

Volume Gain of Brainstem on Medication-Overuse Headache Using Voxel-Based Morphometry

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Abstract

Background: Histopathology identified the anatomical and molecular abnormalities of brainstem nuclei in migraine patients. However, the exact whole brainstem structural changes *in vivo* have not yet been identified in medication-overuse headache (MOH) transformed from migraine. The aim of this study was to investigate the regional volume changes over the whole brainstem in the MOH patients using voxel-based morphometry (VBM) *in vivo*.

Methods: High-resolution three-dimensional structural images were obtained using a 3.0-Tesla magnetic resonance system from 36 MOH patients and 32 normal controls (NCs) who were consecutively recruited from the International Headache Center, Chinese People's Liberation Army General Hospital, from March 2013 to June 2016. VBM was used to assess the brainstem structural alteration in the MOH patients, and voxel-wise correlation was performed to evaluate the relationship with the clinical characteristics.

Results: The brainstem region with increased volume located in the left ventrolateral periaqueductal gray (MNI coordinate: -1, -33, -8), ventral tegmental area (MNI coordinate: 0, -22, -12), bilateral substantia nigra (MNI coordinate: -8, -16, -12, 9, -16, -12), and trigeminal root entry zone (MNI coordinate: -19, -29, -31; 19, -32, -29) in MOH patients compared with NCs. The headache visual analog scale score was positively related with the left rostral ventromedial medulla (RVM) (MNI coordinate: -1, -37, -56; cluster size: 20; $r = 0.602$) in the MOH patients.

Conclusions: The regional volume gain of brainstem could underlie the neuromechanism of impaired ascending and descending pathway in the MOH patients, and the left RVM volume alteration could imply the impaired tolerance of nociceptive pain input and could be used to assess the headache disability in the MOH patients.

Key words: Medication-Overuse Headache; Substantia Nigra; Trigeminal Root Entry Zone; Ventral Tegmental Area; Voxel-Based Morphometry

INTRODUCTION

Medication-overuse headache (MOH) is a secondary headache with excessive drug intake^[1] with a 2–3% 1-year prevalence in the general population and 50% with chronic migraine transformation.^[2,3] Although MOH can be clinically diagnosed according to the preexisting headache disorder and the medication intake history based on the International Classification of Headache Disorders, third edition, beta version (ICHD-III beta),^[1] the potential mechanisms of MOH remain widely unknown. However, the latest magnetic resonance (MR) imaging (MRI) studies about the brain structure and function have increased the understanding of MOH.

In previous studies, altered functional connectivity of the marginal division in migraine was identified in MOH,^[4] and an altered intrinsic functional connectivity architecture was confirmed.^[5] Texture feature analysis also demonstrated that the texture contrast of periaqueductal gray (PAG) could be used to observe the altered imaging characteristics of MOH and also considered as an imaging biomarker for

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MOH diagnosis.^[6] The lateral pain system dysfunction, including the postcentral gyrus, inferior parietal lobule, and supramarginal gyrus presented in MOH^[7] and the altered functional connectivity of the nucleus accumbens and dorsal rostral putamen, was identified in MOH and could be used to discriminate MOH and non-MOH patients.^[8] These functional MRI studies indicated that MOH could lead to altered brain function, which may be associated with the ascending and descending pain pathways in the brainstem. Therefore, the investigation of brainstem structure alteration could provide more valuable information to understand the pain pathway in MOH.

Voxel-based morphometry (VBM) studies demonstrated that supratentorial brain regions presented decreased volume in MOH,^[9,10] and infratentorial brainstem regions showed increased volume in the PAG region,^[9,11] and decreased PAG volume was demonstrated after medication withdrawal in MOH.^[12] Previous brainstem VBM studies demonstrated that migraineurs presented gray matter volume decrease in the spinal trigeminal nucleus, dorsomedial pons, PAG, dorsolateral pons, and medullary raphe,^[13] and another study confirmed the smaller midbrain volumes in migraineurs.^[14] In the aforementioned two studies, the migraineurs were diagnosed without medication overuse according to the ICHD-II and ICHD-III beta. Therefore, it is possible that the supratentorial brain volume would decrease in MOH and the infratentorial brainstem volume would decrease in migraineurs and increase in MOH patients; the latter was the key investigation target in the current study.

In this study, we hypothesize the causes of brainstem volume increase in MOH patients. To address this hypothesis, high-resolution structural images were obtained from 36 MOH patients and 32 normal controls (NCs) using a 3.0T MR system. Second, VBM was performed to investigate the altered brainstem volume in MOH patients. Finally, voxel-wise correlation was performed to identify the relationship between the brainstem volume and the clinical variables.

METHODS

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital (No. S2015-085-01). Written informed consent was obtained from all of the participants before the study, and its protocol was approved by the Ethical Committee of Chinese PLA General Hospital.

Subjects

Thirty-six MOH patients were consecutively recruited from the International Headache Center, Chinese PLA General Hospital, from March 2013 to June 2016. The diagnosis of MOH had to meet the following criteria according to the ICHD-III beta:^[1] (1) a diagnosis of 8.2 MOH; (2) 1.1 and 1.2 migraine; (3) age between 20 and 60 years; (4) right handed;

and (5) the absence of alcohol, nicotine, or other substances. The exclusion criteria included (1) migraine preventive medication used in the past 3 months; (2) any chronic disorders, such as hypertension, diabetes mellitus, and cardiovascular diseases; (3) cranium trauma, psychotic disorder, and the regular use of a psychoactive or hormone medication; and (4) MRI contraindications such as pacemakers, defibrillators, or other implanted electronic devices. Thirty-two NCs were enrolled who should not have had any primary headache disorders or other types of headache in the past year and who had the same exclusion criteria as the MOH patients. All of the patients were given the visual analog scale (VAS) to evaluate their headache intensity. All of the participants received the neuropsychological test including the Hamilton Anxiety Scale (HAMA),^[15] the Hamilton Depression Scale (HAMD),^[16] and the Mini-Mental State Examination (MMSE).^[17] A conventional MRI examination was administered to exclude participants with cerebral infarction, malacia, or tumor lesions. All of the participants were instructed to avoid alcohol, nicotine, caffeine, and other substances for at least 12 h before the MRI examination.

Magnetic resonance imaging acquisition

The brain structural images (an axial three-dimensional T1-weighted fast-spoiled gradient-recalled echo) were acquired using a GE 3.0T MR system (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) with the following parameters: repetition time = 6.3 ms, echo time = 2.8 ms, flip angle = 15°, field of view = 25.6 cm × 25.6 cm, matrix = 256 × 256, number of acquisition = 1, and slice thickness = 1 mm. Conventional MR images were also acquired. All of the imaging protocols were applied to all of the participants. No obvious structural damage and T2-visible lesions were observed based on the conventional MR images.

Magnetic resonance image processing

All of the MR structural image data were processed using Statistical Parametric Mapping (v12.0) software (<http://www.fil.ion.ucl.ac.uk/spm/>) and the SUI extension (<http://www.fil.ion.ucl.ac.uk/spm/>). The image processing included the following steps:^[13] (1) the image origin was set at anterior commissure (0, 0, 0); (2) the infratentorial brain structure was isolated; (3) the isolated structure images were spatially normalized with an unbiased atlas template of the brainstem after each image was cropped and brainstem masked;^[18] (4) the brainstem maps were resliced into the SUI space, and 3-mm full width at half maximum was applied with Gaussian smoothing spatially before the voxel-based statistics [Figure 1].

Statistical analysis

The age was assessed using the independent sample *t*-test, and HAMA, HAMD, and MMSE were assessed using Mann-Whitney *U*-test because of nonnormal distribution. The data with normal distribution presented by mean ± standard deviation and the data with nonnormal distribution by median (interquartile range). Significant

difference was set at a $P < 0.05$. The statistical analysis was performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA).

VBM was performed and statistical parametric mapping was generated with the factorial design specification two-sample t -test covarying with age and sex. Voxel-wise correlation was performed between the brainstem volume and the clinical variables. The minimal number of contiguous voxels was set based on the expected voxels per cluster. The false discovery rate was assessed using multiple comparison corrections ($P < 0.05$).

RESULTS

Clinical characteristics of medication-overuse headache patients and normal controls

There was no significant difference in age between the MOH patients and the NCs ($P > 0.05$). Table 1 demonstrates

Characteristics	MOH ($n = 36$)	NC ($n = 32$)	Statistics	P
Female/male	31/5	20/12	NA	NA
Age (years)	42.47 ± 9.34	41.34 ± 10.89	2.00*	0.65
DD	17.81 ± 5.81	NA	NA	NA
VAS	8.28 ± 1.60	NA	NA	NA
HAMA	19.5 (11.75)	10 (4.75)	4.47†	0.00
HAMD	21 (17)	8 (7.5)	4.80†	0.00
MMSE	27 (4.0)	28 (1.75)	1.79*	0.07

Data were shown as n , mean ± SD or median (interquartile range); * t values using independent sample t -test; † Z value using Mann-Whitney U -test; MOH: Medication-overuse headache; NC: Normal control; DD: Disease duration; VAS: Visual analog scale; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; MMSE: Mini-Mental State Examination; NA: Not available; SD: Standard deviation.

that HAMA and HAMD were higher in the MOH patients (19.5 [11.75] and 21 [17], respectively) than that in the NCs (10 [4.75] and 8 [7.5], respectively) ($P < 0.05$). The MMSE was lower in the MOH patients (27 [4.0]) than that in the NCs (28 [1.75], $P < 0.05$). The mean disease duration was 17.81 ± 5.81 years, and the mean VAS was 8.28 ± 1.60.

Comparison of brainstem volume between medication-overuse headache patients and normal controls by voxel-based morphometry

Table 2 presented that the brainstem regions with volume gain located in the left ventrolateral PAG (vlPAG), ventral tegmental area (VTA), bilateral substantia nigra (SN), and trigeminal root entry zone (REZ) in the MOH patients compared with the NCs [Figure 2]. There was no brainstem region with reduced volume in the MOH patients compared with the NCs.

Voxel-wise correlation analysis between brainstem volume and clinical variables

Voxel-based correlation demonstrated that the left rostral ventromedial medulla (RVM) (MNI coordinate: -1, -37, -56; cluster size: 20; $r = 0.602$) was positively related to the VAS scores [Figure 3]. The other clinical variables, including disease duration, HAMA scores, HAMD scores, and MMSE scores, showed no correlation with brainstem volume.

DISCUSSION

In the current study, the left vlPAG presented increased volume in the MOH patients compared with the NCs, which was in accordance with previous research.^[9,11] However, the difference with previous studies^[9,11] was that the current study reported the detailed increased location of PAG while previous studies only demonstrated that the whole

Anatomic regions	MNI space			Cluster size	t^*	P
	X	Y	Z			
Left ventrolateral periaqueductal gray	-1	-33	-8	10	3.293	0.000
Ventral tegmental area	0	-22	-12	12	3.392	0.000
Left substantia nigra	-8	-16	-12	51	3.546	0.000
Right substantia nigra	9	-16	-12	173	4.023	0.000
Left trigeminal root entry zone	-19	-29	-31	63	3.841	0.000
Right trigeminal root entry zone	19	-32	-29	29	3.268	0.000

*The maximum of t value for the positive cluster representing the statistical difference between MOH and NC. MOH: Medication-overuse headache; NC: Normal control; MNI: Montreal Neurological Institute.

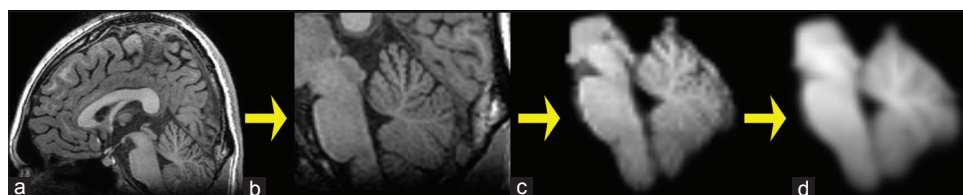


Figure 1: Flowchart of VBM for the infratentorial brain structures. (a) the raw 3D T1WI; (b) the isolated infratentorial structures; (c) the normalized infratentorial structures into the SUIT space; (d) the smoothed infratentorial structures. VBM: Voxel-based morphometry; 3D: Three-dimensional; T1WI: T1-weighted imaging.

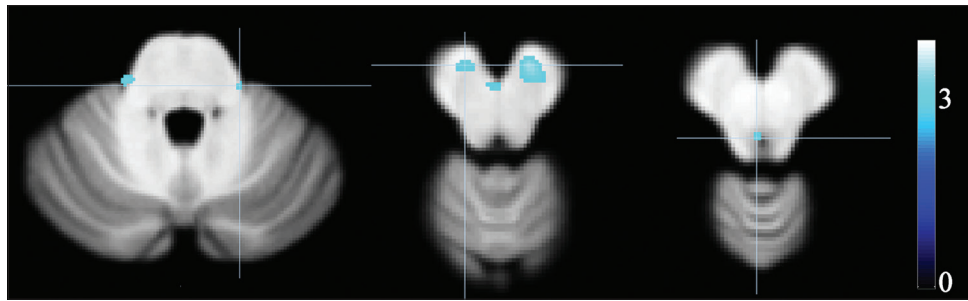


Figure 2: The brainstem regions with volume gain in the MOH patients compared with the NCs. The positive brain regions located in the bilateral trigeminal REZ, bilateral SN, VTA, and left ventrolateral PAG. MOH: Medication-overuse headache; NCs: Normal controls; SN: Substantia nigra; REZ: Root entry zone; VTA: Ventral tegmental area; PAG: Periaqueductal gray.



Figure 3: The brainstem region with positive relation with VAS located in the left RVM. VAS: Visual analog scale; RVM: Rostral ventromedial medulla.

PAG presented increased volume. vlPAG was functionally connected to the descending pain modulation such as the anterior cingulate cortex and the upper pons and medulla.^[19,20] vlPAG also released antinociceptive peptides and increased the sensitivity of PAG neurons and the excitability of the descending PAG output neurons for antinociception,^[21] which was influenced by the gamma-aminobutyric acid receptors and impaired the descending pain control to the signal dorsal horn in a rat study.^[22] Compared with a previous study about the whole PAG volume measurement,^[11] VBM over the entire brainstem could accurately locate the altered PAG subregion volume and vlPAG was identified as the important impaired targeted PAG subregion in MOH, which influenced the descending pain transmission pathway.

The VBM analysis also demonstrated that the bilateral trigeminal REZ presented volume gain in the MOH patients compared with the NCs, which indicated that the increased trigeminal REZ could impair the ascending pain transmission pathway. Previous studies reported that subtle pathological changes in the trigeminal REZ lead to trigeminal neuralgia^[23] and atypical odontalgia,^[24] and subtle structural changes activate the trigeminal nerve and release neuropeptide calcitonin gene-related peptide and other peptides that cause the release of pro-inflammatory mediators, which trigger migraine genesis.^[25] According to previous studies,^[24,26-28] trigeminal neuralgia and trigeminal neuropathy were commonly reported in demyelination, vascular aberrations, and tumors at the trigeminal REZ. However, there were no

definite lesions adjacent to or in the REZ in the current study, and VBM identified the increased volume of the trigeminal REZ in the MOH patients. Therefore, the structural changes of the trigeminal REZ may be the pathognomonic features that impacted the ascending pain pathway in the MOH patients.

Medication overuse could increase the cerebral cortex and trigeminal neuronal excitability, which would make migraine brain easy to suffer from cortical depression and generate central and peripheral sensitization by the trigeminal system.^[29] A previous study also confirmed the sensitization of the trigeminal nociceptive neurons^[30] and pain facilitation of the trigeminal nociceptive systems^[31] in MOH. Therefore, it could be speculated that the repetitive activation of the hypersensitive neurons of the trigeminovascular pathway could facilitate the trigeminal REZ volume gain. However, the accurate neuromechanisms should be further investigated in the future.

The current study demonstrated that the VTA and bilateral SN presented increased volume, which indicated that the mesocorticolimbic dopamine system is implicated in MOH. The mesocorticolimbic dopamine system has been commonly considered as the pleasure or reward pathway in the brain^[32] and strongly participates in the pathophysiology of addiction.^[33] A functional MRI study confirmed that reduced activation in VTA and SN presented in MOH during a decision-making task compared with NCs.^[34] Another functional MRI study demonstrated the activation of the mesocorticolimbic dopamine circuit in MOH patients with medication withdrawal.^[35] The current study confirmed the subtle structural changes of the mesocorticolimbic dopamine system in MOH patients using the VBM technique. Therefore, the volume evaluation of VTA and SN may be used to assess the function of the mesocorticolimbic system and its changes after medication withdrawal in MOH patients in the future.

The voxel-wise correlation provided that the left RVM was positively related to headache intensity, which implied that the left RVM could be considered an imaging biomarker to assess headache intensity. Medication overuse including opioids^[36] and triptans^[37] could induce central sensitization and impair the descending pain modulation from the RVM

and limited the migraineur's ability to tolerate nociceptive inputs.^[38] Therefore, the inability to tolerate the nociceptive inputs would increase headache intensity, which could reasonably explain that the left RVM was positively related to the headache intensity in MOH patients.

Based on previous studies, mood disorders and cognitive impairments could impact the structural^[9] and functional changes^[39-41] in the cerebrum in MOH. However, the psychological scale did not relate to the brainstem volume in the MOH patients in the current study. These findings demonstrated that anxiety, depression, and cognitive impairment did not influence the pain pathways in the brainstem.

There were some limitations to the current study, including (1) it was a cross-sectional study and the longitudinal VBM evaluation could provide more information to understand the neuromechanism of MOH and (2) the subtle structural alterations in the brainstem could effectively assess the brain's pathophysiological condition in MOH with medication overuse. Further brainstem volume assessment should be performed after medication overuse in MOH patients in the future.

In conclusion, the regional volume gain of the brainstem was identified in the MOH patients in this study; it could underlie the neuromechanism of the ascending and descending pathways in MOH. The left RVM volume alteration could imply the impaired tolerance of nociceptive input and can be used to assess headache disability.

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Conflicts of interest

There are no conflicts of interest.

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药物过度使用性头痛患者脑干体积增加：基于体素的形态测量学研究

摘要

背景：组织病理学已明确偏头痛患者脑干核团可发生解剖学及分子学异常改变，然而，由偏头痛转换所致的药物过度使用性头痛的整个脑干结构活体精确结构变化仍无报道。本研究的目的是采用基于体素的形态测量学的方法活体探索药物过度使用性头痛患者脑干结构的局部变化。

方法：于2013年3月至2016年6月在解放军总医院国际头痛中心序贯招募药物过度使用性头痛患者36名、正常志愿者32名，均在3.0T磁共振设备上采集高分辨率脑结构成像。采用基于体素的形态测量学评估药物过度使用性头痛患者脑干结构变化，采用体素式相关性分析评估脑干结构与临床变量的相关性。

结果：与正常志愿者比较，药物过度使用性头痛患者脑干结构增加脑区主要位于左侧腹外侧中脑导水管区（MNI坐标：-1, -33, -8），腹侧顶盖区（MNI坐标：0, -22, -12），双侧黑质（MNI坐标：-8, -16, -12, 9, -16, -12），双侧三叉神经根进入区（MNI坐标：-19, -29, -31; 19, -32, -29）。药物过度使用性头痛患者疼痛视觉模拟量表评分与左侧延脑头端腹内侧区体积呈正相关（MNI坐标：-1, -37, -56，簇大小为20，相关系数为0.602）。

结论：脑干结构的局部体积增加可以解释药物过度使用性头痛患者上行及下行痛觉通路损伤的神经机制。左侧延脑头端腹内侧区体积的变化可以解释伤害性疼痛传入耐受性损伤，且可以用来评估药物过度使用性头痛患者头痛损伤程度。