



RESEARCH

Cerebral lateralization in adolescent girls with premenstrual syndrome

Premenstrual sendromu olan adolesan kızlarda serebral lateralizasyon

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Abstract

Purpose: In this study, it was aimed to compare differences and similarities the cerebral lateralization of adolescent girls with Premenstrual Syndrome (PMS) with the control group. We also aimed to investigate whether there was a relationship between PMS severity and cerebral lateralization.

Materials and Methods: A total of 79 female adolescents aged 14-18 years who met the study inclusion criteria completed the study. A second interview was held with all participants who filled out the Premenstrual Assessment Form (PAF) during the luteal periods of menstrual cycles (1-7 days before menstruation). All participants completed the Harris lateralization test.

Results: The mean age was 192.85 ± 14.54 (range 167 - 216) months. The median PMS score was found to be 2.26 (1.00 - 5.10). While PMS was not detected in 35 (44.30%) participants, mild PMS was detected in 20 (25.32%) participants, moderate in 14 (17.72%), and severe in 10 (12.66%) participants. Sixty-seven (84.81%) participants had right hand dominance and three (3.80%) left hand dominance, nine (11.39%) participants had hand uncertainty. While the hand and eye dominance were on the same side in 41 (51.90%) participants, cross-lateralization (all right hand, left eye) was detected in 11 (13.92%) participants. Indeterminate lateralization (Harris lateralization score of 1 or 2) for the hand and eye was significantly higher in the PMS group.

Conclusion: The findings raise the question of whether lateralization (hand-eye) is less common in individuals with PMS and whether there will be a common etiology for lateralization problem and PMS. Further studies are needed considering the factors that may contribute to this etiology and some of the limitations we have presented in our study.

Keywords: Premenstrual syndrome, adolescence, cerebral lateralization

Öz

Amaç: Bu çalışmada amacımız, Premenstrual Sendromu olan kızlarda serebral lateralizasyon bulgularını sağlıklı adölesanlarla farklılıkları ya da benzerlikleri karşılaştırmaktır. Ayrıca Premenstrüel Sendromun şiddeti ile bu bulgular arasında bir korelasyon olup olmadığını da değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya dahil edilme kriterlerine uygun 14-18 yaş arası 79 kız ergen çalışmayı tamamladı. Premenstrüel Değerlendirme Formu (PDF)'nu dolduran tüm katılımcılar ile menstruasyon sikluslarının luteal dönemlerinde (adet olmadan önceki 1-7. günler arasında) ikinci görüşme yapıldı. Tüm katılımcılar Harris lateralleşme testini tamamladı.

Bulgular: Katılımcıların yaş ortalaması $192,85 \pm 14,54$ (aralık 167-216) ay olarak saptandı. PMS puanı ortancası 2,26 (1,00-5,10) olarak saptandı. 35 (44,30%) katılımcı PMS tanısı almazken, 20 (25,32%) katılımcıda hafif, 14 (17,72%) katılımcıda orta, 10 (12,66%) katılımcıda şiddetli PMS tespit edildi. 67 (84,81%) katılımcıda sağ el dominans ve 3 (3,80%) katılımcıda sol el dominans iken 9 (11,39%) katılımcıda elde belirsizlik olduğu görüldü. 41 (51,90%) katılımcıda el ve göz dominansı aynı tarafta iken, 11 (13,92%) katılımcıda çapraz lateralizasyon (tamamı sağ el, sol göz) saptandı. PMS grubunda el ve göz için belirsiz lateralizasyon (Harris lateralleşme puanı 1 veya 2 olmak) anlamlı derecede yüksek bulundu.

Sonuç: Çalışmamız, PMS tanısı alan grupta, kontrol grubuna göre lateralizasyonun (el-göz) daha az görülmesi lateralizasyon sorununa neden olan durumun PMS için ortak bir etyolojiden kaynaklanıp kaynaklanmadığı sorusunu akla getirmektedir. Etiyolojiye katkıda bulunabilecek faktörler ve çalışmamızda sunduğumuz birtakım kısıtlılıklar göz önüne alınarak yapılacak ileri araştırmalara ihtiyaç vardır.

Anahtar kelimeler: Premenstrual sendrom, adölesan, serebral lateralizasyon

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INTRODUCTION

The menstrual cycle is a physiological cycle in female that includes the follicular phase, ovulation, and luteal phase. Some individuals may be adversely affected in this cyclical process, especially during the luteal period¹. Premenstrual Syndrome (PMS) is a cyclical picture that manifests itself with physical (mastalgia, edema, pain in different parts of the body), emotional (restlessness, anger, anxiety, irritability, social withdrawal), behavioral (sleep and appetite) and cognitive (attention, focus) features in the luteal phase and regress with the onset of menstruation^{2,3}. It was reported that the prevalence of PMS is about 20-40%⁴. In the premenstrual period, the severity of many psychiatric disorders and the frequency of emergency psychiatric hospitalization increase⁵. During this period, neuropsychological functions, verbal and non-verbal memory, working memory, attention and concentration, reaction time, reasoning, language, executive functions (such as planning, impulse control, and cognitive flexibility), motor and visuospatial skills were investigated⁶. Those with PMS symptoms may have cognitive impairments such as concentration, memory, and motor coordination^{7,8}. Findings indicated that poor performance scores had effects on visuospatial and motor skills, verbal memory, working memory, reaction time, attention, and concentration, especially in the premenstrual luteal phase⁹⁻¹².

Cerebral lateralization is the ability that individuals acquire, perform and exhibit by controlling these behaviors according to the side of the cerebral hemispheres they dominate¹³. Many behavioral differences related to hemispheric dominance have been described. Some of these are verbal skills, spatial position and motor function. Many studies have suggested that sex steroid hormones affect cortical asymmetry, but it has not been clearly revealed which sex steroid causes it¹⁴. It has been reported that estrogen cycling may affect cerebral asymmetry in female rats¹⁵. On the other hand, studies have reported that the degree of may show individual differences in some psychiatric disorders such as schizophrenia, affective psychosis, autism spectrum disorder, and specific learning disorder¹⁶⁻¹⁹.

Individuals with PMS perform lower than the normal population in terms of some cognitive skills (verbal skills, working memory, and response speed etc.). However, studies showing that similar skills and functions (verbal functions, spatial position and

motor functions etc.) are affected in individuals with cerebral lateralization problems (with opposite or less lateralization) are noteworthy. The question of whether there is a problem in cerebral lateralization in individuals with PMS was found important. In this context, this study was planned as a preliminary study for future studies in this area, where we act with the idea of common etiology.

Our hypothesis was that there would be less cerebral lateralization in adolescent girls with PMS. As far as we know, there was no study in the literature investigating the relationship between cerebral lateralization and Premenstrual Syndrome. The aim of this study was to compare the cerebral lateralization of adolescent girls with PMS with the control group and to investigate whether there is a relationship between the severity of PMS and cerebral lateralization.

MATERIALS AND METHODS

Sample

The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences (Date: 30 June 2021, Project no: 2021/116), and informed consent was obtained from each participant and parent.

Participants consisted of girls aged 14-18 years who applied to the Child and Adolescent Psychiatry Clinic, Giresun University Maternity and Children Training and Research Hospital between July 2021 and October 2021. After the study had started, every adolescent who met the inclusion criteria was invited to the study. It was planned to apply the relevant tests in the luteal period to all people who participated in the study due to the problems experienced in the luteal period in general at PMS. The followings were determined as the exclusion criteria for the study; a) score below 100 on the Porteus test; b) Having any of the psychiatric disorders present or in the past; c) have a history of a chronic medical (such as diabetes mellitus, cancer), neurological (neurodegenerative diseases, epilepsy or trauma history with loss of consciousness for more than one hour) disease; d) have a known visual or hearing impairment; e) using an oral contraceptives; f) the menstrual cycle was irregular based on the statement.

Tests and scales were applied on the same day by the researchers. The data form prepared by the researchers was filled out. Kiddie Schedule for

Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) was administered to the participants for diagnosing psychiatric disorders in adolescents. After the first evaluation, 91 adolescents' performance was assessed via the Porteus Maze test. And scores of 100 and above 81 adolescents were included in the study; 2 adolescents did not complete the assessment, 79 adolescents with a valid score were asked to fill out the Premenstrual Assessment Form (PAF). 35 patients who scored below 1.7, which is a cut-off score, were designated as 'control group', and 44 adolescents with a score of 1.7 and above were designated as 'PMS group'. Then, all participants were invited to an interview during the luteal periods of their menstrual cycles (1-7 days before menstruation). Harris Tests of Lateral Dominance was performed on all participants.

Measures

Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL)

It is an interview form developed by Kaufman et al. in 1997 to evaluate past and present psychopathologies of children and adolescents²⁰. In 2004, the Turkish validity and reliability study was performed by Gökler et al.²¹. This form has good reliability and validity for diagnosing psychiatric disorders in children and adolescents. A child and adolescent psychiatrist interviewed the child and primary caregiver.

The Porteus Mazes Test (PMT)

This test is used as an individual intelligence test between the ages of 7-14 and aims to reveal the areas of intelligence such as ability to adapt to new situations, planning and determining general ability²². As a result of the test, the mental age of the person is obtained. The intelligence score is obtained by dividing one hundred times the intelligence age by the biological age. The intelligence level is determined by using the Porteus test intelligence division ruler. It has been reported that results similar to adults are obtained in individuals aged 13 and over, the age difference disappears, and a score above 100 is significant in terms of verbal and total IQ scores²³. Therefore, adolescents who scored 100 points or more were included in our study.

Premenstrual Assessment Form (PAF)

The Premenstrual Assessment Form was developed

to measure the symptoms and changes occurring in the premenstrual period. It assesses the prevalence and severity of premenstrual symptoms. It is a 95-item self-report scale and has 18 subscales. These scales include depressive features, lability, atypical depressive features, hysteroid features, hostility/anger, social withdrawal, anxiety, increased feeling unwell, impulsivity, organic mental features, water retention, physical disorders, autonomic changes, fatigue, impairment in social functioning, various mood/behavioral changes, and various physical changes²⁴. In 1994, the Turkish validity and reliability study was performed by Dereboy et al.²⁵. The main score is obtained by dividing the total score obtained from the items marked on this form by the number of questions. A score below 1.7 is defined as 'no PMS', a score between 1.7-2.8 is defined as 'mild PMS', and a score between 2.8-3.7 is defined as 'moderate PMS'. If it is over 3.7, it is defined as 'Severe PMS'. It was found that the form and its sub-dimensions had good internal consistency (Cronbach 0.97, 0.46-0.90, respectively)²⁵.

Harris Tests of Lateral Dominance

In the test developed by Harris, dominance is graded as right, left, diagonal, or indeterminate²⁶. Six items are used to determine hand lateralization, right-handed in five items, left-handed in five items, and left-handed in five items. If a different hand is preferred in at least two of the six items, this individual's hand preference is classified as 'uncertain'. Two items are used to determine eye lateralization. In both of the two items, the eye preference is classified as right in individuals using their right eye, and as left in individuals using their left eye. The eye preferences of individuals who prefer the right eye in one of the items and the left eye in the other are called uncertain. When the lateralization of the hand and eye is evaluated together, the test scores are calculated as follows; the lateralization of the right hand and the right eye is "6", the lateralization of the left hand and the left eye is "5", the lateralization of the right hand and the left eye (cross) is "4", the lateralization of the left hand and the right eye (cross) is "3", right or left lateralization in the hand is "2", indeterminate lateralization in the hand and eye is as "1"²⁷.

Statistical analysis

The data were analyzed using IBM SPSS Statistics version 21.0 software (IBM Corp., Armonk, NY, USA). As a result of the power analysis, the minimum

number of participants required to be included in each group to complete the study with the Minitab 17.0 program with 95% power was determined as 21. The conformity of quantitative data to normal distribution was checked with the Kolmogorov-Smirnov test. Quantitative data were summarized as mean \pm standard deviation and median (smallest value to largest value), while qualitative data were summarized as frequency (percent). Quantitative data were analyzed with the Mann Whitney U test or the Kruskal Wallis test according to the fit for normal distribution and the number of groups. Bonferroni correction was used for pairwise comparisons. Qualitative data were analyzed with the chi-square test or Fisher's exact test. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Seventy-nine adolescent girls were included in the study. The mean age was 192.85 ± 14.54 (range 167 - 216) months. The median PMS score was found to be 2.26 (1.00 - 5.10). While PMS was not detected in 35 (44.30%) participants, mild PMS was detected in 20 (25.32%) participants, moderate in 14 (17.72%), and severe in 10 (12.66%) participants. 67 (84.81%) participants had right hand dominance and 3 (3.80%) left hand dominance, 9 (11.39%) participants had hand uncertainty. Right foot dominance was found in 27 (34.18%) participants, left foot dominance was not found. 41 (51.9%) participants had right eye and 17 (21.52%) left eye dominance, 21 (26.58%) participants had eye uncertainty. While the hand and eye dominance were on the same side in 41 (51.90%) participants, cross-lateralization (all right hand, left eye) was detected in 11 (13.92%) participants (Table 1).

When hand and eye lateralization are evaluated together; There was no significant difference between PMS and control groups for lateralization of the right hand and right eye, lateralization or cross-lateralization of the left hand and left eye. Indeterminate lateralization (Harris lateralization score of 1 or 2) for the hand and eye was significantly higher in the PMS group ($p=0.022$). There was no statistical difference in hand, foot and eye dominance between participants with and without PMS (Table 2, Figure 1). There was no statistically significant correlation between PMS score and lateralization score ($r=-0.066$; $p=0.563$).

Table 1. PMS and Harris tests of lateral dominance findings of the participants

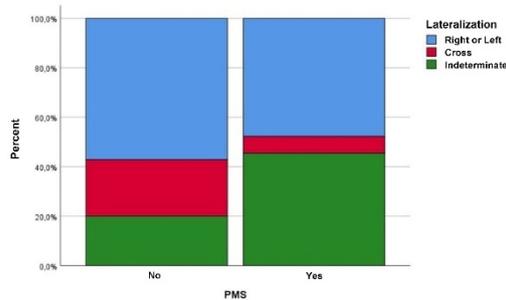
Variable	N(%)
PMS	
No	35 (44.30%)
Below	20 (25.32%)
Mild	14 (17.72%)
Moderate	10 (12.66%)
Hand dominance	
Right	67 (84.81%)
Left	3 (3.80%)
Indeterminate	9 (11.39%)
Foot dominance	
Right	27 (34.18%)
Left	0 (0.00%)
Indeterminate	52 (65.82%)
Eye dominance	
Right	41 (51.90%)
Left	17 (21.52%)
Indeterminate	21 (26.58%)
Cross lateralization	
No	41 (51.90%)
Yes	11 (13.92%)
Indeterminate	27 (34.18%)
Lateralization score	
1	3 (3.80%)
2	24 (30.38%)
3	0 (0.00%)
4	11 (13.92%)
5	2 (2.53%)
6	39 (49.37%)

The data are summarized as frequency (percent).

Table 2. Harris tests of lateral dominance findings

	PMS		p
	No (n=35)	Yes (n=44)	
Hand dominance			
Yes	33 (94.29%)	37 (84.09%)	0.285
Indeterminate	2 (5.71%)	7 (15.91%)	
Foot dominance			
Yes	15 (42.86%)	12 (27.27%)	0.226
Indeterminate	20 (57.14%)	32 (72.73%)	
Eye dominance			
Yes	29 (82.86%)	29 (65.91%)	0.151
Indeterminate	6 (17.14%)	15 (34.09%)	
Lateralization			
Right or left	20 (57.14%) ^a	21 (47.73%) ^a	0.022
Cross	8 (22.86%) ^a	3 (6.82%) ^b	
Indeterminate	7 (20.00%) ^a	20 (45.45%) ^b	

The data are summarized as frequency (percent). The same letters indicate that there is no statistically significant difference between the groups.

**Figure 1. PMS and control group lateralization**

DISCUSSION

The aim of this study was to reveal the differences or similarities in cerebral lateralization of female adolescents with premenstrual syndrome compared to healthy individuals. Indeterminate lateralization (Harris lateralization score of 1 or 2) for the hand and eye was significantly higher in the PMS group ($p=0.022$). The dominance of the 'right' or 'left' cortex, which we evaluated in terms of hand and eye dominance in normal individuals, is significantly less in the group with PMS, and therefore it is possible to

say that we found that brain asymmetry was generally less in the group with PMS. For this reason, it comes to mind that the reasons for the "less" or "decrease" of the asymmetry may be due to the etiology of PMS. Although many factors play a role in the etiology of PMS, the 'sensitive individual' theory is especially mentioned. This theory is that women with PMS experience recurrence of PMS symptoms when given a physiological dose of estrogen or progesterone after medical menopause induction with a GnRH agonist. This suggests that people with PMS symptoms may have different sensitivities at the receptor level, even if their blood levels of sex steroids are similar²⁸. In addition, some experimental studies have shown that sex steroids modulate the transmission of serotonin^{29,30}. In a known study, it was found that serotonin levels were low in people with PMS, especially in the luteal phase³¹. In the light of these studies, our study raises the question of whether the blood level of serotonin, the receptor sensitivities of sex steroids and their metabolites have an effect on the development of brain asymmetry, that is, lateralization. In this sense, measuring the serotonin blood level (especially in the luteal phase), finding some biomarkers that can show the effects of sex steroids and their metabolites at the receptor level, or

fMRI studies to be conducted in this area may guide us.

To our knowledge, this is the first study to examine cerebral lateralization in people with PMS. There is very little research in the literature on cerebral lateralization. Cerebral lateralization is important in the operation and control of some functional skills (such as verb, spatial, sensory and motor skills) depending on cerebral asymmetry^{32,33}. This situation also provides great clues in our understanding and naming of brain functions. Cerebral dominance (left or right) plays an active role in revealing some sensory and motor abilities. For example, left hemispherical dominance for language is paired with right hemispherical dominance for spatial attention^{15,34,35}. A recently published review reports that hemispheric activation is bilateral or right-lateralized in children with dyslexia during language processing³⁶. Stuttering was found to be associated with anomalies related to cerebral lateralization (especially in the prefrontal and occipital regions)³⁷. There are many studies investigating cerebral lateralization through right- or left-hand dominance, right or left eye dominance for different skills. Goodarzi et al. found that left eye dominance was significantly higher in patients with psychiatric disorders compared to the control group, but there was no such difference when hand and foot dominance was examined. It was stated that these patients may have increased activity of the right hemispheres³⁸.

In a wide range of species (including non-human species), hemispheric asymmetries were showed to vary not only with sex, but also with gonadectomy, hormone replacement, and natural fluctuations of endogenous sex steroid hormones¹⁴. Another study, results were obtained that the estrogen cycle affects cerebral asymmetry in female rats. It was observed that they made distinct (right or left) hand preferences during heat periods when estrogen levels were at their highest¹⁵. In this context, it can be thought that sex steroids have an effect on the development of asymmetric hemispheres. Some researchers believe that there is an 'unchanging' aspect of lateralization in brain development. On the other hand, some think that this situation is going through a 'developable' and 'progressive' process. Lenneberg suggested that the hemispheres were equally symmetrical during infancy, and lateralization occurs progressively, especially between the ages of 11-14³⁵. The inclusion of female adolescents over the age of 14 in our study is very important both in terms

of excluding the effect of the period between the ages of 12 and 14, when the menstrual cycle can be physiologically irregular because of the new onset of hormonally, and to exclude the effect of the 'developable of lateralization'.

In humans, the most obvious asymmetry known is hand dominance. In most of the human population, a single hand is clearly dominant in activities such as writing and throwing, and in about 90 percent of the population, the dominant hand is the right hand. Although there is no difference in the structure of the hands, this asymmetry can create some changes in the strength and density of the muscles and bones that support the dominant hand. But these are also a result, not a reason, of the dominance of this hand³⁹. In our study, it was observed that the cases without hand, eye and foot dominance (indeterminate) were at higher percentages in the PMS group. In a meta-analysis study, a 'decreased lateralization' state was mentioned in the group with Autism Spectrum Disorder, similar to our study¹⁹. In our study, bilateral lateralizations (hand-eye) were found to be significantly higher in the patient group diagnosed with PMS compared to the control group. This may suggest that some factors related to PMS (such as hormonal, biological, neurological or environmental) have a debilitating effect on cerebral lateralization and asymmetric development. Studies have claimed that performance in many perceptual-cognitive domains is regularly associated with the development of lateralization and that normative lateralization deviations cause performance reduction. Across the literature, the most common hypothesis is that greater lateralization is a sign of a more developed brain and is associated with better performance³⁴. The current study presents important findings in support of this view.

In this study, we could not consider the age variable because it was performed on young girls between the ages of 14-18 and lateralization test was not performed in the previous periods (from birth). In addition, we do not have objective information about whether there is an attempt to change the hand lateralization of these children. Although some psychological disorders (such as bipolar disorder, schizophrenia, specific learning disability, autism) that were previously evaluated in lateralization studies were excluded in our study, all psychiatric disorders (such as depressive disorder, anxiety disorder) could not be excluded. The high uncertainty of foot selection made it difficult to include foot

lateralization in the evaluation of bilateral lateralizations. Similarly, because of the low left-hand dominance in both the PMS group and the control group, the study needs to be repeated in a larger sample group. Finally, no cranial imaging modalities or electrophysiological studies were performed in our study. Studies involving these methods can shed light on clinical studies with lateralization.

In conclusion, our study will guide further studies as it will contribute to the few studies in the literature on both cerebral lateralization and Premenstrual Syndrome. The findings raise the question of whether lateralization (hand-eye) is less common in individuals with PMS and whether there will be a common etiology for lateralization problem and PMS. In this sense, the blood-serotonin levels of individuals, the effects of sex steroids and their metabolites on the receptor, and further studies in these areas may shed light on brain lateralization differences. Considering the possible etiological factors and the limitations mentioned in our study, further studies are needed.

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