Psychiatric Comorbidity During the Prodromal Period in Patients With Multiple Sclerosis

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Abstract

Background and Objectives

Psychiatric morbidity is common after a multiple sclerosis (MS) diagnosis. However, little is known about psychiatric comorbidity during the prodromal phase (before MS onset). To compare the prevalence and relative burden of psychiatric morbidity in individuals with MS with matched controls before MS onset.

Methods

Using linked administrative and clinical data from British Columbia, Canada, we identified cases with MS through a validated algorithm or from neurologist-diagnosed MS clinic attendees. Cases were matched by age, sex, and geographical location with up to 5 general population controls. We identified psychiatric morbidity through a validated definition and determined its prevalence in cases/controls in the 5 years before the first demyelinating claim of cases with MS ("administrative cohort") or symptom onset ("clinical cohort") and estimated case/control prevalence ratios with 95% CIs. We also compared the yearly number of physician visits for psychiatric morbidity, visits to psychiatrists, psychiatric-related admissions, and psychotropic dispensations pre-MS onset in cases/controls regardless of whether psychiatric morbidity algorithm was fulfilled using negative binomial regression fitted through generalized estimating equations; results were reported as adjusted rate ratios with 95% CIs. We assessed yearly trends through interaction terms between cases/controls and each year pre-MS onset.

Results

The administrative cohort comprised 6,863/31,865 cases/controls; the clinical cohort comprised 966/4,534 cases/controls. Over the entire 5-year period pre-MS onset, 28.0% (1,920/6,863) of cases and 14.9% (4,738/31,865) of controls (administrative cohort) had psychiatric morbidity, as did 22.0% (213/966) of clinical cases and 14.1% (638/4,534) controls. Psychiatric morbidity prevalence ratios ranged from 1.58; 95% CI 1.38–1.81 (clinical cohort) to 1.91; 95% CI 1.83–2.00 (administrative cohort). In the administrative cohort, health care use was higher for cases in each year pre-MS onset (all 95% CIs >1); physician visits were 78% higher in year 5 pre-MS onset and 124% 1 year before; visits to psychiatrists were 132% higher in year 5 and 146% in year 1; hospitalizations were 129% higher in year 5 and 197% in year 1; and prescription dispensations were 72% higher in year 5 and 100% in year 1. Results were not significant in the clinical cohort.

Discussion

Psychiatric morbidity represents a significant burden before MS onset and may be a feature of the MS prodrome.

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Glossary

Introduction

Psychiatric comorbidities, including depression and anxiety, are common in multiple sclerosis (MS), and prevalence rates are higher than expected in the general population.[1,2] However, while much work has focused on people who have already developed MS, little is known about psychiatric comorbidity before medical recognition of MS.[3-6]

In recent years, mounting evidence has pointed to the existence of a prodromal period in MS.[4,7,8] Defined as "early symptoms indicating the onset of a disease or illness," studies have shown that the MS prodrome is measurable at the level of health service use.[4,5,7,9-13] These studies demonstrate that individuals with MS steadily increased their health care use at least 5 years before their first "classic" MS symptom[5-7,9] or first demyelinating event,[5,6,9-13] when compared with a matched general population. In addition, higher serum neurofilament light levels, a biomarker of neuroaxonal damage, can be found up to 6 years before a first classical MS symptom compared with unaffected matched controls, providing biological support for the MS prodrome.[14]

A psychiatric component of the MS prodrome has also been observed. In the 5 years before MS onset, individuals developing MS were approximately 50% more likely than matched individuals from the general population to visit a psychiatrist and to fill a prescription for a drug related to the nervous system, which included the antidepressants.[6] While intriguing, much remains unknown. A better understanding of the extent and burden of early psychiatric morbidity in MS is needed, especially because it can negatively affect quality of life, affect disability progression,[15,16] and possibly increase mortality risk.[17] In addition, expanding our knowledge of the MS prodrome may allow for earlier disease recognition and treatment.[8] The aim of our study was to describe the prevalence and relative burden of psychiatric morbidity in individuals with MS in the 5 years leading up to MS onset relative to matched controls.

Methods

Study Design and Data Sources

This matched retrospective cohort study was conducted in the province of British Columbia (BC), Canada. All residents in BC have access to publicly funded health care services. We accessed a data platform of prospectively collected health administrative and clinical information from the province that is captured electronically and is accessible for research. Data were linked using each individual's unique personal health care number and provided information on virtually every health encounter for all BC residents. Combined, the data platform captured details regarding physician visits (Medical Services Plan [MSP] Payment Information File)[18] and hospitalizations (Discharge Abstract Database),[19] with related diagnoses coded using the *International Classification of Diseases* (ICD) 9/10 system. Medications dispensed at community or outpatient pharmacies in BC were also captured (through PharmaNet),[20] coded by their drug identification number and mapped to the Anatomical Therapeutic Chemical (ATC) classification system 5th level. Demographics, socioeconomic and residency status (MSP Registration and Premium Billing Files),[21] and death dates (Vital Statistics)[22] were also available. Socioeconomic status (SES) estimates were obtained by using an algorithm from Statistics Canada combining each individual's postal code with census-derived mean neighborhood income data measured in quintiles.[23] Data obtained from the BC MS Clinical database included the date of MS symptom onset and disease course (relapsing vs progressive onset), as recorded by an MS neurologist during a routine visit to one of BC's 4 MS clinics. All data were deidentified before analyses.

Study Cohorts

Two cohorts were created—an "administrative" cohort and an MS clinic–derived "clinical" cohort. The administrative cohort comprised all persons with MS fulfilling a validated algorithm requiring ≥3 MS-specific hospital, physician, or prescription claims derived from the health administrative data (eTable 1, links.lww.com/WNL/D118).[24] This algorithm has a sensitivity of 99.5%, a specificity of 98.5%, a positive predictive value of 99.5%, and a negative predictive value of 97.5%.[25] An individual's first demyelinating disease-related claim formed the "administrative index date." The clinical cohort comprised individuals diagnosed with MS in one of 4 BC's MS clinics. These individuals were then linked to their health administrative data. This administrative information was used to assess the psychiatric-related outcomes (outlined further). The date of MS symptom onset, as recorded by an MS neurologist based on a person's medical history, formed the "clinical index date." Thus, the index date definitions for the clinical and the administrative cohorts differed; the former is captured retrospectively (MS symptom onset) during patient contact with an MS clinic and the latter prospectively or in "real time" as the patient moves through the health system (e.g., as a demyelinating-related ICD code). The period before MS symptom onset may better represent the "true" MS prodrome because not every symptom of possible early MS necessarily leads to health care system use or to a record of a demyelinating disease-related claim. All individuals within each cohort were matched with up to 5

controls from the general population (who had no MS or other demyelinating disease-related claims or prescriptions filled for MS-specific DMDs over their entire registered period) by sex, exact year of birth, and postal code at the index year. Controls were randomly selected without replacement from the BC general population. Each control was assigned the same index date as their matched patient with MS. To select incident individuals with MS, both patients with MS and their matched controls were required to be resident in BC for ≥90% of the days in each of the 5 years before the index date. The administrative and clinical cohorts were not mutually exclusive. However, because the definition of index dates differed, each cohort was analyzed separately. Motivated by our prior work,[5,7] we capitalized on an already available dataset; all data were available from January 1, 1996, through until December 31, 2013, for the administrative cohort and through until December 31, 2008, for the clinical cohort. See "Data availability" for details regarding data access.

Outcomes

First, the presence of any psychiatric morbidity (depression, anxiety, bipolar disorder, or schizophrenia) was identified by applying a validated case definition requiring ≥1 relevant psychiatric-related hospital or ≥5 physician claims (on different days) within a 5-year period, with at least 1 claim falling within 5 years preindex date (eTable 2, links.lww.com/WNL/D118).[26] The psychiatric morbidity was considered present during the earliest claim and thereafter. Second, we determined the relative burden of psychiatric morbidity in each of the 5 years preindex dates regardless of whether individuals fulfilled the algorithm for psychiatric morbidity, according to the yearly number of the following: (1) physician visits for any psychiatric morbidity (i.e., any code summarized in eTable 2); (2) visits to psychiatrists, (3) psychiatric-related hospital admissions (eTable 2), and (4) "psychotropic" prescriptions filled (counts, based on the total number of prescriptions filled [ATC fifth level], which were then grouped and reported by pharmacologic class [ATC third level], eTable 3). These yearly numbers were compared between patients with MS and controls. To prevent double counting, physician visits occurring on the same day and with the same *ICD* code for the same individual were considered as a single visit. Overlapping hospital stays were also counted as 1 hospitalization. Similarly, any prescriptions filled on the same day and with the same drug identification number were counted once. Psychiatric morbidity outcomes were assessed using the same approach in both the administrative and clinical cohorts.

Statistical Analysis

The characteristics of the administrative and clinical cohort were summarized at the respective index dates. For patients with MS and matched controls, we estimated the prevalence of psychiatric morbidity for each of the 5 years before the index dates. We also used a conditional logistic regression model to examine the association between the presence of any psychiatric morbidity and MS over the entire 5-year period (with each strata containing 1 case and its matched controls).

To avoid overestimation of the association when the outcome of interest was common (≥10%), we applied the following formula to convert odds ratio (OR) to prevalence ratio with 95% CI: prevalence ratio = OR/([1 − prevalence in the nonexposed group] + [prevalence in the nonexposed group × OR]). OR CIs were transformed to prevalence ratio CIs applying the same formula as well.[27] In addition, the association between MS and the number of yearly physician visits for any psychiatric morbidity, visits to psychiatrists, psychiatric-related hospital admissions, and "psychotropic" prescriptions was examined using negative binomial regression models, fitted through generalized estimating equations with an unstructured working correlation matrix. To take into account any variation in the time spent as a resident in the province during a given year between participants, the logarithm of the time was included as an offset in all negative binomial regression models. To assess the temporal trends, an interaction term between patients with MS and controls and each year of the 5-year prodromal period (−1 to −5) was also included, with "−1" indicating the year before the index date and "−5" indicating the fifth year before the index date. Findings were expressed as adjusted rate ratios (aRRs) with the corresponding 95% CIs. Age at the index date (continuous), sex, SES (quintiles; Q1–5; Q1 as a reference), and index year (as a continuous variable) were included as covariates in the models.

All analyses were conducted using R (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Clinical Research Ethics Boards at the University of British Columbia (#H08-01544 and #H93-70103).

Data Availability

Because we are not the data custodians, we are not authorized to make these data available. With the appropriate approvals, data may be accessed through the Population Data British Columbia. For this study, data access was permitted through until end/February 2023 to perform the following: present findings at the Americas Committee for Treatment and Research in Multiple Sclerosis Forum, San Diego 2023 (selected for a platform presentation); complete this study; and submit for peer-review publication. This was in accordance with the BC Ministry of Health requirements surrounding data access. No further analyses or data linkages are permitted.

Results

The administrative cohort consisted of 6,863 patients with MS and 31,865 matched controls (Table 1). The clinical cohort included 966 patients with MS and 4,534 controls. In both cohorts, women represented more than 70% of the population. The average age at the index dates was higher in the administrative cohort relative to the clinical cohort

Table 1 Characteristics of Patients With Multiple Sclerosis and Matched General Population Controls in the Administrative and Clinical Cohorts, British Columbia, Canada

Characteristics (at the index date)	Administrative cohort		Clinical cohort	
	Patients with MS (n = 6,863)	Controls (n = 31,865)	Patients with MS (n = 966)[a]	Controls (n = 4,534)
Women, n (%)	5,039 (73.4)	23,311 (73.2)	728 (75.4)	3,398 (74.9)
Age, y, mean (SD)	44.9 (13.5)	44.7 (13.4)	37.0 (10.2)	36.9 (10.1)
Age group, n (%)				
<30 y	859 (12.5)	4,081 (12.8)	232 (24.0)	1,082 (23.9)
30–39 y	1,690 (24.6)	7,936 (24.9)	351 (36.3)	1,677 (37.0)
40–49 y	2,137 (31.1)	9,962 (31.3)	288 (29.8)	1,315 (29.0)
≥50 y	2,177 (31.7)	9,886 (31.0)	95 (9.8)	460 (10.1)
Socioeconomic status, n (%)				
1 (most deprived)	1,184 (17.2)	5,476 (17.2)	145 (15.0)	763 (16.8)
2	1,286 (18.7)	5,950 (18.7)	180 (18.6)	812 (17.9)
3 or missing[b]	1,563 (22.7)	7,022 (22.0)	237 (24.5)	1,045 (23.0)
4	1,465 (21.4)	6,826 (21.4)	194 (20.1)	962 (21.2)
5 (most affluent)	1,365 (19.9)	6,591 (20.7)	210 (21.7)	952 (21.0)
Index year, n (%)				
1996–2000	2,001 (29.2)	9,216 (28.9)	589 (61.0)	2,764 (61.0)
2001–2005	2,149 (31.3)	9,914 (31.1)	344 (35.6)	1,618 (35.7)
2006–2010	2,078 (30.3)	9,736 (30.6)	33 (3.4)	152 (3.4)
2011–2013	635 (9.3)	2,999 (9.4)	—	—
MS disease course, n (%)				
Relapsing-onset	N/A	—	904 (93.6)	—
Primary progressive	N/A	—	62 (6.4)	—

Abbreviations: MS = multiple sclerosis; N/A = not available.
[a] There were 24 (2.5%) cases identified in the clinical cohort that were not identified in the administrative cohort.
[b] Information was missing for 150 (2.2%) patients with MS and 693 (2.2%) controls in the administrative cohort and 33 (3.4%) patients with MS and 150 (3.3%) controls in the clinical cohort.

(44 vs 37 years). The distribution of SES quintiles was similar between cohorts. More than 90% of patients with MS in the clinical cohort had relapsing onset MS.

In both cohorts, the prevalence of psychiatric morbidity for patients with MS was higher than that for controls in each of the 5 years before the index dates. Moreover, these differences increased steadily as the index date approached (Figure 1). Over the entire 5-year period, 28.0% (1,920/6,863) of patients with MS and 14.9% (4,738/31,865) of controls in the administrative cohort had a psychiatric morbidity, as did 22.0% (213/966) patients with MS and 14.1% (638/4,534) of controls in the clinical cohort.

In the administrative cohort, the prevalence ratio of psychiatric morbidity in the 5 years before the first demyelinating event among patients with MS was 91% higher than that among controls (prevalence ratio 1.91; 95% CI 1.83–2.00). For the clinical cohort, the prevalence ratio was similarly high for patients with MS (prevalence ratio 1.58; 95% CI 1.38–1.81) in the 5 years before MS symptom onset.

In the administrative cohort, people with MS, regardless of whether they fulfilled the algorithm for psychiatric morbidity, had more all-physician visits for psychiatric morbidity, visits to psychiatrists, psychiatric-related hospital admissions, and "psychotropic" prescriptions during each of the 5 years before their first demyelinating event, compared with the matched controls (Figure 2). For example, the rate of psychiatric-related physician visits was 78% higher in people with MS than in controls in the fifth year before the index date (aRR 1.78; 95% CI 1.59–1.98), increasing to 124% higher in the year before (aRR 2.24; 95% CI 2.03–2.49; Figure 2A). Visits to psychiatrists were 132% higher in the fifth year before the

Figure 1 Prevalence of Psychiatric Morbidity Among Patients With MS and Controls in the Administrative and Clinical Cohorts in the 5 Years Before MS Onset
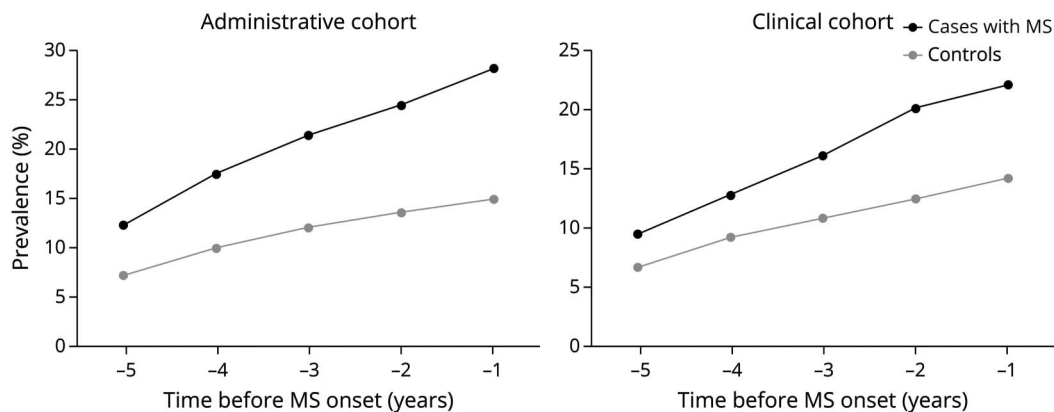
In the administrative cohort, an individual's first demyelinating disease-related claim represented MS onset. In the clinical cohort, MS onset was defined as the date of MS symptom onset, as recorded by an MS neurologist. The period represents the 5-year period before MS onset (e.g., −5 reflects the fifth year before MS onset and −1 the year before MS onset). MS = multiple sclerosis.

index date (aRR 2.32; 95% CI 1.85–2.92) and 146% higher in the year before (aRR 2.46; 95% CI 2.04–2.98; Figure 2B). Psychiatric-related hospital admissions ranged from 129% to 197% higher in the fifth to the first year preindex date (aRR 2.29; 95% CI 1.50–3.50 to aRR 2.97; 95% CI 2.15–4.10; Figure 2C), and the rate of psychotropic prescriptions ranged from 72% to 100% higher over the same periods preindex date in people with MS than in controls (aRR 1.72; 95% CI 1.54–1.93 to aRR 2.00; 95% CI 1.81–2.22; Figure 2D).

While the direction of findings was broadly similar in the clinical cohort, the magnitude of the associations was modest; few reached statistical significance in this smaller population, and the 95% CIs were often wide (eTable 4, links.lww.com/WNL/D118). See eTables 5 and 6 for the results of the covariates included in the models.

Discussion

In this large population population-based study using administrative and clinical data, the prevalence of psychiatric morbidity was higher in people with MS than in matched general population controls in each of the 5 years preceding the first demyelinating event or MS symptom onset. Moreover, these differences increased steadily as MS onset date approached. Over the entire 5-year period before MS onset, the prevalence ratio of psychiatric morbidity was higher for patients with MS than that for controls by 58% before MS symptom onset in the clinical cohort and by 91% before a first demyelinating event in the administrative cohort. When each of the different types of health service use was evaluated, we found that in the administrative cohort, the yearly number of psychiatric-related physician visits and hospital admissions and visits to psychiatrists and psychotropic prescription dispensations increased in magnitude among individuals with MS vs controls across each

of the 5 years before the first demyelinating event. Together, these findings suggest that psychiatric morbidity constitutes a significant burden very early in the MS disease course and may be a feature of the MS prodrome.

Few studies have comprehensively examined psychiatric morbidity in the years leading up to MS onset. For example, a prior Canada-based study from our group found that from 14 morbidities examined in the 5 years before a first demyelinating claim, the prevalence of mood/anxiety disorders exhibited one of the highest differences between patients with MS and controls (present in 24% of patients with MS and 15% of controls, $p < 0.001$).[5] A UK study exploring records of general practitioners also found that up to 5–10 years before a first diagnostic (Read code) for MS or clinically isolated syndrome, individuals with MS were more likely than controls to have a Read code for anxiety and depression (e.g., 11.4% of patients with MS and 9.8% of controls had depression in the 5–10 years before; OR 1.26; 95% CI 1.07–1.47).[10] Our current psychiatric-focused study substantially advances these previous observations by demonstrating differences among patients with MS and controls after applying a validated case definition to identify psychiatric morbidity and exploring psychiatric-related health care use (i.e., physician visits, hospital admissions, and prescription dispensations) for the entire population regardless as to whether individuals fulfilled this algorithm.

Another population-based study in Manitoba, Canada, observed that the incidence of psychiatric disorders was higher up to 5–10 years before a diagnosis of an immune-mediated inflammatory disease (MS, inflammatory bowel disease, or rheumatoid arthritis) vs controls, with an incidence rate ratio for psychiatric comorbidity of 1.60 five years before diagnosis rising to 2.92 the year before for individuals with any of these inflammatory conditions.[4] Together, these findings suggest that psychiatric morbidity are both a relevant feature of the

Figure 2 Rate Ratios of Physician Visits for Psychiatric Morbidity, Visits to Psychiatrists, Psychiatric-Related Hospital Admissions, and "Psychotropic" Prescriptions in the 5 Years Before MS Onset for Patients With MS vs Matched Controls in the Administrative Cohort
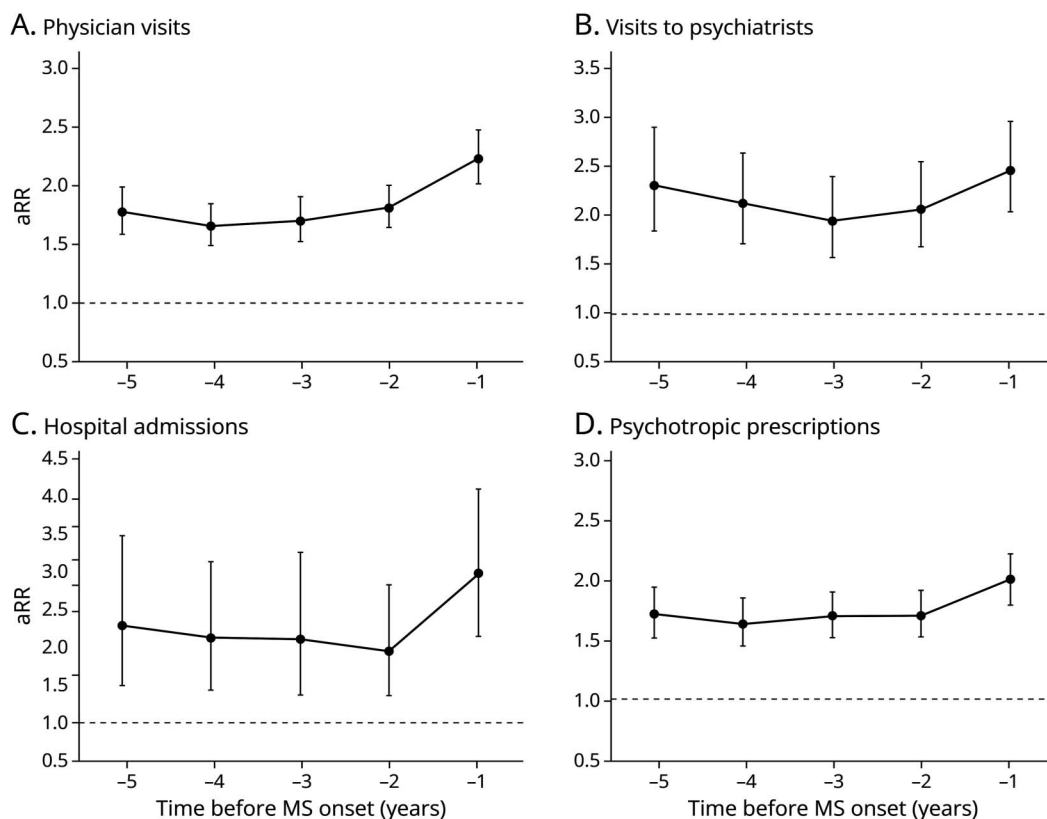
In the administrative cohort, an individual's first demyelinating disease-related claim represented MS onset. In the clinical cohort, MS onset was defined as the date of MS symptom onset, as recorded by an MS neurologist. The period represents the 5-year period before MS onset (e.g., −5 reflects the fifth year before MS onset and −1 the year before MS onset). An adjusted rate ratio greater than 1 indicates a higher rate of visits, admissions, or prescriptions filled in people with MS relative to matched controls. The bars represent 95% CIs. Models were adjusted for age at index date (continuous), sex (categorical), socioeconomic status (quintiles), and index year (continuous). aRR = adjusted rate ratio; MS = multiple sclerosis.

MS prodrome and common in the prodromal phase of other inflammatory conditions. These observations are intriguing and could relate to a number of different factors. For example, psychosocial stress may be directly caused by the other unexplained ongoing prodromal symptoms or the process of navigating the health care system.[5] Other alternatives include that individuals with MS and psychiatric morbidity may have common genetic determinants[28] or share similar risk factors, such as adverse childhood experiences or obesity.[29,30] Furthermore, common etiopathologic pathways, such as low-grade inflammation, could be behind both MS and the psychiatric phenomenon,[31] with evidence supporting the role of inflammation driving the development not only of depression but also of other psychiatric disorders including bipolar disorder, anxiety, and schizophrenia.[32,33] Finally, there is a possibility of confounding. Our results showed that the difference in the prevalence of psychiatric morbidity became substantially more evident as MS onset (the index date) approached, raising the possibility that a progressive increase in inflammation may be sufficient for psychiatric morbidity to manifest but not yet for MS to become apparent.

A better characterization of the MS prodrome may allow for earlier recognition, diagnosis, and management of MS.[34,35] Our findings further advance our understanding of this early stage of the disease by providing a comprehensive assessment of the frequency and relative burden of psychiatric morbidity during the MS prodrome. How best to harness these observations to benefit individuals seeking an explanation for their prodrome-related signs and symptoms, which are also common in the general population, requires further work and careful consideration. Examples could include judicious raising of awareness of the characteristics of the MS prodrome among physician specialties that are often sought by such individuals, including psychiatrists. Such specialties may play a valuable role in the identification of early MS. In addition, because psychiatric comorbidity negatively affects quality of life[15] and MS disability progression,[16] their prompt management may benefit both short-term and longer-term health outcomes in MS.

Study limitations included the potential underestimation or overestimation of the true burden of psychiatric morbidity during the MS prodrome. Underestimation could occur, given

that case definitions used to identify psychiatric disorders in administrative data may experience low sensitivity.[26] Reasons for this may include avoidance of care by people experiencing mental health problems due to social stigma and inability to capture self-managed symptomatology. Undercoding of psychiatric disorders by physicians in the presence of other competing conditions is also possible.[36] In addition, administrative data will not capture encounters with nonphysician providers (e.g., counselors, therapists, psychologists, etc). While these limitations would be expected to affect both patients with MS and controls, it remains possible that the true psychiatric burden during the MS prodrome is much higher than estimated. Equally, the psychiatric burden could be an overestimate due to surveillance bias because people in the prodromal phase interact more frequently with the health care system[7] and therefore may present more opportunities to be diagnosed with a psychiatric disorder.

Strengths of our study include the use of administrative health data within a universal health care setting, which allowed us to capture all physician visits, hospital admissions, and prescription dispensations across nearly the entire province, regardless of the resident's ability to pay, minimizing selection bias. In addition, prospective capture of health-related data virtually eliminates recall bias. Our ability to access both administrative and clinical cohorts was a study strength as well. Differences in the index date definition for both cohorts explain the higher average age at the index date for the administrative cohort relative to the clinical cohort. Nonetheless, our 2 cohorts were similar for the other sociodemographic factors, including sex and SES. Arguably, the period before MS symptom onset, the index date of the clinical cohort, is more representative of the "true" MS prodrome because not every symptom likely attributable to early MS necessarily leads to health care system utilization and/or may not lead to a demyelinating disease-related issue being recognized and recorded. However, our clinical cohort was also rather modest in size, such that while findings were in a similar direction to those observed in the larger administrative cohort, many did not reach significance. We do not expect that age differences between cohorts played a role in this given that the prevalence of psychiatric disorders has not been shown to increase with age in the population with MS.[37-39] Finally, the use of a validated algorithm to identify both MS and psychiatric morbidity was also a study strength.

Psychiatric morbidity represents a contributor to increased health care use by individuals with MS in the 5 years before MS onset. Findings suggest that psychiatric morbidity constitutes a significant burden very early in the MS disease course and may be a feature of the MS prodrome.

Acknowledgment

Study Funding

Disclosure

Publication History

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Helen Tremlett, PhD	Faculty of Medicine (Neurology), University of British Columbia and The Djavad Mowafaghian Center for Brain Health, Vancouver, Canada	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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