Understanding Fluctuations of Multiple Sclerosis Across the Menstrual Cycle

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Abstract

This preliminary study offers a novel questionnaire/temperature chart tool to prospectively evaluate monthly neurologic changes in multiple sclerosis (MS) patients, correlate these changes with the menstrual cycle, and distinguish them from symptoms of premenstrual syndrome (PMS). The study volunteers from the MS Clinic at the University of Utah were five menstruating women with relapsing-remitting disease. They received neither estrogen replacement therapy nor oral contraceptives. Each patient received a Modified Vanderbilt University PMS questionnaire and temperature charts. They recorded basal body temperature daily and graded physical and emotional symptoms during three consecutive menstrual cycles.

At the conclusion of the study, the investigators identified four different responses based on their review of the temperature charts and questionnaires. One response was a consistent increase in neurologic symptoms during the late luteal period, while another response was an absence of such an increase in symptoms. They also identified a PMS response, as well as chronic, severely depressed mood. The Modified Vanderbilt University PMS questionnaire and the temperature chart allow correlation of neurologic symptoms and the menstrual cycle. The investigators feel that the questionnaire/temperature chart combination (reproduced in this article) has the potential to be a valuable tool for prospective, long-term clinical evaluation of female MS patients.

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS), and several factors are thought to influence an individual’s susceptibility to the disease and the disease’s course. Predisposing autoimmune, genetic, and environmental factors have previously been identified; hormonal factors have been identified more recently. MS, like most of the other diseases related to major histocompatibility complex class II alleles (eg, systemic lupus erythematosus and thyroid diseases) predominantly affect women. Pregnancy can provide a temporary favorable effect on disease progression in MS. Pregnant women experience a significantly reduced relapse rate during the third trimester, when estrogen levels are higher. Furthermore, a full-term pregnancy may actually increase the time interval to reaching disability or to having a secondary progressive course.

These observations, along with the investigators’ clinical experience and reports from the literature, were the reasons behind undertaking the current study. An observation that hormonal fluctuations of women’s menstrual cycles influence disease activity in MS is especially
pertinent. Worsened symptoms tend to occur immediately before the onset of menstrual flow. There appears to be a subgroup of women with the relapsing-remitting form of MS in whom either true exacerbations or mild transient neurologic decline consistently relate to the menstrual cycles.\textsuperscript{5-7} These intervals often precede the onset of menses (and therefore correspond to the luteal phase of the cycle). In addition, several recent studies have shown that the number and volume of lesions on gadolinium-enhanced magnetic resonance imaging (MRI) in MS are influenced by the sex hormones of the menstrual cycle.\textsuperscript{5,9}

The causes behind the fluctuations of MS symptoms with the menstrual cycle are not yet clear. However, there is ample evidence for communication between the endocrine and immune systems.\textsuperscript{10,11} In some autoimmune diseases, estrogens apparently increase humoral responses while inhibiting most T-cell–mediated responses. For example, in mice that are prone to systemic lupus erythematosus, estrogen treatment ameliorates symptoms of T-cell–dependent inflammation (eg, sialadenitis and vasculitis) and at the same time exacerbates B-cell–dependent glomerulonephritis.\textsuperscript{12}

It is well accepted that systemic lupus erythematosus depends on B-cell production of high levels of autoantibodies, while rheumatoid arthritis (RA) and MS are T-cell–mediated diseases.\textsuperscript{12} In a common animal model of RA (mice with collagen-induced arthritis), estrogen treatment decreases T-cell proliferation and interferon-\(\gamma\) production, skews T-cell activation from a TH1 to TH2 phenotype, and downregulates the production of proinflammatory cytokines.\textsuperscript{12} In addition, estrogen alters maturation and differentiation of macrophages.\textsuperscript{13} Estrogen also suppresses the cytotoxic function of natural killer cells by inhibiting their maturation in the bone marrow.\textsuperscript{14,15} Thus, the cyclic, hormonally induced fluctuation of cytokines and cellular and humoral immunity may account for cyclic changes in neurologic symptoms.

Hormones could also have a direct effect on the physiology of demyelinated axons. Some steroids are synthesized within the central and peripheral nervous system, mostly by glial cells. These neurosteroids regulate important glial functions, such as the synthesis of myelin proteins.\textsuperscript{16} In cultures of glial cells prepared from neonatal rat brain, progesterone increases the number of oligodendrocytes expressing myelin basic protein. Also, studies on the rodent sciatic nerve have shown that neurosteroids play an important role in myelin repair.\textsuperscript{16} Progesterone and its direct precursor, pregnenolone, are synthesized in the myelin sheath by the Schwann cells.\textsuperscript{16}

There is a clinical and scientific need to determine if there are women who experience worsening of MS-related symptoms during specific intervals of their menstrual cycles. This pilot study afforded the opportunity to prospectively evaluate monthly neurologic changes in MS patients, correlate them with the menstrual cycle, and distinguish them from symptoms of premenstrual syndrome (PMS).

**Methods and Materials**

Forty women (18 to 55 years old) with a documented diagnosis of relapsing-remitting MS as defined by Poser criteria were randomly selected from the patients attending the MS Clinic at the University of Utah.\textsuperscript{17} These women were given a preliminary questionnaire to identify which women met inclusion and exclusion criteria. Premenarcheal, postmenopausal, pregnant, and lactating women were excluded, as were women with a history of total hysterectomy or a serious gynecologic condition that required treatment by a gynecologist, and women who were using estrogen preparations. Eventually, nine patients were enrolled in the study. Before entering the study, all of the patients signed an informed consent form approved by the Institutional Review Board of the University of Utah.
Patients were given a Modified Vanderbilt University PMS Questionnaire and temperature charts (Figures 1 and 2). The questionnaire was modified to include specific questions about neurologic function and symptoms, interspersed between questions about PMS symptoms. The women were instructed to fill out the questionnaire and record their basal body temperature daily for three months (or three menstrual cycles). Five of the nine patients were fully compliant and completed the study.

**Figure 1. Modified Vanderbilt PMS Questionnaire.**
Four patients did not complete the temperature and symptoms forms satisfactorily and were dropped from the study. Specifically, their morning temperature charts were recorded sporadically, which did not allow the preparation of a temperature graph. The clinical characteristics of the patients who participated fully in the study are detailed in the Table. The results were collected and analyzed by investigators unaware of the patients’ clinical courses or neurologic findings.

Table. Characteristics of Study Patients.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>Duration of MS (y)</th>
<th>Clinical Course</th>
<th>EDSS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>8</td>
<td>Relapsing-remitting</td>
<td>1.5*</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>4</td>
<td>Relapsing-remitting</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>7</td>
<td>Relapsing-remitting</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>12</td>
<td>Relapsing-remitting</td>
<td>5.0</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>3</td>
<td>Relapsing-remitting</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*EDSS score varied from 1.5 in the follicular phase to 2.5 in the luteal phase.
EDSS, Expanded Disability Status Scale.

After examining the temperature and symptom charts, the investigators selected Patient 1 for continued observation. Serial neurologic examinations (including Expanded Disability Status Scale [EDSS] scoring) and cranial MRI scans during two follicular and two late luteal phases of her menstrual cycles were reviewed by the investigators. The cranial MRI scans were performed with a 0.5 Tesla Signa MR Scanner (General Electric Medical Systems, Milwaukee, Wisconsin) and included T2, T1, and T1-enhanced images at all four determinations.
Results

Four types of responses were identified from the review of the questionnaires and temperature charts. Patient 1’s neurologic symptoms fluctuated cyclically with her menstrual cycle. Significant worsening of weakness—her predominant neurologic symptom—occurred during the late luteal phase during three menstrual cycles (Figure 3). She did not experience PMS. Her EDSS score varied from 1.5 in the follicular phase to 2.5 in the luteal phase. There were no follow-up determinations of EDSS scores for the rest of the participants. Serial brain MRIs did not reveal enhancement of lesions in either the follicular or the luteal phases of the menstrual cycle.

![Figure 3. Fluctuations of weakness experienced by Patient 1 as related to her menstrual cycle during three menstrual cycles. Patient 1 did not experience PMS.](image)

Patient 2 and Patient 5 demonstrated no correlation between the severity of their neurologic symptoms and the phases of their menstrual cycles. Fluctuations in tremors and fatigue (two of Patient 2’s symptoms) are graphed versus two of her menstrual cycles (Figure 4). Data are not shown for Patient 5.

![Figure 4. Fluctuations of tremors and fatigue as related to menstrual cycle in Patient 2 during two menstrual cycles.](image)

Patient 3 was found to be at risk for major depression as well as for variable suicidal ideations at her long-term follow-up. During the two graphed cycles, her depression did not appear to
correlate with her menstrual cycle (Figure 5). She demonstrated no fluctuation of neurologic symptoms with the cycle.

![Figure 5. Chronic depression and variable suicidal ideation experienced by Patient 3 compared with her menstrual cycles during two menstrual cycles.](image)

Patient 4 was identified as exhibiting the symptoms of PMS but no fluctuation of neurologic symptoms over three cycles (Figure 6). She experienced breast tenderness, headache, and lower abdominal tenderness that occurred predominantly at about the time of her menstrual flow for the duration of the three cycles studied.

![Figure 6. Symptoms of PMS experienced by Patient 4 during three menstrual cycles](image)

Figure 7 shows the two types of neurologic presentations of Patient 1 and Patient 2, neither of whom had any complicating symptoms such as depression or PMS. The graph compares the severity of each patient’s predominant neurologic symptom(s) at each phase of the menstrual cycle, averaged over three cycles. As shown, Patient 1 experienced worsening of her weakness during the luteal and menses phases of the cycle when her estrogen levels were lower. In
contrast, a similar pattern did not emerge for Patient 2. A correlation between variations in MS-related neurologic symptoms and estrogen levels during different phases of the menstrual cycle was observed.

![Figure 7](image-url)

**Figure 7.** Phase-specific symptoms without complicating symptoms, such as depression and PMS, that were experienced by Patient 1 and Patient 2 during three menstrual cycles.

**Discussion**

The investigators designed a new questionnaire based on the Vanderbilt University PMS Questionnaire in an effort to correlate fluctuation of the severity of MS symptoms with the normal menstrual cycle. Four different kinds of response were identified among the five patients completing the trial. It was possible to distinguish among those patients who 1) truly exhibit premenstrual worsening of neurologic symptoms; 2) report worsening subjectively, but do not demonstrate it upon evaluation with the questionnaire; 3) have purely PMS symptoms; and 4) have chronic major depression. These are all unblinded self-reports, and thus are subject to possible patient bias.18

The relationship between MS and the endocrine system is supported by the effect of pregnancy on MS activity. Although none of the five patients in this study was pregnant, the rise in estrogen and improvement in symptoms correlates with the reports of pregnant MS patients. Many studies have shown that pregnant MS patients show a reduction in relapse rate in the third trimester of pregnancy, when the estrogen levels are high.1-4

Conversely, the postpartum period, with its sudden withdrawal of estrogen secretion, is characterized by a two- to threefold increase in the clinical relapse rate.5,3,19-21 We observed that the decrease in estrogen (which would be expected during the luteal/menses phases of our study patients’ cycles) corresponded with an increase in their symptoms. Fortunately, for women with MS, the postpartum increase in relapse rate does not seem to have a permanent detrimental effect on MS activity, or development of sustained disability later in life.21-23 Actually, a full-term pregnancy may delay reaching the end point of disability (walking with a cane or crutch) or having a secondary progressive disease course.2

Menopause, with its low estrogen levels, has been shown to increase the severity of neurologic symptoms in MS patients. Smith and colleagues found that this increase was ameliorated by hormone replacement therapy in the majority of patients studied.7 One of the trial patients (Patient 1) did experience greater weakness during the luteal phase of her cycle, during decreased estrogen production.
The human data are supported by similar findings in animal research. Treatment with synthetic estrogens, which are components of contraceptive pills, decreases development of experimental autoimmune encephalomyelitis in rats.\textsuperscript{24,25} The same effect has been demonstrated in mice following their treatment with pregnancy-related estrogens.\textsuperscript{26}

**Summary and Conclusions**

As our knowledge of the effects of female sex steroids on MS increases, it will become more important to trace symptom fluctuation more precisely. Our Modified Vanderbilt University PMS questionnaire/temperature chart combination makes it possible to evaluate patients prospectively. This small trial has shown that the questionnaire can detect different symptom patterns.

Although there were few patients in this trial, the combination tool identified an MS patient whose subjective increase of MS-related symptoms during the late luteal phase and menses was confirmed by the questionnaire. This worsening was distinct from PMS and could be consistently correlated with the specific phases of the menstrual cycle by using a temperature chart. Another patient reported a cyclic worsening of MS-related symptoms but did not exhibit it when evaluated prospectively with our questionnaire. One trial patient exhibited a separate response in which PMS symptoms accounted for the perceived worsening of MS-related symptoms. In addition, another patient’s chronically depressed mood and serious suicidal ideations were identified and treated by the investigators.

Prospective evaluation of the monthly neurologic changes in women with MS is now possible with the novel tool developed for this trial. As new medications for the treatment of MS become available, it will become very important to be able to correlate fluctuation of the disease with the menstrual cycle for timely medical intervention.

The Modified Vanderbilt University PMS questionnaire/temperature chart combination may be a useful tool in both clinical practice and research. Both charts have been made available to clinicians through this publication. We hope to elicit a response from practitioners to assist in determining whether we should move forward to testing our hypothesis on a larger population. To assist in establishing the validity of this new tool, please contact us at http://medlib.med.utah.edu/kw/ms/research_projects/research.cfml for the forms, patient instructions, and additional information. Our report represents an ongoing effort to develop objective criteria for identification of MS patients whose disease activity, course, and possible progression may be influenced by female ovarian steroids.

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**References**


