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Increased incidence of psychiatric disorders in immune-mediated inflammatory disease

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ABSTRACT

Objective: Although psychiatric comorbidity is known to be more prevalent in immune-mediated inflammatory diseases (IMID) than in the general population, the incidence of psychiatric comorbidity in IMID is less understood, yet incidence is more relevant for understanding etiology.

Methods: Using population-based administrative (health) data, we conducted a retrospective cohort study over the period 1989–2012 in Manitoba, Canada. We identified 19,572 incident cases of IMID including 6119 persons with inflammatory bowel disease (IBD), 3514 persons with multiple sclerosis (MS), 10,206 persons with rheumatoid arthritis (RA), and 97,727 age-, sex- and geographically-matched controls. After applying validated case definitions, we estimated the incidence of depression, anxiety disorder, bipolar disorder and schizophrenia in each of the study cohorts. Using negative binomial regression models, we tested whether the incidence rate of psychiatric comorbidity was elevated in the individual and combined IMID cohorts versus the matched cohorts, adjusting for sex, age, region of residence, socioeconomic status and year.

Results: The relative incidence of depression (incidence rate ratio [IRR] 1.71; 95%CI: 1.64–1.79), anxiety (IRR 1.34; 95%CI: 1.29–1.40), bipolar disorder (IRR 1.68; 95%CI: 1.52–1.85) and schizophrenia (IRR 1.32; 95%CI: 1.03–1.69) were elevated in the IMID cohort. Depression and anxiety affected the MS population more often than the IBD and RA populations.

Conclusions: Individuals with IMID, including IBD, MS and RA are at increased risk of psychiatric comorbidity. This increased risk appears non-specific as it is seen for all three IMIDs and for all psychiatric disorders studied, implying a common underlying biology for psychiatric comorbidity in those with IMID.

1. Introduction

Immune-mediated inflammatory diseases (IMID) are chronic conditions characterized by immune dysregulation and inflammation [1]. Inflammatory bowel disease (IBD), multiple sclerosis (MS) and rheumatoid arthritis (RA) are IMIDs which share several epidemiologic and clinical features, including their high prevalence in Western countries [2][3,4], substantial burden on affected individuals [5–7] and chronicity punctuated by acute exacerbations and often progressive disability.

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Depression and anxiety are leading causes of disability worldwide [8]. Psychiatric disorders are associated with reduced quality of life [9,10] and increased mortality [11]. Psychiatric comorbidity, particularly depression and anxiety, is common in IMID, and more common than in the general population [12,13]. Most studies have focused on the prevalence of psychiatric comorbidity in IMID [13,14]. Prevalence captures the burden of illness, but is the product of incidence and disease duration making it a poor measure for comparisons across diseases due to the influence of differences in age of onset and prognosis. In contrast, incidence assesses disease risk, and is more appropriate for understanding etiology. Population-based studies of the incidence of psychiatric comorbidity are lacking in IMID. Prior studies have often evaluated only one or two psychiatric disorders, limiting the ability to identify whether a specific IMID confers a general or condition-specific increased risk for psychiatric comorbidity. Comparative assessments across IMID are also lacking but could offer insights into the reasons for the burden of psychiatric comorbidity in these conditions. If common patterns of risk for psychiatric disorders were identified across IMID this could implicate a common underlying biology.

Using population-based data sources, we determined the incidence of psychiatric comorbidity, including depression, anxiety, bipolar disorder and schizophrenia, in IBD, MS and RA, and in age-, sex-, and geographically-matched cohorts from the general population. Based on prior findings in MS of a generally increased incidence of psychiatric disorders [15], we hypothesized that the incidence of all of the psychiatric comorbidities would be elevated in all of the IMIDs evaluated.

2. Methods

2.1. Study setting

We conducted this retrospective cohort study in Manitoba, Canada which has a population of approximately 1.3 million. Health care in Manitoba is universal and publicly funded. The province maintains administrative databases of the health services delivered; the data are collected at the time the service is delivered. This study was approved by the University of Manitoba Health Research Ethics Board and data access was approved by the Manitoba Health Information Privacy Committee.

2.2. Data sources

We used administrative databases housed at the Population Health Data Repository at the Manitoba Centre for Health Policy, covering the period April 1, 1984-March 31, 2013. The population registry includes demographic data, dates of health care coverage, and residence location (postal code) for each provincial resident. Physician claims data capture the date of service, and one physician-assigned diagnosis recorded using the International Classification of Diseases (ICD), 9th revision, Clinical Modification (ICD-9-CM). The discharge abstract database captures hospitalizations, including admission and separation dates, and up to 25 diagnoses recorded using (ICD)-9-CM codes up to 2004 and ICD 10th revision, Canadian version (ICD-10-CA) codes thereafter. Since 1995, the Drug Program Information Network (DPIN) captures all outpatient prescription dispensations, including the date, drug name, and drug identification number (DIN), which is linked to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System. The databases were linked at the individual level using an anonymized unique identifier to preserve confidentiality.

2.3. Study populations

Using validated case definitions (eTable 1), we identified all Manitobans with IBD, MS and RA during the study period [16–18]. The date of diagnosis (index date) was the date of the first health claim for the condition of interest during the study period. To identify incident cases, we excluded individuals with relevant claims during a five year period before the index date. Since administrative data began in 1984, the earliest incident cases could be identified in 1989.

Subsequently, we identified general population cohorts, matched 5:1 on sex, year of birth within $\pm$ 5 years, and forward sortation area (first 3 digits of postal code) to each individual with an IMID. Anyone with any ICD-9-CM or ICD-10-CA diagnosis codes for IBD, demyelinating disease, RA and related disorders was excluded as were individuals receiving MS-specific disease-modifying therapies that constituted part of the case definition for MS [19]. Each control was assigned the index date of its matched case.

2.4. Psychiatric disorders

We applied case definitions for identifying depression, anxiety, bipolar disorder, schizophrenia, and any common mental disorder (CMD, which included ≥ 1 of depression, anxiety disorders, bipolar disorders) validated in MS and IBD populations in Manitoba (eTable 1) [20,21]. To estimate incidence of psychiatric disorders after the diagnosis of the IMID of interest, the first claim for the psychiatric disorder had to occur after the index date for the IMID, and be preceded by a five-year period with no claims for that psychiatric disorder. At the end of a study period, new cases (that is, those with a first claim for a psychiatric disorder) may lack sufficient follow-up time to accumulate the health care contacts (hospital, physician or prescription claims) required to meet the case definition for that disorder leading to artefactual reductions in incidence of the disorder. Therefore we report incidence for April 1, 1989 through March 31, 2012. We calculated 95% confidence intervals (95%CI) assuming a negative binomial distribution.

2.5. Covariates

Covariates included sex (male as reference group), age (18–24 [reference group], 25–44, 45–64, ≥ 65), study year, socioeconomic status (SES) in quintiles (lowest quintile of SES as reference group), and region (urban or rural [reference group]). SES was derived by linking postal code to dissemination-area level census data and was determined using the Socioeconomic Factor Index version 2 (SEFI-2) which incorporates information regarding average household income, percent of single parent households, unemployment rate and high school education rate; scores less than zero indicate higher SES [22]. Urban regions included Winnipeg (population $>$ 600,000) and Brandon (population $>$ 47,000). Since the case definitions for any CMD, depression and anxiety disorder included prescription claims, which were only available as of 1995, we included a binary model covariate indicating whether the disorder occurred before or after the availability of these data.

2.6. Analysis

We tested for differences in incidence rates of each psychiatric comorbidity between the cohorts (IMID and matched cohorts) using unadjusted and covariate-adjusted negative binomial regression models, accounting for differences in follow-up time by including the log of person-years as the model offset. In a matched cohort design a matched analysis is unnecessary [23], and adjustment is unnecessary to control for confounding due to the matched variables if follow-up time is the same in both cohorts. If follow-up time is not the same or unmatched covariates are considered, then adjustment is needed. Additional adjusted models contained the two-way interaction of cohort$*$year to test whether temporal trends differed between the IMID and matched cohorts. To compare the incidence rates between IBD, MS and RA cohorts we repeated our analyses including a term that identified the IBD, MS and RA cohorts, separately. Finally, we repeated our analyses stratified by IMID cohort. We report incidence rate ratios (IRR) and 95%CI.

Statistical analyses were performed using SAS V9.4 (SAS Institute Inc., Cary, NC).