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Determinants and incidence of depression in multiple sclerosis: A prospective cohort study

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ABSTRACT

Objective: To estimate the incidence and explore potential determinants of incidence of depression in MS.
Methods: A prospective cohort study used a sample of 192 patients from the southern Alberta MS clinic registry. Participants completed baseline risk factor assessment questionnaires using either online, mail or telephone surveys, and completed the Patient Health Questionnaire every 2 weeks for 6 months to assess depressive symptoms in real time. Risk factors assessed included biopsychosocial variables such as socioeconomic status, illness-related factors, childhood risk factors, psychosocial factors, and health behaviors. Cox proportional hazard models were fit to estimate predictors of incidence.
Results: 2-week incidence of depression for females was 0.019 (95% CI 0.013–0.029) and for males was 0.044 (0.026–0.074). Strongest predictor of depression incidence risk included fatigue impact, low mobility, resiliency, self-esteem, self-efficacy, and coping style.
Conclusion: Depression in MS exhibits a risk factor profile similar to that of depression in the general population, with the additional impact of MS illness-related factors. Potentially modifiable risk factors, such as coping with stress and resiliency, present opportunities for focus of further research in depression in MS treatment and prevention efforts. Some differences in determinants of incidence were found compared to the prevalence risk factors, highlighting the danger of using cross-sectional data to make assumptions about risk. For example, the finding that depression incidence was higher for men is opposite to the higher depression prevalence estimates found for women as well as the consensus in the literature.

1. Introduction

Multiple sclerosis (MS) is the most common disabling neurological condition in young people, and those with MS have an elevated prevalence of anxiety disorders [1], major depression (MD) [2–5] and bipolar disorder [6]. Major depression has negative effects on health-related quality of life in MS [7–10] and may have a negative impact on treatment adherence and functioning [11]. Functional impairment due to depression is especially burdensome since people with MS are faced with the demands of coping with an unpredictable and incurable neurological condition.

The literature on risk factors for MD in MS [12–20] has focused on psychosocial factors such as coping style, self-esteem, mastery, resilience, anxiety and social support, as well as MS-related factors such as fatigue, lesion burden, disease severity, pain and relapse. The broader research literature on depression has examined additional factors [21–24] that could influence prognosis and response to treatment of MD, such as childhood trauma. Several cross-sectional studies have also examined the relationships between MS and depression risk factors [25–27]; however a firm conclusion cannot be drawn about the risk relationship for the most important biopsychosocial factors. Whereas the literature is quite consistent in showing a lifetime prevalence of about 50% for MD in the MS population, [16,28] the prevalence rates do not help to establish depression risks, nor to identify high versus low risk groups. Prevalence is influenced by incidence, prognosis of illness and mortality. To assess risk, prospective data collection is essential, and the current lack of incidence data is a knowledge gap for depression in multiple sclerosis. A key measure to evaluate risks is the incidence

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proportion, the proportion of the population at risk of newly developing depression over a defined time period. The number of cases at baseline must be identified to determine incidence (to exclude those from the at-risk population), and at risk participants must then be followed over a defined risk interval to assess who becomes depressed and who does not. The current MS and depression research literature lacks an epidemiologic study with a representative cohort followed longitudinally and including assessment of biopsychosocial risk factors.

The study had a mixture of exploratory and confirmatory goals. Because the relevant literature is scarce, it was considered important to explore a large set of potential predictors. Several a priori hypotheses were formulated in order to more strongly confirm these expected associations: 1) Women will have higher incidence estimates of MD than men 2) Younger people with MS will have a higher incidence of depression; 3) Family history of depression will be associated with an increased incidence of depression; 4) Lower levels of social support will be associated with a higher incidence of depression; 5) Experience of childhood trauma will be associated with a higher incidence of MD; 6) Emotion-focused coping will be associated with a higher incidence of MD; and 7) A greater time from first symptoms of MS will be associated with a lower incidence of MD.

2. Methods

2.1. Study population

The study design was a 6 month prospective cohort study. The sampling frame was a patient registry maintained by the MS Clinic, University of Calgary, which oversees the care of the overwhelming majority of MS patients in Calgary and Southern Alberta, representing approximately 4000 clients. Of these, there were 3099 eligible patients who had not previously opted out of research, not been discharged from the MS Clinic, and had a diagnosis of MS recorded on at least one visit during 2003–2009. Participant recruitment took place between June 2011 and January 2012. A random sample of 500 patients were sent a recruitment letter by mail from the clinic director and invited to contact the research team directly to discuss participation in the study.

Study inclusion criteria were the ability to speak and understand English, ability to read and understand the consent form, and ready access to a computer with internet connection or a telephone. Respondents were excluded they were planning to move out of Southern Alberta in the six months of the study period.

Data collection took place between June 2011 and August 2012 and used a multimodal data collection approach. Participants were offered the options of online, telephone and mail questionnaires; they could switch modes during the study period. The baseline data collection was divided into two interview times (at the time of enrollment and 2 weeks later) in order to limit the questionnaire length and thus reduce respondent burden. Similarly, the risk factor modules were divided into two parts and repeated at different regular times (2,3,4 and 6 months) (see supplementary material Table S1 for risk factors assessed in each module).

Potential risk factors were included in this study based on findings in the literature related to depression in the general population [22,29]. Additional potential determinants were added based on information from the literature relating specifically to the MS population [16–19]. In keeping with the largely exploratory aims of the study the goal was to assess a comprehensive set of biopsychosocial variables, including socioeconomic status (SES), illness-related factors, childhood risk factors, stress-related and psychosocial factors, as well as current health behaviors (Table S1).

2.2. Measures

The PHQ-9, a validated, short tool [30] based on the DSM-IV criteria for major depression, was used as the outcome measure. This scale has excellent intra-subject reliability for repeated measures, both for self- and telephone-administered (0.9–0.95) [31]. The items on this scale include depressed mood, loss of interest or pleasure in activities, sleep changes, decreased energy or fatigue, appetite changes, feelings of worthlessness, concentration deficits, psychomotor agitation/retardation, and suicidal ideation. The items refer to the occurrence of these symptoms in the preceding 2 weeks. Participants completed the PHQ-9 every 2 weeks so any change in depression scores were captured as they unfolded (the DSM-IV criteria also reflect a 2-week interval). A score of 10 + was interpreted as evidence of MD. Symptom impact was assessed by a question about how difficult any symptoms reported had made it to do their work, take care of things at home or get along with others. Previous depressive episodes and comorbidities were self-reported in response to questions in the baseline interview. The Generalized Anxiety Disorder scale (GAD-7) [15]was also used; high anxiety was defined as a GAD-7 cut-point score of 10 or higher.

The Coping in Stressful Situations Scale (CISS) is a 40-item, self-report scale that separates coping into three main sub-scales [32] of task-oriented, emotion-focused and avoidance-oriented. Task-oriented coping involves using strategies to confront and solve a problem, cognitively reframe it, or minimize its effects; emotion-focused coping uses strategies including emotional responses, self-preoccupation and fantasizing, while avoidance-coping includes social diversion by seeking out other people as a way of avoiding the stressful situation, or distraction by escaping the situation and seeking out a substitute task [33]. This is not a commonly used coping scale in the MS literature, but was chosen for its brevity and content. The majority of the MS coping with stress literature uses assessment instruments developed by Folkman [34], which categorizes coping strategies into two dimensions instead of three: problem-focused and emotion-focused [13].

Ambulation questions from a modified version of the self-report EDSS [35] were used to calculate impairment level, represented by a mobility score. Persistent MS symptoms were assessed using the question: “Do you now have any of the following persisting MS symptoms? Persisting symptoms are those that have been present, most days, for at least 6 months”. The listed symptoms included: visual problems, weakness, dizziness or vertigo, tremor, fatigue, difficulty speaking or swallowing, problems with bladder or bowel function and problems with memory, calculations or reasoning. Additional detail on measures used can be found in the supplementary material Table S2.

This study was approved by the University of Calgary Conjoint Health Research Ethics Review Board. All participants provided written informed consent.

2.3. Statistical analysis

While we had exploratory and some a priori hypotheses about risk factor associations, the statistical analysis plan did not include a priori decisions about necessary risk factor adjustments. Also, because the sample size was modest in relation to the large number of variables to be explored it was not feasible to include all covariates in initial models. Rather, the analysis was conducted interactively, guided by a progression of univariate (incidence), bivariate (unadjusted associations) and multivariable techniques. Since at the time the study was done, there were no other studies that had examined all of these risk factors, we approached the analysis in an explanatory way, without adjusting p-values for multiple comparisons.

Data was censored by either loss to follow-up or at study completion after 6-months. The 2-week point prevalence of MD was calculated at the baseline assessment. In order to estimate predictors of incidence, both Kaplan-Meier survival functions and Cox proportional hazard models were fit. The proportional hazards assumption was assessed for each variable with a graphical approach, using log-log survival curves. If the proportional hazards assumption was not met, the Cox proportional hazard model estimates were not used; Kaplan Meier (KM) estimates were calculated and KM curves displayed. The Breslow method