


# Research Submission

## Allodynia in Menstrually Related Migraine: Score Assessment by Allodynia Symptom Checklist (ASC-12)

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**Objective.**—The aim of this study was to compare the allodynia score in headache attacks related and not related to menstruation in women diagnosed with menstrually related migraine without aura.

**Background.**—Allodynia is an important symptom in migraine and has been associated with migraine chronification. No study has yet compared prospectively allodynia in menstrual vs non-menstrual attacks within the same cohort of patients.

**Methods.**—This is a prospective cohort study, where participants had the 12-item Allodynia Symptom Checklist (ASC-12) assessed after 1, 2, 4, and 24 hours from the onset of migraine attacks in 2 different conditions, with menstrual migraine attack (MM+) and with non-menstrual migraine attack (MM−).

**Results.**—A total of 600 women with headache complaints were screened from March 2013 to July 2014 in a headache outpatient or headache tertiary clinic. From these, 55 participants were recruited, and 32 completed the study. Participants' mean age was 27 years, BMI was 22.1, menarche age 12 years, migraine history was 11.5 years, and most women were young (ranged from 17 to 44 years of age), were in higher school (13/32 = 41%), single (20/32 = 63%), and used contraceptives (22/32 = 69%). Multiple pairwise comparisons of ANCOVA's test showed significant higher ASC-12 scores in MM+ group compared to MM− group at 2 hours [mean, 95% CI of difference: 2.3 (0.31, 4.7),  $P = .049$ ]. For the ASC-12 categorical scores (absent, mild, moderate, and severe) MM+ yielded higher scores than MM− at 1 hour ( $z = -3.08$ ,  $P = .021$ ) and 4 hours ( $z = -2.97$ ,  $P = .03$ ).

**Conclusion.**—This study demonstrated that in the patients from tertiary headache center assessed, menstrual-related migraine attacks augment allodynia scores in the beginning of attacks compared to non-menstrual migraine attacks.

**Key words:** allodynia, migraine, woman, menstruation, menstrually, headache

**Abbreviations:** ASC-12 Allodynia Symptom Checklist, MM+ menstrual migraine attack, MM− non-menstrual migraine attack, MRM menstrually related migraine

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**Conflict of Interest:** Mario Fernando Prieto Peres is a speaker, board member, consultant: Europharma, Eli Lilly, Teva, Novartis, Hefesto. Eliana Meire Melhado is a speaker, board member, consultant: Eli Lilly, Teva, Novartis, Allergan, Libbs. Hýkaro Leonelli Thiers Rister, Débora Renata Galego; Arão Belitardo de Oliveira, Isadora Abib Buttarello; Inaê Silveira Belucio; Juliana Maria Oliveira Marcos; Maria Luiza Tonhá Xavier declare no conflict of interest.

## INTRODUCTION/BACKGROUND

Cutaneous allodynia is pain in response to non-noxious stimuli, when stimuli are applied to normal skin. Allodynia is important in migraine and receives more interest in studies because it is recognized as a central sensitization signal during migraine attacks. It is suggested as a risk factor for chronicity of migraine.<sup>1-3</sup> Clinical and population-based studies have reported that cutaneous allodynia affects about two thirds of migraine patients and appointed female sex, obesity, depression, temporomandibular disorders, and higher severity and frequency of attacks<sup>1,4,5</sup> as risk factors for its development. Furthermore, it has been suggested that allodynia can have a negative influence on the response to treatment with triptans. Therefore, it is possible to establish the identification of allodynia is important in the choice of treatment and to establish the disease prognosis.

Migraine is a prevalent neurological disorder that affects 4 out of 10 women and 2 out of 10 men, especially before 35 years of age.<sup>6</sup> Around the age of 30, migraine is 3 times more prevalent in women than in men.<sup>7</sup> Menstrual migraine is a migraine subtype. Population-based and clinical studies have shown that 20-60% of women with migraines report an association with menstruation,<sup>8-10</sup> Attacks are more likely to occur between 2 days before menstruation and the first 3 days of bleeding.<sup>11-13</sup> Less than 10% of women report menstrual attacks only and not in other moments of the cycle (pure or true menstrual migraine).<sup>8-10,13,14</sup> Most women with regular menstrual attacks also experience migraine headaches at other times of month (menstrually related migraine; MRM).<sup>8,13</sup> The term menstrual migraine is used to engage both conditions.

It is unclear if cutaneous allodynia varies in menstrual vs non-menstrual attacks. Thus, a sample of women with menstrual migraine was selected and menstrual and non-menstrual attacks were compared, in order to clarify whether allodynia is more prevalent and severe in menstrual attacks. We hypothesized that menstrual related migraine attacks has an effect on allodynia, reflecting higher score of allodynia during menstrual-related migraine attacks compared to non-menstrual migraine attacks (MM-).

**Main Hypothesis.**—H1: Pain attacks in women with menstrual-related migraine exhibit higher allodynia scores than non-menstrual related crises.

## METHODS

**Study Design and Participants.**—This is a primary analysis of a prospective cohort study.

Women patients who sought outpatient or private practice for headache complaint were screened by the neurologist responsible for the study. Therefore, the selection was performed by a headache specialist neurologist, who proposed the study by reading the Subject Information and Consent Form (approval number of the ethics council: 12936913.9.0000.5430) at the time of patient appointment.

**Procedures.**—Participants were followed up for a month. At a moment of inclusion, a group of 5 trained academics from the Medical School instructed the women included in the study to fill out the headache diary and in self-administered the 12-item Allodynia Symptom Checklist (ASC-12) 8 times.<sup>15</sup> This activity was performed in a headache attack, after 1, 2, 4, and 24 hours from the onset of a menstrual-related headache attack and at a non-menstrual attack (at the same time).

Menstrual pain crises were defined as attack that happens 2 days before until 3 days after the first day of menses (ICHD3) (−2 to +3 days from the first day of menses).

**Inclusion Criteria.**—Patients with menstrual-related migraine according to ICHD3,<sup>13</sup> headache frequency between 1 and 14 attacks per month, without preventive treatment for more than 1 year, taking acute medication for the migraine attack more than 1 hour after the attack begun.

**Exclusion Criteria.**—Patients were excluded if presented more than 15 days of headache in the previous month, started migraine prevention before the data collection period, comorbidity with fibromyalgia, rheumatoid arthritis and other rheumatologic disorders, menopause, or pregnancy.

**Assessments.**—Anamnesis, physical and neurological examination, and the diagnosis of migraine were made by the neurologist, questionnaires were applied by medical students from Centro Universitário Padre Albino, Catanduva, São Paulo, Brazil.

The ASC-12 was chosen as a reliable, quick, and simple tool, since the questionnaire has excellent psychometric characteristics and has been validated with regard to the quantitative sensory test (QST).<sup>15</sup> The

questionnaire consists of 12 questions and allows the identification of cutaneous allodynia and its classification in terms of severity. The questionnaire was validated for Portuguese language and it is able to diagnose and classify allodynia in the Brazilian population, in order to facilitate the identification of symptoms in clinical studies, clinical practice, and population based studies in a reliable and fast manner (ASC-12).

Menstrual migraine crises were defined as headache which occurs between 2 days before the onset of menstrual flow up to 3 days after it (−2 to +3). Non-menstrual headache attack (MM−) was defined in this study as a headache crisis that happens out of menstrual period (out of −2 to +3).

Catanduva is a 120,000 inhabitants city, located 400 km west from São Paulo. Its economy is based on sugarcane plantations and small local industries.

**Outcomes.**—According to the main and secondary hypotheses, headache attacks in women with MRM are more associated with allodynia and more severe allodynia than attacks not related to menstruation.

**Standard Protocol Approvals, Registrations, and Patient Consents.**—The study was registered to Plataforma Brazil (site: <http://www.saude.sp.gov.br/centro-de-referencia-e-treinamento-dstaidsp/pesquisa/comite-de-etica-em-pesquisa/projetos-de-pesquisa-plataforma-brasil>) and approved by the Ethics Committee of the Medical School linked to Plataforma Brazil (CAAE: 12936913.9.0000.5430). All participants gave informed written consent.

**Statistical Analysis.**—No statistical power calculation was conducted prior to the study; thus, the sample size was based on a sample of convenience. The nature of the hypothesis testing was 2-tailed testing. As the distribution of variables did not violate the assumption of normality (Shapiro-Wilk's test) and homogeneity (Levene's test), ASC-12 scores were analyzed by 2-way repeated measure ANCOVA, wherein the between-group factors were migraine attack conditions (menstrual migraine attack [MM+] vs MM−) and within-group factors were the times elapsed following migraine attack onset (1, 2, 4, and 24 hours). If the assumption of sphericity was violated, the degrees of freedom were adjusted by Greenhouse-Geisser's correction. Body mass index

(BMI), use of contraceptive, age at migraine onset, years living with migraine, and age at menarche were set as covariates, and were included all at once in the analysis. Bonferroni's adjustments in the confidence intervals were computed for the identification of significant differences of multiple pairwise comparisons. Eta squared ( $\eta^2$ ) was adopted as a measure of effect size.

For ASC-12 categorical scores analysis, the Friedman test was used to compare mean ASC-12 scores ranks, which were defined as follows: "Absent" = 1, "Mild" = 2, "Moderate" = 3, and "Severe" = 4. For multiple comparisons, we performed Wilcoxon post hoc test, and the *P* values obtained were corrected by Bonferroni's adjustments.

A *P* value <.05 was considered statistically significant for all analyses. All analyses were performed in the SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY).

## RESULTS

**Participant Enrollment and Demographics.**—A total of 600 women with headache complaints were met in the period from March 2013 to July 2014 in a neurology clinic and a neurology ambulatory. From this total, 55 participants were included in the study after signed free and informed consent form. Then they were subjected to medical interview, general physical, and neurological examination, and invited to respond to ASC-12. The women answered the questionnaire 8 times (1, 2, 4, and 24 hours after the onset of menstrual pain crisis, and after 1, 2, 4, and 24 hours of a pain attack not associated with menses).

Twenty-three of the 55 women (41.8%) were excluded from study [by withdrawal (4/23), missing location (3/23), failure to fill out tool properly (5/23), someone took symptomatic medication within 1 hour from the onset of pain attack (6/23), and others started prophylaxis before completing the tool (5/23)].

Participants' characteristics are summarized in Table 1. Averages of allodynia scores are on Table 2.

The allodynia assessment in a menstrual pain crisis (MM+) demonstrated that 34% (11/32), and 34% (11/32) of woman presented severe allodynia after 1 and 2 hours from the onset of pain crises, respectively.

The assessment of cutaneous allodynia in a non-menstrual headache attack (MM−), after 1, 2, 4,

**Table 1.—Participants' Demographic Characteristics**

Age (years)	27 (6.7)
BMI (kg/cm <sup>2</sup> )	22.1 (2.8)
Age at migraine onset (years)	16 (6.5)
Years living w/migraine (years)	11.5 (7.4)
Age at menarche (years)	12 (1.0)
Ethnicity	
Black	1 (3%)
White	31 (97%)
Education	
Elementary	3 (9%)
Secondary	16 (50%)
Higher	13 (41%)
Marital status	
Married	11 (34%)
Single	1 (3%)
Divorced	20 (63%)
Contraceptives	
No	10 (31%)
Yes	22 (69%)
Profession	
Student	14 (44%)
Lawyer	3 (9%)
Manageress	2 (6%)
Nurse	2 (6%)
Secretary	2 (6%)
Other (1 each)	9 (29%)

and 24 hours from the onset of pain attack show that 44% (14/32), and 56% (18/32) of women reported themselves with no allodynia (absent) after 1 and 2 hours from the onset of non-menstrual headache attack, respectively (Table 3).

There was a time and group interaction effect for ASC-12 scores [ $F(4, 248) = 2.922, P = .037, \eta^2 = 0.062$ ]. There were significant within-group differences in ASC-12 scores from 1 to 24 hours [ $F(3, 58) = 26.1, P < .001, \eta^2 = 0.571$ ]. Multiple pairwise comparisons showed and increased ASC-12 scores at 1, 2, and 4 hours compared to 24 hours for either MM– or MM+

conditions (Fig. 1). For between-group effects, there was a significant effect of the covariate age of menarche [ $F(1, 57) = 10.8, P = .002, \eta^2 = 0.171$ ], years living with migraine [ $F(1, 57) = 4.9, P = .030, \eta^2 = 0.06$ ] and age at migraine onset [ $F(1, 57) = 5.4, P = .020, \eta^2 = 0.079$ ], but no effect of BMI [ $F(1, 57) = 0.12, P = .732, \eta^2 = 0.015$ ], or contraceptive use [ $F(1, 57) = 2.6, P = .110, \eta^2 = 0.018$ ], on ASC-12 scores between MM– and MM+ conditions. Multiple pairwise comparisons showed significant higher ASC-12 scores in MM+ group compared to MM– group at 2 hours [mean, 95% CI of difference: 2.3 (0.31, 4.7),  $P = .049$ ], but no significant change at 1 hour [1.8 (–0.1, 3.8),  $P = .060$ ], 4 hours [1.4 (–0.7, 3.5),  $P = .199$ ], and 24 hours [–0.03 (–1.26, 1.2),  $P = .961$ ] (Fig. 1).

Table 3 summarizes the proportion of patients in each ASC-12 categorical score level across time and condition. For ASC-12 categorical data, the Friedman test indicated that there are differences between the average score ranks among the conditions and time period,  $\chi^2(7, N = 32) = 57.827, P < .001$ . The post hoc Wilcoxon test with Bonferroni adjustment showed that attacks during menstruation scored significant higher than outside menstruation at the time points 1 hour ( $z = -3.08, P = .021$ ) and 4 hours ( $z = -2.97, P = .030$ ), but were not significant different at 2 hours ( $z = -2.59, P = .164$ ) and 24 hours ( $z = -.36, P = .875$ ). Multiple pairwise comparisons are shown in the Table 4.

## DISCUSSION

In this study, we prospectively assessed the allodynia score in the same patient sample at 2 different occasions, outside the menstrual period and during the menstrual period. The main finding of our study is that menstrual migraine attacks has an effect on allodynia,

**Table 2.—Allodynia Scores**

Groups	1 Hour		2 Hours		4 Hours		24 Hours	
	MM+	MM–	MM+	MM–	MM+	MM–	MM+	MM–
ASC-12	5.97 (5.01)	4.09 (3.72)	6.28* (5.82)	3.96 (4.59)	4.4 (5.13)	3 (4.43)	1.19 (2.17)	1.22 (3.03)

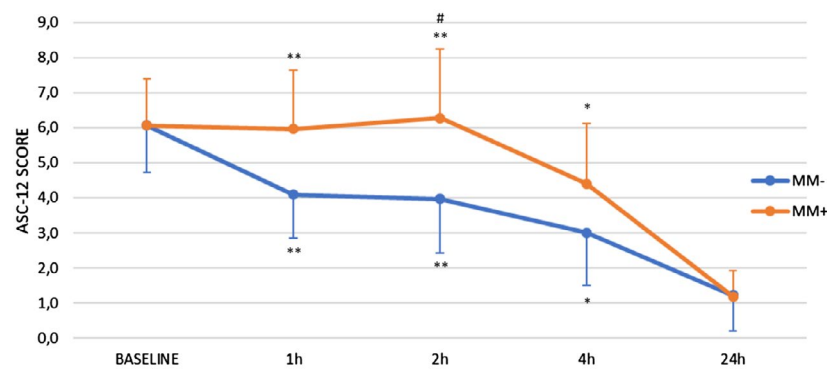
\* $P < .05$  vs MM– at 2 hours; ANCOVA's pairwise comparison.

Data are expressed as mean (SD).

MM+ = menstrual migraine attacks; MM– = non-menstrual migraine attacks.

**Table 3.—Allodynia Categorical Score in Women During the Menstrual Crisis (MM+) and Non-Menstrual Crisis (MM–), Measured 1, 2, 4, and 24 Hours After the Onset of Pain Attack. Data Expressed as Count (%)**

ASC-12	1 Hour		2 Hours		4 Hours		24 Hours	
	MM+	MM–	MM+	MM–	MM+	MM–	MM+	MM–
Absent (0-2)	12 (37%)	14 (44%)	14 (43%)	18 (56%)	17 (54%)	20 (62%)	27 (84%)	28 (88%)
Mild (3-5)	4 (13%)	8 (25%)	3 (9%)	5 (16%)	3 (9%)	5 (16%)	4 (13%)	2 (6%)
Moderate (6-8)	5 (16%)	7 (22%)	4 (13%)	3 (9%)	3 (9%)	3 (9%)	0	0
Severe (9-15)	11 (34%)	3 (9%)	11 (34%)	6 (19%)	9 (28%)	4 (13%)	1 (3%)	2 (6%)



**Fig. 1.—Allodynia symptoms checklist-12 scores of migraine attacks at MM+ and MM– conditions. Data are shown as mean ± 95% CI. \* $P < .05$ ; \*\* $P < .01$ ; within-group difference, vs “24 hours”. # $P < .05$ ; between-group difference, vs “MM–”. [Color figure can be viewed at wileyonlinelibrary.com]**

eliciting higher scores than non-menstrual attacks at the beginning (1-4 hours) of attacks.

Importantly, the external validity of our data is restricted to an audience of women, who are suffering from migraine and present allodynia in their menstrual cycles with migraine, in addition to other disorders related to the menstrual cycle such as premenstrual syndrome, dysmenorrhea, and endometriosis.

Burstein et al in 2000 studied allodynia in migraine patients showing that in migraine with allodynia, central sensitization of second-order brainstem trigeminal neurons was involved in addition of peripheral sensitization of first-order neurons, in some patients, central sensitization of third-order trigeminal neurons in the thalamus were observed.<sup>16</sup>

Central sensitization, an increased excitability of spinal and medullary dorsal horn neurons resulting from ongoing input from C-fiber nociceptors, may lead

to cutaneous allodynia, a neurologic condition characterized by pain elicited by ordinary non-nociceptive stimulation of the skin.<sup>17,18</sup> During migraine, facial cutaneous allodynia is likely to be a clinical manifestation of sensitization at the level of the trigeminal nucleus caudalis.<sup>19,20</sup>

Allodynia most often develops during the first few hours of an attack, although patients with chronic migraine are sometimes allodynic between attacks.<sup>21</sup>

In 1 study, the presence of allodynia was associated with inadequate 2-hour pain freedom and 24 hours pain response. The presence of allodynia significantly increased the likelihood of an inadequate treatment response for both of these outcomes (NSAIDs, triptan, and others).<sup>21</sup> In our study medication to migraine crises was guided to be done 1 hour or more after the onset of pain crisis. This practice was to uniform the symptoms of women.

**Table 4.—Multiple Comparisons of Allodynia Categorical (Ranked) Score in Women During the Menstrual Crisis (MM+) and Non-Menstrual Crisis (MM–), Measured 1, 2, 4, and 24 Hours After the Onset of Pain Attack**

	<i>z</i>	<i>P</i> Value
Between MM+ vs MM– comparisons		
MM+ (1 hour) vs MM– (1 hour)	–3.08	.021
MM+ (2 hours) vs MM– (2 hours)	–2.59	.164
MM+ (4 hours) vs MM– (4 hours)	–2.97	.030
MM+ (24 hours) vs MM– (24 hours)	–.36	.875
Within MM– comparisons		
1 hour vs 2 hours	–.45	.709
1 hour vs 4 hours	–.96	.341
1 hour vs 24 hours	–2.68	.080
2 hours vs 4 hours	–1.21	.240
2 hours vs 24 hours	–2.96	.032
4 hours vs 24 hours	–2.53	.192
Within MM+ comparisons		
1 hour vs 2 hours	–.35	.766
1 hour vs 4 hours	–1.33	.204
1 hour vs 24 hours	–3.86	.000
2 hours vs 4 hours	–1.58	.125
2 hours vs 24 hours	–3.67	<.001
4 hours vs 24 hours	–3.30	<.001

Population-based and clinical studies show that between 20 and 60% of women with migraines report an association with menstruation.<sup>8-10</sup> Attacks are more likely to occur between 2 days before menstruation and the first 3 days of bleeding.<sup>8,11-13</sup> Menstrual attacks are more severe and incapacitating, and they are less responsive to symptomatic medications, compared to crises in other periods of the menstrual cycle.<sup>10,22-27</sup> Menstrual migraine is also associated with menstrual distress and disability.<sup>28,29</sup>

As the menstrual period presents higher incapacitation, it is expected that allodynia may occur more frequently during this period. Two recent studies have reported that women have more allodynia than men; however, the studies did not evaluate the menstrual period.<sup>30,31</sup>

Güven et al studied migraine features in menstrually related and non-menstrual migraine in 332 patients. Longer duration, more frequent accompanying symptoms, including allodynia was found in menstrually related attacks.<sup>32</sup> As in Güven et al study, we measured the allodynia symptoms scale, but we investigated it in more detail, collecting allodynia data in several time points along the migraine attack. Our methodology could detect a finding not reported

previously, allodynia affected menstrual headache attacks longer than non-menstrual-related migraine.

Analyses of data from a multicenter, randomized, double-blind, placebo-controlled trial demonstrated that the clinical characteristics of MRM, defined as migraine headaches occurring from 2 days before to 2 days after the first day of menstrual flow, are similar to non-MRM with regard to their association with aura, allodynia, phonophobia, photophobia, nausea, level of pain intensity, and level of functional disability. In addition, almotriptan was similarly effective for the treatment of MRM and non-MRM as measured by efficacy outcomes that included 2-hour pain free, 2-hour pain relief, relief from migraine-associated symptoms, and return to normal function.<sup>33</sup> At the other hand, in others analysis, in MRM group, the number of patients with premonitory symptoms was higher and allodynia developed more frequently during the attack in this group,<sup>32</sup> as well as our study. MRM has been reported to be more frequent than non-menstrual migraine in patients who develop cutaneous allodynia during migraine attacks.<sup>34</sup>

The fact that menstrual crises present higher severity may be related to sex hormones. It is well known that estrogen, through widely distributed receptors in the brain, can electrophysiologically and morphologically modulate neuronal activity. There is high concentration of estrogen receptors in the hypothalamus. Brain areas related to migraine are associated with estrogen biosynthesis. Positron emission tomography has been used in order to measure estrogen in humans. As a result, estrogen can modulate allodynia behaviors that are related to migraine, mood changes, and dietary cravings. It is important to highlight that some structures, such as the amygdala, show changes during the menstrual cycle, more specifically, an increase in the volume of gray matter in the dorsal part of the left, during the premenstrual phase, when compared with the late follicular phase. Besides that, an increase in the hippocampal volume could be observed in the postmenstrual phase.<sup>35</sup>

A population-based study has shown that cutaneous allodynia is associated with female sex, headache frequency, increased body mass index, disability, and depression among migraineurs. Besides that, allodynia is more intense and common in migraine turned into headache than in other forms of cephalaea.<sup>1</sup>

Symptoms of allodynia in migraine were associated with current anxiety, depression, and several chronic pain conditions<sup>36</sup> and also presents with younger age of migraine onset, and with cigarette smoking, in addition to confirming several previously reported findings.<sup>36</sup> In our study, years living with migraine was associated with severe allodynia as well as age of menarche. No study analyzed age of the menarche and allodynia. However, in 1 study, independent of age and family history of migraine, each 1-year delay in onset of menarche decrease the odds of migraine by 7%, but, was not related to non-migraine headaches. The authors concluded that early puberty increases the risk of developing migraines by young adulthood and emphasized the need for understanding the pathophysiological links between puberty and developmental changes that occur in the brain during that period and the mechanisms of onset of the migraine disease and its trajectory.<sup>37</sup> Our study did not demonstrate an effect of neither contraceptives use as the Turkish populational analyses nor BMI in contrast to others in that cutaneous allodynia associated with increased BMI.<sup>1,38</sup> The small sample size of our study may have influenced these discrepant results.

Based on the fact that cutaneous allodynia maps onto the migraine biology, identifying factors that map onto disease biology as well as risk factors for clinical and anatomic progression for diseases have emerged as a very important public health priority because it may provide a foundation for more aggressive preventive intervention.<sup>1</sup> When identifying women with migraine and menstrual migraine, it is necessary to indicate effective preventive measures for the control of the disease. There are risk factors that are related to the progression of diseases, especially migraine,<sup>1</sup> such as the fact of being a woman, which is a not modifiable risk factor for chronification but can be mitigated if women are treated early, since migraine becomes chronic more commonly than in men.

The weakness of this study was the small sample size, a predominantly white population, and participants from a tertiary clinic. These facts limit the generalizability of our findings. Further studies, with larger sample, are needed in order to confirm the hypothesis that allodynia is not only more prevalent and severe in menstrual migraine attacks in women but also to show

how puberty and other hormones issues can interfere at the brain environment.

The strength of the study was its prospective design with participants tested as “controls” of themselves to compare menstrual vs non-menstrual attacks.

## CONCLUSION

The results of this study demonstrated that:

- Menstrual headache attacks have an influence on allodynia with higher allodynia scores when compared to non-menstrual-related attacks at 1, 2, and 4 hours after the onset of attack.
- There was a significant effect of the covariates age of menarche and migraine history on allodynia, but no effect of BMI or contraceptive use.
- Importantly, the external validity of our data is restricted to an audience of women, who are suffering from migraine and present allodynia in their menstrual cycles with migraine.
- These results show the need for further, prospective studies with more cases to validate the complexity of allodynia in women and their relationship to the menstrual cycle.

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