Patients report worse MS symptoms after menopause: Findings from an online cohort

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Abstract

Background: Many women with multiple sclerosis (MS) are postmenopausal, yet the impact of menopause on MS symptoms is unknown.

Objective: To investigate patient-reported impact of menopause in a large online research platform, PatientsLikeMe (PLM).

Methods: A detailed reproductive history survey was deployed to PLM members, and responses were linked to PLM's prospectively collected patient-reported severity score (MS Rating Scale, MSRS). The MSRS has previously shown good correlation with physician-derived EDSS scores.

Results: Of the 513 respondents, 55% were postmenopausal; 54% of these reported induced menopause. Median age at natural menopause was 51. Surgical menopause occurred at an earlier age ($p < 0.001$) and was associated with more hormone replacement therapy use ($p = 0.02$) than natural menopause. Postmenopausal status, surgical menopause, and earlier age at menopause were all associated with worse MSRS scores ($p \leq 0.01$) in regressions adjusting for age, disease type and duration.

Conclusion: Postmenopausal patients in this study reported worse MS disease severity. Further, this study highlights a utility for online research platforms, which allow for rapid generation of hypotheses that then require validation in clinical settings.

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1. Introduction

The onset of multiple sclerosis (MS) is typically during the reproductive years (Paty et al., 1997) and thus most female subjects will undergo menopause after MS onset. The impact of the menopausal transition (Harlow et al., 2012) on MS course has not been explored. Estrogen has been linked with both inflammation and neuroprotection in animal models of MS (Gold and Voskuhl, 2009b; MacKenzie-Graham et al., 2012), and therefore the loss of ovarian sources of estradiol occurring at menopause could be hypothesized to result in either reduced inflammation, or worse clinical decline (Bove, 2013).

Patient-reported reproductive histories have yielded insights important to the care of patients with MS, such as a need for counseling surrounding reproductive decision-making (Alwan et al., 2013). In cross-sectional studies, 40-54% patients reported post-menopausal worsening of symptoms in two small studies (Holmqvist et al., 2006; Smith and Studd, 1992) but not in a third larger one (Wundes et al., 2011). Respondents also differed in their perceptions of the effect of hormone replacement therapies (HRT) on MS course: while in the earliest study, 75% patients reported that HRT led to symptomatic improvement {Smith and Studd, 1992, #365}, in the latter two over three quarters of respondents reported that HRT had little utility {Holmqvist et al., 2006 #369; Wundes et al., 2011, #765}.

Given observations of increased risk of cognitive decline after menopause in healthy women, particularly early surgical menopause (Rocca et al., 2011), we hypothesized that MS severity would be worse in women who have gone through menopause, even accounting for disease duration. We leveraged the frequent sampling of data from a large online population of individuals motivated to contribute to research in order to investigate the effect of menopausal status on a patient-reported disease severity score.

2. Materials and methods

2.1. Data source

PatientsLikeMe (www.patientslikeme.com; PLM) is an online structured research platform, whose members reporting MS are largely comparable in demographic and disease characteristics to a large referral center and a large online patient registry (Bove et al., 2013b).

2.2. Subjects

We identified 1301 female "active users" aged 18 or above from the over 29,750 PLM members reporting MS, as previously described (Bove et al., 2013b). We emailed them an invitation to complete an online reproductive questionnaire (Appendix 1) in June 2012. An automated reminder message was sent three days later. Members elected to respond ($N=$ 513), opt out ($N=112$), or not respond ($N=317$); response rate among members who opened their emails was 54%. After 15 days, the survey was closed.

2.3. Reproductive variables

Menopausal *status* was categorized as "cycling", "perimenopausal" (last menses 3-12 months prior to survey), or "postmenopausal" (either no menses in prior 12 months, or loss of menses due to surgical intervention). Menopause *type* was categorized as resulting from (1) natural physiology, (2) surgical intervention (hysterectomy and/or bilateral oophorectomy), or (3) chemotherapy or radiation. Menopause *age* was defined using the Stages of Reproductive Aging +10 Workshop convention as: "age at last menses beyond which no menses occurred for one year (natural), or date of surgery (surgical)" (Harlow et al., 2012). *HRT use* was categorized dichotomously as "ever" vs. "never" use, as systemic (patch+oral) vs. local (gel, cream and ring), and whether initiated within 3 years of menopause or thereafter, a time period even more restrictive than the typical 5-year perimenopausal "window of opportunity" (Bove et al., 2014; Shao et al., 2012).

2.4. Disease severity score

In the MS Rating Score (MSRS, free under Creative Commons License), patients rate their disability on a 0-4 scale in 7 areas (walking, use of upper extremities, speech disturbance, vision, dysphagia, cognitive or affective disturbance, and sensory disturbance; Appendix 2). Composite scores range from 0 to 28. The patient-reported MSRS has shown high internal consistency, concordant validity with the Patient Determined Disease Steps (PDSS), and demonstrated adequate known-groups validity (Wicks et al., 2012). In a clinic population, the MSRS has demonstrated good correlations with physician-derived EDSS (MSRS composite score $r_s=0.61$, MSRS walking domain $r_s=0.74$) (Bove et al., 2013b).

2.5. Ethics statement

Ethical approval for this study was obtained from the Partners Healthcare Human Research Committee Institutional Review Board.

2.6. Statistical analysis

We compared demographic and menopausal characteristics according to menopausal type using *t*-tests and the ANOVA procedure. We estimated age at natural menopause using a Kaplan–Meier curve; cycling or perimenopausal subjects were censored at date of questionnaire and surgical or chemotherapy induced menopausal subjects were censored at the date of menopause.

We assessed whether disease severity was associated with menopausal status by performing a linear regression comparing MSRS at last data entry across three menopausal groups (premenopausal, natural menopause, and surgical menopause). This regression model adjusted for patient age, disease type (progressive onset vs. relapsing onset vs. unknown) and disease duration. In the post-menopausal women, a second linear regression model including age at menopause was added to the model with the other predictors. Women reporting menopause induced by chemotherapy were excluded due to potential confounding, as chemotherapy can be used to treat