OBSERVATION

Premenstrual Multiple Sclerosis Pseudoexacerbations

Role of Body Temperature and Prevention With Aspirin

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Background: Many women with multiple sclerosis (MS) experience transient neurologic symptom worsening and fatigue in conjunction with the menstrual cycle. Aspirin reduces MS fatigue in some patients.

Objective: To describe 3 women with MS who experienced stereotypic, temperature-independent neurologic symptoms and diurnal fatigue in the mid-to-late luteal phase of the menstrual cycle. Aspirin treatment prevented the symptoms.

Design and Setting: Case series at the Mayo Clinic outpatient MS clinics, Scottsdale, Ariz, and Rochester, Minn.

Patients: Three women with relapsing-remitting MS.

Interventions: Body temperature measurement, symptom diary, and oral aspirin.

Main Outcome Measures: Body temperature, Modified Fatigue Impact Scale, and evaluation of neurologic symptoms and signs.

Results: Morning oral body temperature did not differ during symptomatic vs asymptomatic portions of the luteal phase ($P=0.55$). Aspirin (650 mg twice daily) prevented symptoms but did not significantly alter the luteal phase body temperature.

Conclusions: Aspirin prophylaxis may prevent luteal phase-associated MS pseudoexacerbations. However, the observed relationship between the luteal menstrual phase and MS symptom worsening is not fully explained by thermoregulation, which implicates other hormonal or immunologic mechanisms.

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Transient worsening of medical conditions in relation to the menstrual cycle is a well-recognized phenomenon. Many women with multiple sclerosis (MS) experience premenstrual pseudoexacerbations, which are defined as recrudescence or aggravation of existing focal neurologic symptoms. The events may be stereotypical and maintain a consistent temporal relationship to the onset of menses over consecutive cycles. We describe 3 patients who experienced uniform and recurrent premenstrual pseudoexacerbations, and we hypothesized that the events would be associated with relative body temperature elevation and that aspirin (acetylsalicylic acid [ASA]) would relieve the symptoms owing to its antipyretic effect and ability to reduce MS-related fatigue.

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responding phase of the post-ASA treatment cycles to determine whether there was an association of treatment effect with body temperature. Data were analyzed using the 2-sided Wilcoxon rank sum test ($P = .05$).

**RESULTS**

Demographics and clinical event details are summarized in **Table 1**. Each woman had regular menstrual cycles (28±2 days). Common features among patients included diurnal fatigue and predictability of symptom onset and duration. Cyclic pseudoexacerbations began 9 to 14 months after the last MS exacerbation. The recurrent focal neurologic symptoms had been features of a prior true attack that had resolved. None of the women used oral contraceptives, regular doses of aspirin or other nonsteroidal anti-inflammatory drugs, acetaminophen, or interferon beta. One woman used glatiramer acetate but without relationship to the pseudoexacerbations.

The **Figure** illustrates the temporal relationship of the neurologic symptoms to each menstrual phase and its association with body temperature. The pseudoexacerbations occurred in the mid-to-late luteal phase. Examination of patient 1 during the symptomatic phase confirmed worsening of preexisting right lower extremity weakness that was associated with a 1-point increase in the Expanded Disability Status Scale score and a 1.5-second increase in her timed 25-ft walk test. Patient 2 noted diplopia and had an internuclear ophthalmoparesis that was not objectively different than during asymptomatic intervals. Patient 3 had fixed lower extremity weakness and impaired sensation at baseline; during her pseudoexacerbation, her 25-ft walk time increased by 1.1 seconds. During the observation period, each patient underwent 1 brain magnetic resonance imaging scan while experiencing a pseudoexacerbation. When compared with magnetic resonance imaging studies performed prior to the onset of recurrent premenstrual symptoms, the studies did not detect new or gadolinium-enhancing lesions in any patient.

As expected, morning oral body temperature was elevated during the luteal phase (postovulation) compared with the follicular and menstrual phases of the cycle (**Table 2**). However, there was no difference in median body temperature on symptomatic days compared with asymptomatic days ($P = .55$) during the luteal phase.

Daily treatment with oral ASA (650 mg twice daily) prevented the stereotypic neurologic symptoms in all patients. Aspirin prophylaxis also markedly reduced fatigue severity and prevented an objective change in neurologic examination findings during the premenstrual phase. Prior to ASA treatment, the median visual analog scale score was 74 (interquartile range=56-88) during the symptomatic portion of the luteal phase.

**Table 1. Characteristics of Patients and Premenstrual Pseudoexacerbations**

<table>
<thead>
<tr>
<th>Patient/ Age, y</th>
<th>Disease Duration, y</th>
<th>EDSS Score</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Timing of Pseudoexacerbation</th>
<th>Consecutive Monthly Pseudoexacerbations, No.</th>
<th>ASA Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Onset Before Menses, d</td>
<td>Event Duration, d</td>
<td></td>
</tr>
<tr>
<td>1/29</td>
<td>4.5</td>
<td>2.5</td>
<td>Fatigue, bilateral LE paresthesias, right LE weakness</td>
<td>Increased LE weakness, increased T25W</td>
<td>6-7</td>
<td>3-5</td>
<td>11</td>
</tr>
<tr>
<td>2/33</td>
<td>2.0</td>
<td>1.0</td>
<td>Fatigue, diplopia</td>
<td>Latent INO</td>
<td>9-12</td>
<td>3-4</td>
<td>4</td>
</tr>
<tr>
<td>3/36</td>
<td>2.0</td>
<td>1.5</td>
<td>Fatigue, urinary urgency, left LE weakness</td>
<td>Increased T25W</td>
<td>5-8</td>
<td>4-7</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, acetylsalicylic acid (aspirin); EDSS, Expanded Disability Status Scale; INO, internuclear ophthalmoplegia; LE, lower extremity; T25W, timed 25-ft walk.
Symptoms. The asymptomatic portion was defined as the luteal phase dates preceding and following symptoms. Differences between groups were analyzed using reported in 43% to 82% of women with MS in retro-
tom worsening is much more common, having been
phase. Approximately 3 days before menses, aggrava-
tion of motor symptoms (30% of women), sensory
symptoms (13%), coordination (12%), vision (10%),
and sphincter symptoms (7%) were reported in 1 study;
women with premenstrual symptoms were less likely to
be using oral contraceptives.\(^3\) The authors speculated
that a variety of mechanisms may be responsible
for premenstrual symptom worsening, including
temperature-dependent conduction block, direct hor-
monal effects, and indirect hormonal influences on
cytokine networks.\(^3\)

<table>
<thead>
<tr>
<th>Phase*</th>
<th>Pre-ASA</th>
<th>P Value</th>
<th>Post-ASA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual phase (days 1-4)</td>
<td>36.4 (36.3-36.6)</td>
<td>.13 vs follicular</td>
<td>36.3 (36.2-36.6)</td>
<td>.25 vs pre-ASA</td>
</tr>
<tr>
<td>Follicular phase (days 5-13)</td>
<td>36.3 (36.2-36.7)</td>
<td>&lt; .001 vs luteal</td>
<td>36.2 (36.1-36.5)</td>
<td>.09 vs pre-ASA</td>
</tr>
<tr>
<td>Luteal phase (days 14-28)</td>
<td>36.8 (36.8-37.1)</td>
<td>NA</td>
<td>36.7 (36.7-37.1)</td>
<td>.30 vs pre-ASA</td>
</tr>
<tr>
<td>Luteal phase (symptomatic)</td>
<td>36.8 (36.8-37.1)</td>
<td>.55 vs luteal asymptomatic</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Luteal phase (asymptomatic)</td>
<td>36.8 (36.7-37.1)</td>
<td>NA</td>
<td>36.7 (36.7-37.1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, acetylsalicylic acid (aspirin); NA, not applicable.
*The symptomatic segment of the luteal phase included the dates during which the patient reported a typical increase in diurnal fatigue and focal neurologic
symptoms. The asymptomatic portion was defined as the luteal phase dates preceding and following symptoms. Differences between groups were analyzed using a
2-tailed Wilcoxon rank sum test; \(\alpha = .05\).

Transient MS symptom worsening can occur as a result
of disordered homeostasis or external environmental in-
fluences. Brief events lasting minutes to hours may be
related to heat exposure or exercise (Uhltoff phenom-
enon) or even circadian changes in body temperature.\(^3\)
Symptoms or signs sustained for longer than 24 hours
are termed pseudoexacerbations to distinguish them from
ture MS exacerbations associated with new central ner-
vous system inflammatory demyelinating disease activity.
Pseudoexacerbations usually consist of a recurrence
of previously experienced symptoms, which may be ste-
reotypic and resolve when the underlying trigger (infection,
fever, medication, or metabolic derangement) is
treated or removed.

The menstrual cycle, especially the luteal and men-
strual phases, influences conditions such as asthma,
migraine, and epilepsy.\(^1\) Premenstrual and menstrual
factors have been implicated in causing true MS exacer-
bations, perhaps through hormonal influences on
inflammatory pathways.\(^2\) However, premenstrual symp-
tom worsening is much more common, having been
reported in 43% to 82% of women with MS in retro-
spective studies,\(^2,3\) and typically occurs in the late luteal
phase.\(^7\) Approximately 3 days before menses, aggrava-
tion of motor symptoms (30% of women), sensory
symptoms (13%), coordination (12%), vision (10%),
and sphincter symptoms (7%) were reported in 1 study;
women with premenstrual symptoms were less likely to
be using oral contraceptives.\(^3\) The authors speculated
That contrast to our hypothesis, symptom occurrence and
therapeutic response to ASA were not associated with body
temperature in our patients. Our data are consistent, how-
ever, with reports demonstrating that salicylates do not
affect normal thermoregulatory mechanisms in afebrile
subjects\(^8\) and that prostaglandin inhibitors fail to blunt
luteal phase body temperature elevation related to the pro-
gesterone-estradiol ratio.\(^9\)

Sex hormone concentrations influence cytokine pro-
files; estrogens may limit T\(_{H1}\) cytokines such as tumor
necrosis factor alpha while progesterone may enhance
production of the T\(_{H2}\) cytokine interleukin 4.\(^10\) Such rela-
tionships have been implicated in a tendency for in-
creased risk of exacerbation in the late luteal phase, at
which time there is a sharp decline in concentrations of
both hormones from their postovulatory peaks.\(^6,7\) Our pa-
ients’ symptoms typically began at a similar point in the
luteal phase. Whether the cytokine alterations noted ear-
lier are relevant to the pathogenesis of premenstrual pseudo-
exacerbations is unclear, but they have been associ-
ated with alterations in nerve conduction, which is a
postulated mechanism for transient neurologic symp-
tom worsening.\(^11\)

Diurnal fatigue was a prominent and invariable feature
of our patients’ pseudoexacerbations. We recently reported the results of a randomized, placebo-
controlled study demonstrating that ASA reduced
MS-related fatigue and postulated that the mechanism of
benefit may be mediated through hypothalamic output
via neuroendocrine or autonomic pathways.\(^3\) Our cur-
rent observations suggest that the benefit of ASA on MS-
related fatigue may not be related to its effect on body
temperature. The open-label nature of our observations
is a limitation because of the possibility of placebo ef-
ects or bias on the part of the patients or examiner. There-
fore, our results require confirmation in the context of a
randomized, controlled trial.
Premenstrual MS symptom worsening may mimic classic pseudoexacerbations and be prevented by moderate doses of aspirin. The pathogenic mechanisms responsible for these events and their aspirin-responsiveness remain unknown but may be independent of body temperature or at least not fully explained by temperature variation. The evaluation of oral body temperature was a potential limitation of our methods. It remains possible that smaller variations in core body temperature, detectable using more sensitive rectal or ingestable measurement devices, are responsible for some aspect of symptom generation or response to ASA therapy. Further evaluation of the impact of temperature as well as that of other potential factors, such as sex hormones, physiological variables, and immunological factors, on reliable and sensitive measures of neurologic function (such as evoked potentials or measures of visual contrast sensitivity) are needed to better understand mechanisms and interactions underlying these clinical observations.

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REFERENCES