Psychotic disorders in MS: Population-based evidence of an association

Abstract—Administrative data from a Canadian province were accessed to assess the association of psychotic disorders with multiple sclerosis (MS). Physician-assigned *ICD-9-CM* codes were used to classify MS and psychotic disorder status. A significant association was observed. Additional research is needed to determine the clinical importance and treatment needs of this population.

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Scott B. Patten, MD, PhD; Lawrence W. Svenson, BSc; and Luanne M. Metz, MD

There are case reports and clinical studies describing the occurrence of psychotic syndromes in multiple sclerosis (MS). These reports have variably described syndromes resembling schizophrenia,¹ delusional disorders,² affective psychoses,^{1,3} or delirium.^{4,5} One study reported more lesions in periventricular white matter surrounding the temporal horns of the lateral ventricles in MS patients with psychotic syndromes.¹

Recent reviews have concluded that the occurrence of psychotic disorders in MS is uncommon, perhaps not exceeding chance expectation.⁶ However, it has not thus far been possible to base such assertions on epidemiologic evidence. The lack of population-based studies probably relates to prohibitive sample size requirements.⁶ In the Canadian province of Alberta, two circumstances combine to make an epidemiologic investigation possible. First, the province has a high prevalence of MS. Second, a universal health care system leads to data availability for the entire population of the province.

Methods. Data for this study derive from a universal public health care insurance system in the Canadian province of Alberta: the Alberta Health Care Insurance Plan (AHCIP). In Alberta, to be paid for services, physicians must submit a “fee for service” billing to the AHCIP. These billing submissions include a diagnosis, using the *International Classification of Disease*, ninth edition, *Clinical Modification (ICD-9-CM)*; for information on this coding system, see http://www.cdc.gov/nchs/products/elec_prods/subject/icd96ed.htm. AHCIP data can be used for surveillance and epidemiologic research and are particularly useful for rare diseases that would otherwise be difficult to study.

The current analysis included all residents of Alberta who were aged 15 years or older in 2002 ($n = 2.45$ million). For MS case identification, a longitudinal record maintained by the provincial government’s Health Surveillance Branch was used. This record covers the period 1985 to 2003. Cases of MS are defined as

those with two or more physician services for MS (*ICD-9-CM* 340) during this period.

A similar procedure was used to identify subjects with psychotic disorders. Two relevant *ICD-9-CM* diagnostic code submissions assigned between 1994 and 2003 were used to identify subjects with psychotic disorders. The shorter time interval was selected so that subjects with a distant history of psychosis would not be included. Codes categorized by *ICD-9-CM* as “non-organic” and “non-affective” psychotic disorders—295 (schizophrenia-spectrum disorders), 297 (delusional disorders), and 298 (other non-organic psychoses)—were used to define the psychotic disorders category. An organic psychotic disorders category was further defined using broad *ICD-9-CM* categories that include organic psychotic disorders—292 (drug-induced psychotic disorders), 293 (other transient organic psychotic disorders), and 294 (other organic psychotic disorders). Dementia and alcohol-related psychoses were excluded from this definition.

Logistic regression was used to evaluate the association between psychotic disorders and MS. Initially, all three-way (age group by sex by MS) and two-way (age group by sex, age group by MS, sex by MS) interaction terms were included in the models. The Wald test, in SAS,⁷ was used to identify variables that could be removed from the model, based on $p > 0.05$.

Results. The study sample ($n = 2.45$ million) consisted of 1.22 million men (49.6%) and 1.23 million women (50.4%) ranging in age from 15 to 107 years (mean age 42.4 years). There were 10,367 people with MS. The total population of the province in 2002 was 3.13 million, leading to an estimated MS prevalence of 330 per 100,000. MS was more common in women (odds ratio [OR] 2.6; 95% CI 2.4 to 2.7). The prevalence of psychotic disorders was 1.3%, and that of organic psychotic disorders was 0.5%.

The prevalence of psychotic disorders increased with age in subjects without MS. In those with MS, the prevalence was highest in the 15- to 24-year age group (figure 1). The difference between the two groups diminished with age. The prevalence of organic psychotic disorders also increased with age, but people with MS consistently had a higher prevalence (figure 2).

Separate logistic regression models were fit for psychotic disorders and organic psychotic disorders. In the model for psychotic disorders, there was no evidence of three-way interactions (Wald χ^2 values: 0.07, 2.56, 0.22; $p = 0.78, 0.11, 0.63$) or of MS by sex interaction (Wald χ^2 1.99; $p = 0.16$). However, all three MS by age group interaction terms were significant, as were all three of the age group by sex interactions. The model predicted four different effects of MS, with the associated ORs being 6.6 in the 15- to 24-year age group, 2.2 in the 25- to 44-year age group, 1.9 in the 45- to 64-year age group, and 1.1 in the 65 years and older age group. A detailed summary of the model is presented in the table. The only regression term that does not achieve significance in this model is the main effect for MS. In view of the interactions, this can be inter-

From the Department of Community Health Sciences and Department of Psychiatry (Dr. Patten), Department of Community Health Sciences (Mr. Svenson), and Department of Clinical Neurosciences, University of Calgary (Dr. Metz), and University of Calgary Multiple Sclerosis Clinic, Alberta (Dr. Metz); Health Surveillance Branch, Department of Health and Wellness, Government of Alberta (Mr. Svenson); and Department of Public Health Sciences, University of Alberta (Mr. Svenson), Canada.

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Address correspondence and reprint requests to Dr. Scott B. Patten, Department of Community Health Sciences and Department of Psychiatry, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, Canada T2N 4N1; e-mail: patten@ucalgary.ca

Figure 1. Prevalence (%) of psychotic disorders by multiple sclerosis (MS) and age group.

preted as meaning that a significant association between MS and psychotic disorders may not exist at or above age 65 years. A logistic regression model predicting organic psychotic disorders was similar, except that the main effect of MS was significant, providing evidence of an association in all age groups. In keeping with the tabular analysis, the model predicts peak prevalence in subjects aged 65 years or older, at approximately 3%. However, the strongest relative effect is found in the 15- to 24-year age group because of the very low prevalence in non-MS subjects. Here, the OR was 11.1, compared with 7.4 in the 25- to 44-year age group, 5.6 in the 45- to 64-year age group, and 1.9 in the 65 years and older age group.

Discussion. This study is the first to provide epidemiologic evidence of an association between MS

Figure 2. Prevalence (%) of organic psychotic disorders by multiple sclerosis (MS) and age group.

and psychotic disorders in the general population. Age but not sex was found to modify the observed association of psychotic disorders with MS. The main weakness of the study relates to a lack of clinical detail in the data source. This is, to some extent, inevitable when administrative data are used for research.

Because the prevalence of MS is less than one-half of 1% of the population even in a high-prevalence area such as Alberta and psychotic disorders affect only a small proportion of these individuals, the impact of this comorbidity on population health may not be great. However, among people with MS, a prevalence in the range of 2 to 3% is by no means trivial. The treatment needs of this group should now be characterized so that appropriate clinical and service delivery strategies can be developed.

Table Logistic regression models predicting psychotic disorder prevalence

Parameter	Psychotic disorders*			Organic psychotic disorders		
	Estimate	Wald χ^2	Pr> χ^2	Estimate	Wald χ^2	Pr> χ^2
Intercept	-3.99	40,051.33	<0.0001	-4.10	37,958.22	<0.0001
Female by age 15-24 y	-0.77	314.21	<0.0001	-0.62	61.67	<0.0001
Female by age 25-44 y	-0.49	245.31	<0.0001	-0.49	110.42	<0.0001
Female by age 45-64 y	-0.15	23.22	<0.0001	-0.20	18.58	<0.0001
Age 15-24 y by MS	1.84	23.56	<0.0001	1.77	10.96	0.0009
Age 25-44 y by MS	0.73	10.86	0.0010	1.08	25.16	<0.0001
Age 45-64 y by MS	0.58	7.41	0.0065	1.36	49.52	<0.0001
Female	0.39	240.61	<0.0001	0.10	12.82	0.0003
Age 15-24 y	-0.77	650.01	<0.0001	-2.04	1,687.36	<0.0001
Age 25-44 y	-0.40	275.78	<0.0001	-1.52	2,274.01	<0.0001
Age 45-54 y	-0.40	255.65	<0.0001	-1.32	1,617.41	<0.0001
MS	0.05	0.06	0.8050	0.64	13.68	0.0002

* Excluding "affective" and "organic" psychotic disorders.

MS = multiple sclerosis.

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Corrections

The triumvirate of acute hypertension

In the online-only Resident and Fellow Page in the July 26 issue, “The triumvirate of acute hypertension” (*Neurology* 2005;65:E5) by M.L. Bell and E.F.M. Wijdsicks, there is an error in the figure legend. The second sentence should read “These lesions are absent on diffusion weighted images (not shown) and consistent with **vasogenic** edema.” The authors regret the error.

Creutzfeldt–Jakob disease manifesting as posterior cortical dementia

In the *NeuroImage* “Creutzfeldt–Jakob disease manifesting as posterior cortical dementia” (*Neurology* 2005;65:330) by H. Nodera, A. Mori, Y. Izumi, T. Sakamoto, and R. Kaji, the authors wish to replace panel B of the figure. The original image was T2-weighted, although the legend stated it was diffusion-weighted. The corrected, diffusion-weighted panel is reproduced below.

(B) Diffusion-weighted MRI showing “ribbon-like” cortical hyperintensity, consistent with acute cortical injury commonly seen in the early stage of Creutzfeldt–Jakob disease.

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