The European Research Journal 2023;9(3):495-501 Original Article

DOI: 10.18621/eurj.994103 *Radiology*

Is primary dysmenorrhea affected by gray matter volumetric changes in the brain?

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ABSTRACT

Objectives: We aimed this study to investigate the relationship between gray matter volume differences women who suffer from primary dismenorrea (PD) and asymptomatic women.

Methods: Brain magnetic resonance (MRI) imaging of 113 PD patients and 113 healthy women were performed. The volume of gray matter structures was calculated with the VolBrain automatic calculation system.

Results: Cut-off values were found by ROC analysis for right, left and total volumes in both groups. A caudate lobe volume above 6.33 cm3 is 99.1% sensitive and 77.9% specific for a diagnosis of PD. In addition, the volumes of other pain-related gray matter regions were decreased in PD patients ($p < 0.001$).

Conclusions: Atrophic changes in the medial GM structures in the brain in women with PD may cause hyperalgesia and the quantitative determination of these morphological changes may play an important role in the diagnosis of PD.

Keywords: Primary dysmenorrhea, gray matter volumetry, magnetic resonance imaging, thalamus, hippocampus, caudate nucleus

Primary dysmenorrhea (PD) is characterized by pain in the lower abdomen during the menstrual cycle without an underlying organic disease. It is more common especially in the adolescent age [1]. In PD pathophysiology is held responsible myometrial hypercontractility, especially due to increased release of prostaglandins [2]. Myometrial hypercontractibility causes menstrual pain. In addition, it has been stated that the neurohypophyseal hormones vasopressin and oxytocin also contribute to the process. Women with PD suffer from both lower abdominal pain and symptoms such as headache, nausea, and vomiting [3]. PD is an important factor in decreasing the quality of life and the ability to perform daily activities due to all these symptoms [4]. Although endocrine evaluations have been made for the etiology of PD in some previous studies, the central mechanisms underlying PD remain largely uncertain. PD should also be seen as one of the central sensitivity syndromes due to systemic symptoms such as headache, nausea and vomiting. Since there is a cyclical nature of pain and painless periods in PD, it has been suggested in previous publications that neuroimaging can explain the brain mechanisms in determining the pathophysiology of PD [5]. In previous studies, normal and abnormal brain changes that occur in PD are examined [6, 7]. In

Received: ***September 11, 2021;*** *Accepted:* ***November 26, 2022;*** *Published Online:* ***June 21, 2022***

How to cite this article: *Kaplan E, Kaplan S. Is primary dysmenorrhea affected by gray matter volumetric changes in the brain? Eur Res J 2023;9(3):495-501. DOI: 10.18621/eurj.994103*

e-ISSN: 2149-3189

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addition, in a previous study, it was stated that voxel changes in gray matter (GM) volume on magnetic resonance imaging (MRI) may be associated with PD [8].

Determining brain structure and brain volume in MRI images is used to understand the etiology of diseases associated with atrophy [9]. Manual segmentation volume measurement in MRI was used to determine neuroanatomical structures, but its application is limited because it takes time [10]. Automated brain volume analysis from MRI images is a modern and fast computer-aided diagnosis (CAD) management. There are many software packages available that provide quick and easy brain segment volume measurements.

VolBrain (VB) is a software package that automatically measures brain volume. The volume measurement is presented in centimeter cube (cm3) and as a percentage by measuring the brain volume from both the main brain parenchyma structures and small structures, It also specifies the normal volume and percentage ranges according to the gender and age of the patient. Presents the volume measurements obtained from the brain parenchyma as a result file [9].

The purpose of this study is to investigate the relationship between GM volume differences women who suffer from PD and asymptomatic women.

METHODS

This study is a case-control study conducted by examining brain MRI images of 113 female patients diagnosed with primary dysmenorrhea between January 2019 and October 2020 at the gynecology outpatient clinic of Adıyaman Training and Research Hospital. Brain MRI images of 113 female patients who were not diagnosed with PD and whose brain MRI images were recorded in our system were included in the study as the control group.

The diagnosis of primary dysmenorrhea was made by a gynecologist with 10 years of experience. The Gracey box scale, which is used to evaluate pelvic pain, was used for pain assessment in patients. Patients with a pelvic pain intensity score of 9 or more and an unpleasantness score of 7 or more were included in the study [11].

For patients with PD diagnosis, being in the reproductive age between 18-45 years of age, having no known pelvic pathology (adenomyosis, endometriosis, previous pelvic inflammatory disease, etc.), having brain MRI images in the hospital database, and not having a history of minor and / or major surgery in the last two years are the criteria for inclusion.

Patients under 18 years of age, having additional pathologies that may cause chronic pelvic pain, being diagnosed with / receiving migraine even if suffering from PD, being a tension headache, being diagnosed with known intracranial hypo / hypertension, intracranial mass, cerebrovascular disease, previous cerebral venous thrombosis or a history of neurological disease such as demyelinating pathologies (such as multiple sclerosis, acute disseminated encephalomyelitis) were exclusion criteria. In addition, patients with complaints of menstrual irregularity, menorrhagia and menometrorrhagia and using oral contraceptives due to these complaints were excluded from the study.

Imaging Parameters

MRI imaging was carried out in the periovulatory phase of the menstrual cycle 12-16 days. T1-weighted,

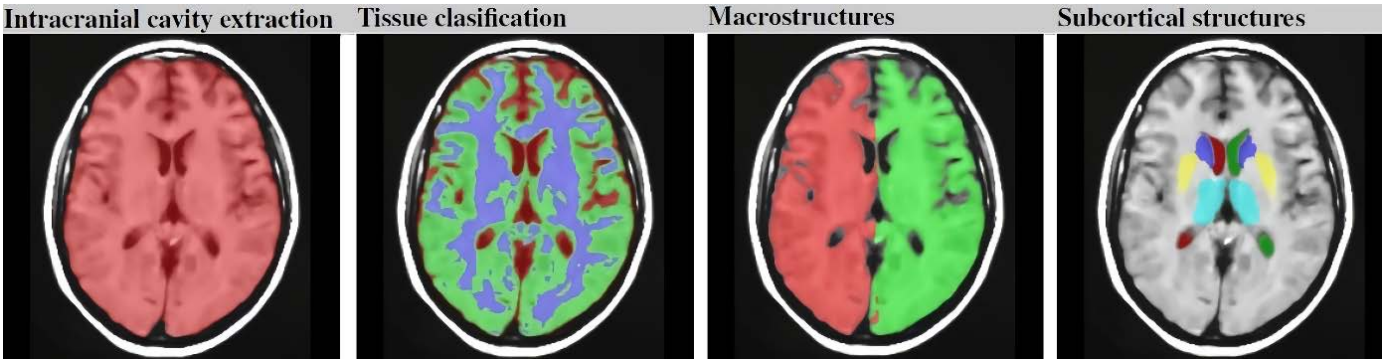

Fig. 1. Images presenting highlighted subcortical structures, as occurred from the processing of VolBrain.

3-dimensional gradient-echo anatomic MRI scans using a 3-dimensional fast spoiled gradient recall sequence (TR = 8.548 ms, TI = 400 ms, flip angle = 15_, matrix = 256 _ 256 _ 124, in-plane field of view = 260 _ 260 _ 1.5 mm3) on a 1.5-T MRI scanner (Gyroscan Intera, Philips Medical Systems, Best, The Netherlands).

Volume Measurement with VB

Evaluation of MRI images was done by a 5-year-experienced radiologist. Analysis was done with VB software from VB internet platform. DICOM images were converted to NIFTI format using ITK Snap software before being transmitted to VB. The relevant volumes of the brain structures of patients with PD were measured using NQ software, and a "multiple structure report" and a "general report" were created about the data (Fig. 1).

The hippocampus is part of the limbic system and plays a role in learning, decision making and memory formation. It also contributes to the processing of pain and the formation of attention and anxiety associated with pain [12, 13]. The amygdala plays a role in pain anticipation and emotional processing of pain [14, 15]. It has also been reported to be associated with lower back pain [15]. The thalamus has many roles, from transmitting sensory and motor signals to regulating consciousness and wakefulness [17]. Studies on patients suffering from chronic pain have noted a decrease in GM volume in areas such as the thalamus. These pain processing regions have also been reported in chronic pain conditions such as migraine and cluster headache [18-21, 22-25]). Right, left and total volumes were measured and noted for each patient from each of these regions.

Statistical Analysis

SPSS 22 program was used to analyze the data. Kolmogrow Smirnov test was used as normal distribution test. Mann Whitney U test and ROC analysis were used in the analyzes. A value of $p < 0.05$ was considered significant.

RESULTS

Demographic characteristics and clinical symptoms of the PD group and control group in this study are shown in Table 1.

When the volumetric measurements made for the PD patient group and the healthy female group (HG) were compared, the caudate nucleus, globus pallidus, thalamus and hippocampus volumes decreased in women with PD ($p < 0.001$), and the amygdala volume increased in women with PD ($p = 0.005$). When the GM total volume was compared, there was no significant difference between the groups ($p = 0.060$) (Table 2).

The effect of GM volumes on diagnostic decision making for PD distinction was evaluated by ROC analysis and the cut off values are given in Table 3. It was found that the caudate nucleus volume was a very good diagnostic test for PD, while the putamen and globus pallidus volumes were good diagnostic tests ($p < 0.001$). A caudat nucleus volume above 6.33 cm3 is 99.1% sensitive and 77.9% specific for the diagnosis of PD. Putamen volume above 8.06 cm3 is 81.4% sensitive and 46% specific for the diagnosis of PD. If the thalamus volume is above 5.21 cm3, it is 81.4% sensitive and 67.3% specific for the diagnosis of PD. Globus pallidus volume above 1.85 cm3 is 86.7% sen-

Table 1. Demographics and clinical characteristics of the participants

	PD	HG
Age (years)	24.9 ± 4.21	27 ± 3.26
Menstural cycle (Days)	27.8 ± 1.9	28.9 ± 2.2
Menstural phase (Days)	3-7	3-9
Disease duration(years)	5.3 ± 2.7	0
Average pain intensity GBS	15.7 ± 3.2	2.4 ± 1.1
Average pain unpleasantness GBS	13.1 ± 2.1	3.8 ± 1.7

Data are shown as mean±standard deviation or minimum-maximum. HG = Healthy Group, PD = Primary dismenorrea, GBS = Gracey Box Scale

Table 2. Gray matter volume comparisons according to the presence of primary dysmenorrhea

	Groups										
	HG					PD					
	X	SD	Median	Min	Max	X	SD	Median	Min	Max	*p* value
Caudate R	3.40	0.35	3.54	2.79	3.76	2.78	0.27	2.75	2.40	3.29	**< 0.001**
Caudate L	3.43	0.26	3.52	3.00	4.02	3.02	0.27	2.97	2.65	3.54	**< 0.001**
Caudate T	6.84	0.59	7.23	5.79	7.44	5.81	0.38	5.82	5.11	6.36	**< 0.001**
Putamen R	4.04	0.38	4.12	3.09	4.97	3.19	0.86	3.71	1.75	4.22	**< 0.001**
Putamen L	3.86	0.22	3.91	3.45	4.35	3.29	0.50	3.37	2.52	4.02	**< 0.001**
Putamen T	7.91	0.53	7.98	7.00	9.32	6.49	1.33	7.08	4.27	8.12	**< 0.001**
Thalamus R	5.22	0.84	5.36	3.76	7.12	4.31	0.49	4.14	3.69	5.19	**< 0.001**
Thalamus L	5.19	1.04	5.60	3.71	7.45	4.67	0.55	5.13	3.84	5.23	**< 0.001**
Thalamus T	10.41	1.86	10.95	7.48	14.57	8.99	0.92	9.18	7.53	10.42	**< 0.001**
Globus Pallidus R	1.02	0.23	1.00	0.65	1.48	0.75	0.15	0.72	0.28	1.00	**< 0.001**
Globus Pallidus L	0.99	0.25	1.01	0.70	1.39	0.71	0.14	0.65	0.48	0.92	**< 0.001**
Globus Pallidus T	2.01	0.43	1.98	1.39	2.68	1.46	0.29	1.37	0.75	1.92	0.468
Hippocampus R	3.97	0.57	3.94	3.08	4.90	3.86	0.49	3.75	3.32	5.22	**0.001**
Hippocampus L	3.57	0.70	3.65	2.61	5.70	3.78	0.46	3.79	3.21	4.61	**0.016**
Hippocampus T	7.53	1.20	7.20	5.70	10.56	7.65	0.82	7.37	6.55	9.72	0.921
Amygdala R	0.62	0.12	0.60	0.47	0.82	0.61	0.09	0.62	0.44	0.75	**< 0.001**
Amygdala L	0.72	0.08	0.74	0.42	0.79	0.65	0.11	0.68	0.46	0.80	**0.038**
Amygdala T	1.34	0.15	1.28	0.92	1.56	1.27	0.18	1.33	0.97	1.47	**< 0.001**
Accumbens T	0.18	0.05	0.19	0.11	0.28	0.27	0.09	0.26	0.16	0.55	**0.005**
Accumbens R	0.30	0.11	0.24	0.06	0.46	0.26	0.10	0.27	0.08	0.41	0.556
Accumbens L	0.48	0.14	0.47	0.17	0.65	0.46	0.20	0.51	0.09	0.78	0.468
GMR	608.40	137.74	546.85	497.25	1057.35	563.94	66.32	552.16	471.60	669.91	0.985
GMT	303.18	67.52	274.48	248.69	525.20	279.40	34.24	275.62	232.49	334.10	0.060
GML	305.1	70.23	272.52	248.56	532.15	284.85	32.39	279.78	239.22	336.12	0.867

R = Right, L = Left, T = Total, HG = Healthy Group, PD = Primary dismenorrea, GM = Gray matter, SD = standard deviation, Min = minimum, Max = maximum

sitive and 59.3% specific for the diagnosis of PD. On the other hand, if the nucleus acumbens volume is below 0.23 cm3, the diagnosis of PD is 76.1% sensitive and 80.5% specific (Fig. 2).

DISCUSSION

This study reveals brain morphological changes such as GM volumes in women suffering from PD in comparison with healthy female patients. There are significant changes in GM volumes in patients with PD, and it has decreased compared to healthy women. Especially the caudat nucleus volume being above 6.33 cm3 has a high specificity and sensitivity for the diagnosis of PD. These findings show that spontaneous cyclic recurrent pain such as PD can be explained by quantitative measurements of macroscopic brain structures.

The relationship between the hippocampus and

Table 3. Gray matter volumes validity results

	AUC	*p* value	Cut-off	Sensitivity	Specificity
Caudate R	0.883	< 0.001	3.16	90.3	77.9
Caudate L	0.872	< 0.001	3.26	85.8	77.9
Caudate T	0.890	< 0.001	6.33	99.1	77.9
Putamen R	0.794	< 0.001	4.11	86.7	61.9
Putamen L	0.807	< 0.001	3.85	81.4	67.3
Putamen T	0.741	< 0.001	8.06	81.4	46.0
Thalamus R	0.817	< 0.001	4.65	80.5	83.2
Thalamus L	0.688	< 0.001	5.21	81.4	67.3
Thalamus T	0.747	< 0.001	10.08	81.4	67.3
Globus Pallidus R	0.819	< 0.001	0.95	86.7	68.1
Globus Pallidus L	0.833	< 0.001	0.89	86.7	59.3
Globus Pallidus T	0.852	< 0.001	1.85	86.7	59.3
Accumbens T	0.770	< 0.001	0.23	76.1	80.5

R = Right, L = Left, T = Total, AUC = Area Under the ROC Curve

chronic processes such as depression, post-traumatic stress disorder, and chronic back pain has been investigated and it has been reported that the hippocampus plays a role in the underlying mechanisms [12]. MRI has been used to evaluate the correlation of hippocampal structural volume in pathologies characterized by chronic headache that previously occurred with cyclical triggers such as migraine [22]. In addition, in the studies conducted by Liu and Chen [12] in patients suffering from episodic migraine, it was reported that

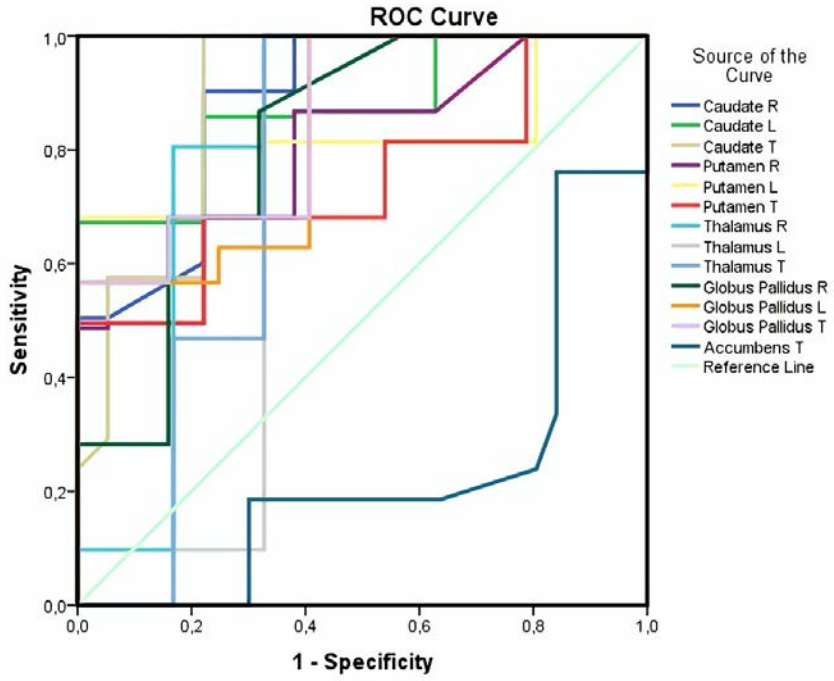

Fig. 2. ROC analysis chart and AUC values by regions. ROC = Receiver Operating Characteristic, AUC = Area Under the ROC Curve

the hippocampal volume was higher than in healthy groups. It is known that the thalamus transmits peripheral nociceptive stimulation to the necessary areas in the brain for sensory separation [23]. Macroscopic GM changes may also be associated with changes in spinal synapse density, changes in cell size, and changes in interstitial fluid and blood flow [24]. Considering this, it can be thought that the peripheral cyclic nociceptive stimulation in the thalamus tries to reduce the effect due to the menstrual cycle by rearranging and therefore, it undergoes volumetric changes adaptively. In this study, supporting these data in female patients suffering from cyclically occurring chronic pelvic pain, the hippocampus, bilateral putamen and caudate nucleus volumes of women suffering from cyclic pain have changed and their removal has decreased, unlike the studies. This may be a result of constant exposure to hormonal cyclic changes. Consistent with these studies, thalamus and hippocampus volumes were decreased in patients suffering from chronic pain such as primary dysmenorrhea. This data supports that volume changes in these regions in patients with PD also play a role in the patient clinic. In addition, the determination of volume cut-off values that can be evaluated in predicting the diagnosis of PD in the described areas with increased volume is also very important. Measuring the volume of these structures in female patients of reproductive age who admitted to neurology outpatient clinics with headache complaints without knowing the diagnosis and clinic of PD can also be a guide for diagnosis and may allow women to be directed for correct treatment and diagnosis. Morover these study results helps to distinguish between PD and other gynecological and non-gynecological syndromes that cause chronic pelvic pain accompanied by underlying pathologies.

In female patients suffering from episodic migraine, connections were discovered in the hippocampus, bilateral insula, right amygdala, bilateral putamen and caudate nucleus pain-related regions in the healthy female group compared to the patient female group [25]. PD, just like migraine, can be considered as a chronic disease with episodic features but limited to the menstrual phase [26].

Strengths of this study; the study was planned as a case control and the volume of all GM area which were thought to contribute to the formation and transmission of pain was measured for both the right and left brain lobes, and the necessary analyzes were made to determine the diagnostic value and the volume values with high sensitivity and specificity were determined. In addition, it was calculated using an easily accessible automatic software program for volume analysis. In many previous studies, it has been shown that the VB program performs volume measurement accurately and quickly [27].

Limitations

Our study has some limitations. First of all, the study was conducted in a single center and volumetric brain parenchymal changes that may be due to factors such as race and origin were not taken into consideration. In addition, in patients with PD who participated in the study, MRI scans were performed only in the periovulatory phase. Further studies including the menstrual phase can be performed for morphological evaluations related to this cyclic pain.

CONCLUSION

The results of this study show that atrophic changes in the medial GM structures in the brain in women with PD may cause hyperalgesia and the quantitative determination of these morphological changes may play an important role in the diagnosis of PD. In order to generalize the results of the study to the population, studies with larger patient populations are needed.

Authors' Contribution

Study Conception: EK; Study Design: EK; Supervision: N/A; Funding: SK; Materials: SK; Data Collection and/or Processing: EK, SK; Statistical Analysis and/or Data Interpretation: EK, SK; Literature Review: SK; Manuscript Preparation: EK and Critical Review: EK, SK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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