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Comorbidity in multiple sclerosis: Past, present and future

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Ruth Ann Marrie is a Professor of Medicine and Community Health Sciences at the University of Manitoba. She received her undergraduate degree in chemistry and her medical degree from Dalhousie University, both with Distinction. She completed neurology training at McGill University. This was followed by a Fellowship in Multiple Sclerosis (MS) at the Cleveland Clinic, supported by a Sylvia Lawry Physician Fellowship Award from the National Multiple Sclerosis Society. Subsequently, she obtained a PhD in Epidemiology from Case Western Reserve University. Presently, she holds the Waugh Family Chair in Multiple Sclerosis. Her research aims to understand the influence of comorbid factors, such as other chronic diseases, health behaviors and critical illness on a range of MS-related health outcomes. Other areas of research interest include etiologic factors for MS, patient-reported outcomes, and pediatric MS.

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Abstract

Purpose: Multiple sclerosis (MS) is an inflammatory and degenerative condition affecting the central nervous system. Like many neurologic diseases, it is chronic and incurable, and confers a substantial burden on affected individuals, their families and society. Although many individuals suffering from a serious chronic disease also suffer from comorbid conditions, the important consequences of their interaction often receive little attention. This was particularly true for MS two decades ago. Broadening our perspective by better understanding the effects of comorbidity on an individual with a particular chronic disease offers us an opportunity to improve understanding of prognosis, personalize disease management, develop new therapeutic approaches and illuminate the pathophysiology of disease.

Source: Studies examining the incidence, prevalence and outcomes related to comorbidity in MS will be discussed, along with areas requiring further investigation.

Conclusion: Comorbidity is highly prevalent in MS throughout the disease course. Comorbid conditions, including depression, anxiety, hypertension, hyperlipidemia, diabetes and chronic lung disease, adversely affect a broad range of outcomes. Less is known about the effects of MS on outcomes related to these comorbid conditions. These findings highlight an urgent need to determine how to best prevent and treat comorbidity in MS.

Although many individuals suffering from a serious chronic disease also suffer from comorbid conditions [1], the important consequences of their interaction often receive little attention [2]. This was particularly true for multiple sclerosis (MS) two decades ago. Yet comorbidity has detrimental effects in all patient populations and on many health outcomes, including quality of life, functional status and mortality [2]. Broadening our perspective by better understanding the effects of comorbidity on an individual with a particular chronic disease offers us a valuable opportunity to improve understanding of prognosis, personalize disease management, develop new therapeutic approaches and illuminate the pathophysiology of disease.

Multiple sclerosis is an inflammatory and degenerative condition affecting the central nervous system. Like many neurologic diseases it is chronic, incurable, and confers a substantial burden on affected individuals, their families, and society [3]. The prevalence of MS in Canada is among the highest worldwide [4]. By 2031, the number of Canadians living with MS is projected to be 133,635, and their total health care costs will reach \$2B annually [5]. Interventions that improve outcomes and reduce these costs are needed.

The clinical manifestations and long-term outcomes of MS vary substantially from one person to another, but the reasons for this variation remain poorly understood. Early efforts to predict long-term outcomes emphasized disease-specific characteristics, such as age at symptom onset, onset symptoms and relapse severity, but findings conflicted, and prognostication early in the disease was poor [6-8]. More recent efforts have indicated that non-modifiable and modifiable factors that reflect the individual's biology and

life history (biography) may influence outcomes, including genetic factors, race, ethnicity, socioeconomic status, health behaviours and comorbid conditions (Figure 1) [9-12]. Of these, comorbidity, has emerged as influential at many points in the clinical trajectory of MS (Figure 2).

Prevalence of comorbidity in multiple sclerosis

Multiple definitions of comorbidity exist. Throughout this article, comorbidity refers to the total burden of chronic illness other than the “index disease” [2,13], in this case MS. When the focus is not any particular index disease, the co-occurrence of chronic diseases is referred to as multimorbidity [13]. Comorbidity and multimorbidity are distinct from complications, which arise from the underlying index disease, although this distinction may be difficult in clinical practice; for example, depression is common in MS and occurs more often in persons with MS than in persons without MS. More marked MS-related microstructural changes in the brain are associated with depression [14], but psychosocial factors unrelated to MS may also affect the risk of depression. Nonetheless, it is important to distinguish between comorbidity and complications because their underlying mechanisms differ, clinical management differs, and should be handled differently in epidemiologic studies, as discussed elsewhere [13].

Early studies examining comorbidity in MS focused heavily on autoimmune disease [15,16], likely because of the immune-mediated etiology of MS. In 1972, Baker et al. reviewed the hospital records of 326 persons with MS and described nine patients who suffered from comorbid

FIGURE 1. Factors that may influence outcomes in multiple sclerosis

autoimmune diseases affecting the thyroid, stomach, adrenal gland, skin (pemphigus vulgaris) and joints (rheumatoid arthritis) but lacked a comparator group; thus, it was uncertain whether these conditions occurred more often than expected [17].

In the last decade, the scope of comorbidities studied has expanded considerably from the early focus on autoimmune disease to include many other conditions, including those most common in the general population, such as hypertension and hyperlipidemia. In 2015, a systematic review of 249 studies reported that comorbidity is very common in MS, with the most prevalent conditions reported as depression (23.7%), anxiety (21.9%), hypertension (18.6%), hyperlipidemia (10.9%) and chronic lung disease (10.0%). This review, and subsequent population-based studies, have also observed that several comorbidities occur more often among persons with MS than in persons without MS, including depression, anxiety, bipolar disorder, irritable bowel syndrome, fibromyalgia, epilepsy, inflammatory bowel disease and psoriasis [18,19].

While most of the studies of comorbidity prevalence focused on prevalent MS cohorts, several focused on cohorts of persons with newly diagnosed MS. Among these individuals, the most common physical comorbidities are

hypertension, chronic lung disease and hyperlipidemia [20,21]. Moreover, the prevalence of multiple comorbidities is higher in the MS population than in an age-, sex- and geographically-matched non-MS population at least five years before MS diagnosis [20]. These comorbidities included depression, anxiety, hypertension, diabetes, ischemic heart disease, fibromyalgia, chronic lung disease and epilepsy. Because age is strongly associated with disease duration and with the accumulation of physical and cognitive impairment [22,23], age-specific prevalence estimates provide some insight as to the accumulation of comorbidity throughout the disease course. Psychiatric comorbidity, including depression and anxiety disorders, does not increase in prevalence with age [24]. In contrast, the prevalence of most other comorbidities studied (diabetes, hypertension, hyperlipidemia [25], ischemic heart disease [26], fibromyalgia [27], and irritable bowel syndrome [28]) does rise.

Effects of comorbidity in multiple sclerosis

Comorbidity adversely influences MS throughout the disease course, including the severity of disability at diagnosis, the rate of subsequent disability progression, relapse rate, symptom severity, health-related quality of life, treatment and mortality [29]. Some examples of these effects are discussed below.

Relapses are highly characteristic of MS, but the association between comorbidity and relapse risk has received little attention. Initial studies reported that lipid levels and the severity of depression and anxiety were not associated with relapses [30,31]; however, more recent studies have drawn different conclusions. In an internet-based study, participants with three or more comorbidities were more likely to report a relapse in the prior year than participants without comorbidities [32]. A Canadian study found that individuals with relapsing onset MS who had three or more comorbidities at enrollment had a higher relapse rate over the following two years; migraine and hyperlipidemia were associated with a higher relapse rate [33].

Cross-sectional and longitudinal studies suggest that physical and psychiatric comorbidities are also associated with greater disability progression throughout the disease course [34-37]. In a retrospective cohort study involving 3,166 participants with MS, each additional physical comorbidity was associated with a mean annual increase in the Expanded Disability Status Scale (EDSS) score of 0.18 (0.09-0.28) [36]. Among 8,983 participants in the North

FIGURE 2. Clinical trajectory of multiple

American Research Committee on Multiple Sclerosis (NARCOMS) registry, the presence of diabetes, hypertension, ischemic heart disease or peripheral vascular disease (that is, any “vascular comorbidity”) at diagnosis, was associated with requiring a cane to walk six years earlier than the absence of any vascular comorbidity [37]. A small study of 228 patients with MS found that symptoms of depression at baseline were not associated with progression of disability 10 years later [38]. This finding contrasts with the findings of two longitudinal studies that used administrative data to identify diagnosed psychiatric disorders. In a Canadian retrospective cohort study involving 2,312 participants with MS, the presence of any mood or anxiety disorder was associated with a mean increase in the EDSS score of 0.28 (0.13-0.44) [39]. In a Swedish retrospective matched-cohort study involving 4,519 patients with MS and 4,972 controls, the combination of MS and psychiatric comorbidity synergistically increased the risk of receiving a disability pension [40].

Comorbidity is also associated with altered cognitive function. Forty to seventy percent of persons with MS develop cognitive impairment [41]; processing speed is the most commonly affected domain. Elevated symptoms of anxiety are associated with reduced information processing speed and lower verbal learning and working memory in MS [42-44]. Elevated symptoms of depression are associated with reduced processing speed, and impaired working memory and executive function [45-48].

Physical and psychiatric comorbidities are associated with reduced health-related quality of life [49-51]. The effects of these comorbidities may be direct, as well as indirect, mediated by fatigue. One study suggested that the direct and indirect effects of depression and anxiety were almost as large as the effects of disability status on health-related quality of life [52], highlighting the potential clinical impact of failing to identify and appropriately treat these comorbidities.

Several studies in North American and European population suggest that comorbidity is associated with increased mortality in MS [53-55].

Depression and MS have synergistic effects on mortality, highlighting the importance of identifying and treating depression [56].

None of these studies has been able to adequately account for the confounding effects of treatments for the comorbidities on MS outcomes; for example, statins have pleiotropic effects that contribute to their effects on clinical outcomes independent of their effects on cholesterol [57], and reduced brain atrophy in a Phase II trial in progressive MS [58,59]. Fluoxetine, a commonly used antidepressant, has immunomodulatory effects [60] and reduced the accumulation of new gadolinium-enhancing lesions over a 24-week period in an exploratory placebo-controlled clinical trial [61]. Future studies will need to address this issue, but this will require much larger sample sizes given variability in comorbidity management.

Although clinical trials of disease-modifying therapies in MS often exclude individuals with comorbidity, observational studies suggest that comorbidity influences treatment decisions as well as tolerability. In a study of 10,698 Canadians with incident MS, the likelihood of starting a disease-modifying therapy decreased as the number of comorbidities increased [36]. In an Italian study of 2,076 newly-diagnosed persons with MS, the presence of comorbidity was associated an increased hazard of switching therapies due to intolerance (hazard ratio 1.42; 1.07-1.87), particularly when the therapy chosen was interferon-beta [62].

Effects of multiple sclerosis on comorbidity

Most studies have focused on the (unidirectional) influence of comorbidity on the MS trajectory, but the relationships between MS and comorbid conditions are likely to be complex and bidirectional. Persons with MS have greater health care utilization than persons without [63,64], which could lead to earlier comorbidity diagnosis (surveillance hypothesis) [65]. A clinician could mistakenly attribute new comorbidity symptoms to MS [66], or MS symptoms might be less significant than other health problems (the competing demands hypothesis) leading to under-diagnosis or delayed diagnosis [65]. Several studies suggest that having multiple comorbid conditions influences the quality of care for hypertension or diabetes [67,68], but these issues have not been examined in MS despite their clinical relevance.

Conclusions

The prevalence of comorbidity is high in MS and increases with age, at a time when disability and complexity of care are increasing. Comorbidity adversely affects a broad range of outcomes in MS, but further studies are needed to disentangle the confounding effects of the treatment of comorbidity on these outcomes. The effects of MS on comorbidity outcomes should be explored as well. Finally, the high burden of comorbidity in MS highlights the need to identify and implement models of care that effectively prevent and treat comorbidity in this population.

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