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 ($P=.55$). 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.[1] Many women with multiple sclerosis (MS) experience premenstrual pseudoexacerbations, which are defined as recrudescence or aggravation of existing focal neurologic symptoms.[2,3] 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.[4]

METHODS

We identified 3 women with relapsing-remitting MS who reported predictable, unvarying, self-limited premenstrual symptoms that included 1 or more focal neurologic symptoms or signs and diurnal fatigue. The events lasted 3 to 5 days and resolved at or just prior to the onset of menses. We instructed each patient to record her morning oral body temperature before rising from bed, the onset and duration of her menstrual period, and type, severity, and change in fatigue and neurologic symptoms. Fatigue was rated using a 100-mm visual analog scale. Neurologic examinations were performed in the late morning. After data collection for 2 cycles, we treated each patient with oral ASA (650 mg twice daily) and collected data for at least 2 more cycles.

We divided the menstrual cycle into the following 3 phases: menstrual (day 1 [date of menses onset] to day 4); follicular (days 5-13); and luteal (day 14 [presumed date of ovulation] to day 28). Median morning body temperature during the luteal phase was compared with that of the follicular and menstrual phases; we expected higher temperatures following ovulation. We determined the association of body temperature with the presence of neurologic symptoms by comparing the median temperature during the symptomatic portion of the luteal phase with that of the asymptomatic portion. Finally, we compared the median temperature during each phase of the pre-ASA treatment cycles with that during the cor-

Table 1. Characteristics of Patients and Premenstrual Pseudoexacerbations

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

Abbreviations: ASA, acetylsalicylic acid (aspirin); EDSS, Expanded Disability Status Scale; INO, internuclear ophthalmoplegia; LE, lower extremity; T25W, timed 25-ft walk.

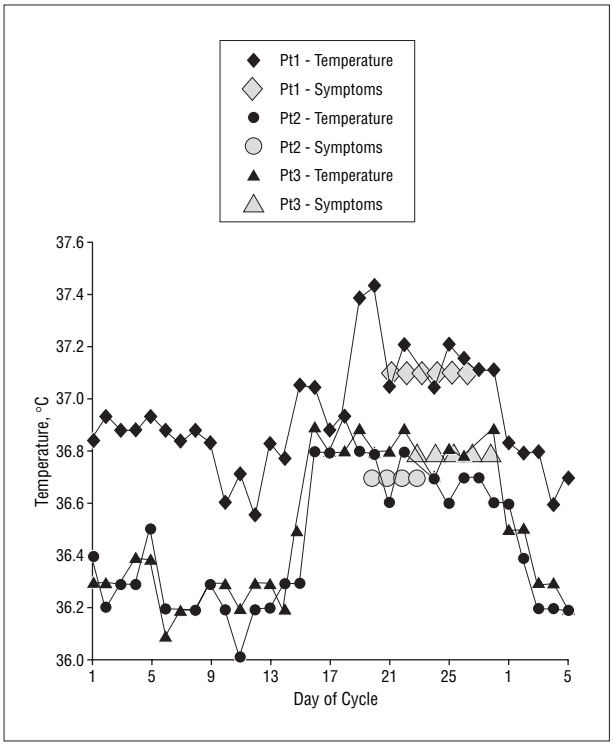

Figure. Relationship of morning oral body temperature to the development of neurologic symptoms during 1 menstrual cycle. Symptoms denotes the segment of time during which the identified patient was symptomatic during the luteal phase. Day 1 indicates date of menses onset. Pt indicates patient.

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 ($\alpha = .05$).

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 2. Relationship of Body Temperature and Symptoms to Menstrual Cycle Phases

	Median (Interquartile Range) Morning Body Temperature, °C			
Phase*	Pre-ASA	*P* Value	Post-ASA	*P* Value
Menstrual phase (days 1-4)	36.4 (36.3-36.8)	.13 vs follicular <.001 vs luteal	36.3 (36.2-36.6)	.25 vs pre-ASA menstrual
Follicular phase (days 5-13)	36.3 (36.2-36.7)	<.001 vs luteal	36.2 (36.1-36.5)	.09 vs pre-ASA follicular
Luteal phase (days 14-28)	36.8 (36.8-37.1)	NA	36.7 (36.7-37.1)	.30 vs pre-ASA luteal
Luteal phase (symptomatic)	36.8 (36.8-37.1)	.55 vs luteal asymptomatic	NA	NA
Luteal phase (asymptomatic)	36.8 (36.7-37.1)	NA	36.7 (36.7-37.1)	NA

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; $\alpha = .05$.

compared with only 31 (interquartile range=18-41) during the entire luteal phase in post-ASA treatment cycles ($P<.001$). Median morning body temperature did not differ when comparing pre-ASA and post-ASA treatment luteal phases ($P=.30$). After 2 successful treatment cycles, 2 patients tried a revised regimen that required receiving ASA 12 days before predicted menses (5 days prior to usual symptom onset) and discontinuing it the day of menses onset. This approach was also effective.

COMMENT

Transient MS symptom worsening can occur as a result of disordered homeostasis or external environmental influences. Brief events lasting minutes to hours may be related to heat exposure or exercise (Uhthoff phenomenon) or even circadian changes in body temperature.[5] Symptoms or signs sustained for longer than 24 hours are termed *pseudoexacerbations* to distinguish them from true MS exacerbations associated with new central nervous system inflammatory demyelinating disease activity. Pseudoexacerbations usually consist of a recurrence of previously experienced symptoms, which may be stereotypic and resolve when the underlying trigger (infection, fever, medication, or metabolic derangement) is treated or removed.

The menstrual cycle, especially the luteal and menstrual phases, influences conditions such as asthma, migraine, and epilepsy.[1] Premenstrual and menstrual factors have been implicated in causing true MS exacerbations, perhaps through hormonal influences on inflammatory pathways.[6] However, premenstrual symptom worsening is much more common, having been reported in 43% to 82% of women with MS in retrospective studies,[2,3] and typically occurs in the late luteal phase.[7] Approximately 3 days before menses, aggravation 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 hormonal effects, and indirect hormonal influences on cytokine networks.[3]

Contrary to our hypothesis, symptom occurrence and therapeutic response to ASA were not associated with body temperature in our patients. Our data are consistent, however, 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 progesterone-estradiol ratio.[9]

Sex hormone concentrations influence cytokine profiles; 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 relationships have been implicated in a tendency for increased 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 patients' symptoms typically began at a similar point in the luteal phase. Whether the cytokine alterations noted earlier are relevant to the pathogenesis of premenstrual pseudoexacerbations is unclear, but they have been associated with alterations in nerve conduction, which is a postulated mechanism for transient neurologic symptom 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.[4] Our current 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 effects or bias on the part of the patients or examiner. Therefore, 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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