1b (IFNβ-1b), IFNβ-1a, glatiramer acetate or natalizumab, at any time during follow-up was compared, as was the average time to reach the case definition (third claim for patients with ≤3 years of follow-up, or seventh claim for those with >3 years of follow-up), the number of distinct all-cause hospitalizations and the number of physician visits during follow-up. An additional analysis was performed in which pregnancy-related hospitalization claims were excluded on the basis that they are not representative of a medical illness, unlike other hospitalizations. Hospitalizations specifically for MS (as the primary diagnosis, or listed anywhere on the discharge report) were also compared. The presence of specific comorbidities in the 8 years surrounding the index date (4 years prior and 4 years post) was examined. Comorbidities were selected based on their high prevalence amongst people with MS and the availability of validated algorithms to identify them using health administrative data in MS populations [12,13,26]. The following comorbidities were identified by validated algorithms [12,13,26] based on ICD-9/10 diagnostic codes from physician billings and hospital admissions (Appendix S1, Table S2) and compared between the clinic and non-clinic cases: hypertension, hyperlipidaemia, diabetes, chronic lung disease, migraine, and mood or anxiety disorders. Finally, the total number of distinct prescription medication classes dispensed in the year following the index date was compared between the clinic and non-clinic cases as a comple-

mentary and more global measure of comorbidity. A similar measure was shown to be the best predictor of future physician visits and healthcare expenditures relative to five other measures of comorbidity in a cohort of older adults in BC [27]. The DINs were used to group medications according to the World Health Organization Anatomic Therapeutic Chemical (WHO-ATC) [28] classification system; the second level (main therapeutic group) was used to define unique drug classes.

Statistical analysis

Comparisons between clinic cases and non-clinic cases were assessed using Pearson's chi-squared test for categorical variables and the Student's *t* test or Wilcoxon rank sum test for continuous variables. The number of hospitalizations and physician visits during follow-up were analysed using negative binomial regression with findings reported as incidence rate ratios with 95% confidence intervals. To account for the differences in follow-up time, the logarithm of the follow-up time was included as an offset. The presence of each of the comorbidities of interest during the 8 years surrounding the index date (4 years before and 4 years after) was compared between clinic and non-clinic cases using logistic regression. All cases had full data for the 4 years prior to the index date, but those with less than 4 years of follow-up after the index date were excluded from the comorbidity comparisons. As a sensitivity analysis, the potential influence of excluding the cases with insufficient follow-up was assessed by restricting the comparison of comorbidities to the 4-year time period prior to the index date. Findings were reported as odds ratios with 95% confidence intervals. The count of distinct medication classes dispensed in the year following the index date was compared between the two groups using Poisson regression, with findings reported as rate ratios. All models were adjusted for age (continuous), sex and index year (continuous). Analyses were performed using SAS Statistical Software Package 9.4 (SAS Institute Inc., Cary, NC, USA).

This study was approved by the University of British Columbia's Clinical Research Ethics Board (approval # H10-01361). BC Ministry of Health, BC Vital Statistics Agency and BC PharmaNet approved access to administrative health data.

Results

There were 2841 incident MS cases in BC between 1996 and 2004; these included 1648 clinic cases (58%) and 1193 non-clinic cases (42%). The clinic cases represented 58%–66% of the total for each year between 1996 and 2003, dropping to 38% in the final year (2004). The proportion of men and women and distribution across the SES quintiles did not differ between the clinic and non-clinic groups. Although the clinic incident cases reached the administrative case criterion within a similar time period compared with the non-clinic incident cases, the clinic cases were approximately 5 years younger at the time of their incident claim (41 vs. 46 years old). Nearly half of the clinic cases had received a prescription for a DMT (51%) at some point during follow-up; not unexpectedly, this proportion was significantly greater than that seen with the non-clinic cases (1%). The characteristics of the clinic and non-clinic cases are shown in Table 1.

The non-clinic cases had higher rates of hospitalizations (all-cause, either with or without pregnancy-related admissions); however, when the analysis was limited to hospitalizations in which the primary diagnosis was specifically for MS, the non-clinic group had lower rates (Table 2). The same pattern emerged for physician visits, in which non-clinic cases had higher rates of physician service use in general, but significantly lower rates specifically coded as MS (Table 2).

Differences in comorbidities were also found amongst the 2650 patients (1600 clinic cases and 1050 non-clinic cases) with sufficient follow-up for this comparison (i.e. 4 years prior to and 4 years following their index date). After adjustment for age, sex and index year, the non-clinic cases had higher odds for meeting each of the definitions of hypertension, chronic lung disease, diabetes, and mood or anxiety disorder at some point during the 8 years surrounding the index date (Table 3), but the odds of hyperlipidaemia did not differ significantly between the two groups (Table 3). These findings were no different when the period for comorbidity measurement was restricted to the 4 years prior to the index date, with inclusion of all cases (data not shown). The non-clinic group had higher rates of comorbidity in general, as measured by the number of distinct prescription medication classes dispensed in the year following the index date (Table 3).

There were 87 clinic cases, the majority of whom had their incident claim in the most recent registration year (2004), who had not met the administrative claim definition by the end of administrative claims follow-up (2008) and were not included in either group for the main analyses. A repeat of the above analyses with inclusion of these cases, all of whom had been diagnosed with MS by an MS specialist neurologist, resulted in no changes to the findings or their interpretation (data not shown).

Table 1 Characteristics of the MS clinic and non-clinic cases

	Incident MS cases (1996–2004) (n = 2841)		
	Clinic cases n = 1648	Non-clinic cases n = 1193	P
Sex			
Females	1242 (75%)	878 (74%)	0.31[a]
Males	406 (25%)	315 (26%)	
Prescription filled for an MS disease-modifying drug at any time during follow-up	847 (51%)	13 (1%)	<0.001[a]
SES quintile[c]			
1 (low)	277 (17%)	209 (18%)	0.38[a]
2	286 (18%)	226 (20%)	
3	347 (22%)	257 (22%)	
4	342 (21%)	236 (20%)	
5 (high)	359 (22%)	226 (20%)	
Age at incident claim in years			
Median (1st quartile; 3rd quartile)	41.1 (33.4; 47.9)	45.8 (37.7; 54.9)	<0.001[b]
Index year			
1996	169 (10%)	116 (10%)	<0.001[a]
1997	212 (13%)	111 (9%)	
1998	184 (11%)	131 (11%)	
1999	196 (12%)	147 (12%)	
2000	205 (13%)	126 (11%)	
2001	207 (12%)	134 (11%)	
2002	191 (12%)	122 (10%)	
2003	175 (11%)	121 (10%)	
2004	109 (7%)	185 (16%)	
Time to meet case definition (years)[d]			
Median (1st quartile; 3rd quartile)	1.6 (0.7; 3.0)	1.7 (0.6; 3.8)	0.28[b]
Available follow-up time from index date (years)			
Median (1st quartile; 3rd quartile)	8.3 (6.3; 8.4)	7.3 (4.7; 9.9)	<0.001[b]

[a]Pearson's chi-squared test; [b]Wilcoxon rank sum test; [c]SES quintile, as measured at the index date, missing for 78 cases; [d]beginning of time period to meet case definition measured at index date.

Table 2 Comparison of health service utilization between MS clinic and non-clinic cases

	Incidence rate ratio (95% CI)	Adjusted incidence rate ratio[a] (95% CI)
Hospitalizations (all cause; excluding pregnancy)	2.05 (1.85–2.28)	1.73 (1.55–1.92)
Hospitalizations (all-cause; including pregnancy)	1.97 (1.78–2.17)	1.72 (1.56–1.90)
Hospitalizations (MS as primary diagnosis)	0.67 (0.52–0.89)	0.65 (0.49–0.86)
Hospitalizations (MS reported anywhere on the discharge report)	0.90 (0.76–1.08)	0.83 (0.67–0.96)
Physician visits (all cause)	1.24 (1.18–1.30)	1.14 (1.08–1.20)
Physician visits (MS specific)	0.49 (0.46–0.52)	0.43 (0.41–0.46)

CI, confidence interval. Reference group is the MS clinic group. Rate ratios >1 indicate a higher rate for non-clinic cases relative to clinic cases.
[a]Adjusted for sex, age and index year.

Discussion

The characteristics of individuals with definite MS who registered at an MS clinic and individuals who met an administrative definition of MS and had not registered at an MS clinic in BC, Canada, were compared and several differences were identified. People with MS who did not register at an MS clinic were older, accessed health services more frequently and had a higher risk of comorbidity than those registered with an MS clinic. In addition, whilst the groups were comparable in their sex distribution and SES, only 1% of the non-clinic patients had filled a prescription for an MS-specific DMT.

Our findings have several important implications: (i) even within a publicly funded healthcare system a high number of individuals with MS may not access an MS specialty clinic and may be managed in the

Table 3 Comparison of comorbidity between MS clinic and non-clinic cases

Specific comorbidity	Odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Chronic lung disease	1.70 (1.30–2.21)	1.66 (1.27–2.19)
Hyperlipidaemia	1.45 (1.03–2.03)	0.98 (0.68–1.40)
Hypertension	1.95 (1.57–2.44)	1.41 (1.11–1.78)
Diabetes	1.82 (1.39–2.39)	1.58 (1.19–2.10)
Migraine	1.21 (0.99–1.50)	1.34 (1.08–1.67)
Mood or anxiety disorder	1.24 (1.06–1.45)	1.25 (1.06–1.48)
General comorbidity	**Rate ratio (95% CI)**	**Adjusted rate ratio[a] (95% CI)**
Number of prescription classes dispensed in year following index date	1.17 (1.10–1.24)	1.08 (1.02–1.15)

CI, confidence interval. Reference group is the MS clinic group. Odds ratio or rate ratio >1 indicates higher odds for the non-clinic cases relative to the clinic cases. [a]Adjusted for sex, age and index year.

community; (ii) the needs of MS patients managed in the community may differ from those referred to an MS clinic, including management of comorbidity; (iii) depending on the research question, studies that use clinic-based MS cohorts may not be generalizable to those that do not seek MS specialist care; (iv) access to total population-based health administrative data offers the opportunity to gain a broader understanding of MS.

Using the validated administrative algorithm, approximately 60% of people who were newly diagnosed with MS (i.e. incident cases) and living in BC between 1996 and 2004 were estimated to be registered at one of the four specialty MS clinics in the province. In BC, MS clinics are part of the universal health programme and offer comprehensive care to people living with MS, including MS specialist neurologists and nurses, neuro-ophthalmologists, physiotherapists, psychiatrists and social workers. To attend a specialty MS clinic one must be referred by a physician. Importantly, these clinics are the only resource for DMT prescriptions under the BC government's reimbursement scheme; consequently, only 1% of the non-clinic cases were prescribed a DMT during the study period. Whilst prescribing patterns and drug reimbursement policies vary between jurisdictions, our findings may indicate that the population-based rates of DMT use, as reported in other studies (i.e. outside of BC), might be lower than previously thought [29–31].

The only other study, to our knowledge, that compared a group of MS cases that had attended an MS clinic to a group that had not was based in Lorraine, France, and focused on demographic and disease characteristics [11]. Similar to our findings, they found no differences in the sex distribution, but an older age at onset in the non-clinic cases. Age at MS symptom onset could not be captured from the administrative data, but the age at first demyelinating claim was 5 years older on average in the non-clinic group. It is possible that the non-clinic cases were older at MS symptom onset, but it is also possible that the findings indicate a delay in the medical recognition of MS [25,32–34]. As the non-clinic cases were more likely to have comorbidity, it is conceivable that their early MS symptoms were not noticed or misattributed to a comorbid condition, thereby contributing to a delayed diagnosis [33]. It is not possible to tell whether these individuals were less likely to be referred to an MS clinic or if they actively chose not to attend; however, it may represent a missed opportunity to offer treatment (pharmacological or non-pharmacological). It is also possible that having 'mild' disease may limit attendance at an MS clinic.

This is the first study to our knowledge to compare comorbidities and health service utilization between clinic and non-clinic MS cases. The non-clinic MS cases were burdened with more comorbidities than the MS clinic cases, even after accounting for the age difference. They were more likely to have hypertension, diabetes, chronic lung disease, migraine, or a mood or anxiety disorder around the index date as well as a higher burden of global comorbidity, based on prescriptions filled. The importance of comorbidities in chronic diseases such as MS has been highlighted recently [12,26,35]. Emerging work indicates that comorbidity is associated with a delayed MS diagnosis and a higher level of disability at diagnosis [33]. Our results suggest that patients who accessed a specialty MS clinic had less comorbidity; thus, estimates from a clinic-based sample may underestimate the true burden of comorbidity in MS. This emphasizes the importance of broader population-based estimates [12] that are derived from both MS clinic and non-clinic users.

Health service utilizations in the non-clinic group for all-cause hospitalizations and physician visits were higher than in the clinic group, and these were independent of age. In contrast to this, it was observed that the clinic patients had a higher rate of physician visits and hospitalizations specifically for MS. Whilst the former is not unexpected in a group of patients accessing an MS clinic, the reason for their higher rate of hospitalizations for MS is less obvious. It is possible that the MS clinic cases generally have more active disease [36] (e.g. more frequent relapses) [36] for which they are more likely to seek care and perhaps require hospitalization.

Study limitations included an inability to access and compare MS-specific clinical features across the MS clinic and non-clinic patients, such as disease course (i.e. relapsing-onset or primary-progressive) or relapse frequency. There was insufficient information to estimate how far the cases resided from an MS clinic; distance may have influenced attendance at clinic. Study strengths included a large cohort of 2841 cases, comprising all incident MS patients in the province of BC over a 9-year incidence period. Our study also captured longitudinal data, with 18 years of follow-up, and access to extensive population-based administrative health data linked to a province-wide MS clinical database. Furthermore, the incident MS cases and the specific comorbidities were identified using algorithms that were tested and validated in Canadian MS cohorts [14,25].

The MS algorithm was estimated to have a sensitivity of 88% and a specificity of 68% (with a confirmed diagnosis of MS by an MS specialist neurologist as the gold standard) amongst all individuals in Nova Scotia, Canada, with at least one demyelinating disease claim [14]. Specificity would naturally increase considerably amongst the general population, for whom the vast majority have never had a demyelinating claim. Using a similar seven claim definition in the Canadian province of Ontario yielded an estimated specificity of 100% [37]. Nonetheless, it is possible that inclusion of a small number of false positive cases in the non-clinic group may have contributed to some of the differences observed, although this would be unlikely to be high enough to influence interpretation of findings. No false positive MS cases would have been included in the MS clinic group because all included cases had been diagnosed with definite MS by a specialist MS neurologist using the most current internationally recognized criteria; 1648 of 1735 clinically confirmed MS cases were correctly identified by the algorithm which indicates that the algorithm has very high sensitivity in the BC MS population. The 87 cases that were not identified by the algorithm were more likely to have had their incident claim in 2004, and therefore had less follow-up time or opportunity to meet the administrative case definition.

The BC clinical database was broadly representative of new cases of MS in the province of BC, in that it captured the majority of incident MS cases, and the sex distribution and SES were comparable to the wider MS population. Importantly, nearly all of the patients who received a DMT were captured by the BCMS database, which allows for comprehensive monitoring of the long-term safety and effectiveness of these drugs. Our results indicate that people who attended MS clinics were younger at their first MS-related claim, suggesting an earlier age at first medical recognition of their MS. Studies of clinic populations have been enormously valuable in developing therapies, understanding the natural history of MS and generally advancing our knowledge of this complex disease; however, the MS community should remain mindful that a broader MS population exists and may differ in both subtle and important ways to those assessed in MS specialty clinics.

Acknowledgements

This study was supported by the Canadian Institutes of Health Research (CIBG 101829) and the Rx&D Health Research Foundation. We thank the BC Ministry of Health, BC Vital Statistics Agency and BC PharmaNet for approval and support with accessing provincial data; and Population Data BC for facilitating approval and use of the data. All inferences, opinions and conclusions drawn in this paper are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

Disclosure of conflicts of interest

Kyla McKay, Feng Zhu, Lorne Kastrukoff and Elaine Kingwell report no disclosures. Helen Tremlett is funded by the Multiple Sclerosis Society of Canada (Don Paty Career Development Award); is a Michael Smith Foundation for Health Research Scholar and the Canada Research Chair for Neuroepidemiology and Multiple Sclerosis. She has received research support from the National Multiple Sclerosis Society, the Canadian Institutes of Health Research and the UK MS Trust; speaker honoraria and/or travel expenses to attend conferences from the Consortium of MS Centres (2013), the National MS Society (2012, 2014), Bayer Pharmaceuticals (2010), Teva Pharmaceuticals (2011), ECTRIMS (2011, 2012, 2013, 2014), UK MS Trust (2011), the Chesapeake Health Education Program, US Veterans Affairs (2012), Novartis Canada (2012), Biogen Idec (2014) and the American Academy of Neurology (2013, 2014, 2015). Unless otherwise stated, all speaker honoraria are donated either to an MS charity or to an unrestricted grant for use by her research group. Ruth Ann Marrie receives research funding from CIHR, Public Health Agency of Canada, Manitoba Health Research Council, Health Sciences Centre Foundation, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Rx&D Health Research Foundation and the National Multiple Sclerosis Society, and has conducted clinical trials funded by sanofi-aventis.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1:
Table S1. Diagnosis (ICD-9 and ICD-10) codes used to identify MS and demyelinating diseases of the central nervous system.
Table S2. Diagnosis (ICD-9 and ICD-10) codes and algorithms used to identify comorbidities.

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