Clinical Radiology 74 (2019) 898.e1–898.e5

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Grey matter changes in patients with vestibular migraine

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ARTICLE INFORMATION

Article history:
Received 26 February 2019
Accepted 22 July 2019

AIM: To identify structural changes in the brain regions of patients with vestibular migraine (VM) so as to better understand its pathophysiology.

MATERIAL AND METHODS: The differences in grey matter (GM) in patients with VM, patients with migraine without aura (MWoA), and healthy controls (HC) were investigated. Using a GE Signa 3 T magnetic resonance imaging (MRI) system, 3D structural images were acquired from 18 VM, 21 MWoA, and 21 age-, gender-, and education level-matched HC using a T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence. The volumetric abnormalities of GM were estimated by voxel-based morphometry. Analysis of variance and Bonferroni multiple comparisons were applied.

RESULTS: Compared with HC, patients with VM had significantly increased GM volume of the right medial superior frontal gyrus (p=0.008) and the right angular gyrus (p=0.009). Compared to patients with MWoA, patients with VM also had significantly increased volume of the right medial superior frontal gyrus (p=0.001), the right angular gyrus (p=0.008), and the left middle frontal gyrus (p=0.001).

CONCLUSIONS: The GM volume of some brain regions of patients with VM is significantly larger than the other two groups. The increased GM volume in these brain regions in patients with VM may be related to self-adaptation of the nervous system, leading to an abnormal brain sensitization. Some of the brain regions with increased GM volume identified in this study were involved in assessment, integration, and expectations of pain and were strongly related to mood and anxiety.

Introduction

Migraine and dizziness are common symptoms in the general population. Epidemiological data indicate a strong link between migraine and vestibular symptoms,[1] and approximately 30%–50% of migraine sufferers experience symptoms of vertigo or dizziness with at least one migraine attack.[2,3] Vestibular migraine (VM) is the accepted term for describing vestibular symptoms that have a causal relationship with migraine.[4] It is a neurological disorder characterized by vestibular symptoms, including vertigo, dizziness, or imbalance.[5] A population-based study showed that VM affected roughly 1% of the general population, with a female predominance, which is the second most common cause of episodic vertigo after benign paroxysmal positional vertigo (BPPV).[6]

VM is an explicit diagnostic entity that was included in the appendix of the third edition beta version of the

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https://doi.org/10.1016/j.crad.2019.07.015

International Classification of Headache Disorders (ICHD-III beta)[7] in 2013. VM is often under-diagnosed by clinicians despite a relatively high prevalence. At present, the pathophysiology of VM is still unclear, and most hypotheses are based on knowledge of migraine. It has been proposed and widely recognized[8] that VM is likely a central nervous system disease. There is increasing evidence of overlap between VM and migraine pathways.[9] Several studies have shown that the interaction between nociceptive and vestibular system may play an important role in the pathophysiology of VM.[10]

Magnetic resonance voxel-based morphometry (VBM) is the most commonly used method for measuring grey matter (GM) structural differences. VBM is a whole-brain structure analysis method, which automatically analyses the pre-processed high-resolution magnetic resonance imaging (MRI) structural data in various chronic pain syndromes, including migraine.[11] It is easy to operate, sensitive, objective, and repeatable; however, the mechanism of VBM GM density change is not very clear, which may reflect the change of dendritic complex, the number of axons, or just the water content. Studies have shown abnormalities in the GM of pain processing areas of migraine.[12] The present study evaluated the pattern of GM abnormalities in the brain regions of VM patients and verified the relationship between VM and migraine.

Materials and methods

Participants

Written informed consent was obtained from all participants according to the approval of the ethics committee of the local institutional review board. Thirty-nine right-handed patients (18 VM, 21 migraine without aura [MWoA] patients) were recruited from the neurology outpatient department of The Affiliated Hospital of Qingdao University, Qingdao, China. All patients fulfilled the diagnostic criteria of the international classification of headache disorders.[8] Patients with MWoA had no vestibular symptoms and patients with VM met criteria of definite VM. The participant's age ranges from 18 to 60 years. All patients were in attack-free state for at least 3 days prior to MRI acquisition, the day of the MRI, and 3 days after MRI. Furthermore, they did not have any way to prevent migraine, vertigo, or dizziness. Twenty-one right-handed, sex, age, and education-level matched healthy participants served as controls. The control group had no primary headache or chronic pain, nor did they have a family history of migraine or a history of neurological disorders (including migraine). Patients with VM, those with MWoA and healthy controls did not report other neurological, psychiatric, audiovestibular, diabetes mellitus, hypertension, vascular/heart diseases, hypercholesterolaemia, or other major systemic disorders. Moreover, participants who abused alcohol, nicotine, or other substances were excluded. All participants underwent conventional MRI prior to entering the study to ensure that there were no structural abnormalities. No study participant showed visible T2-weighted hyperintensities, especially in the deep white matter (WM).

MRI acquisition

Imaging was acquired on a GE MRI machine operating at 3 T using a conventional eight-channel quadrature head coil. Every participant was in a supine position and the head was fixed with a sponge pad. The structural images of the brain were generated on each participant by a three-dimensional T1-weighted magnetization prepared rapid gradient echo (3D T1-MPRAGE) sequence with following parameters: 5.5 ms repetition time (TR), 1.8 ms echo time (TE), 9° flip angle, 1 mm section thickness, 256 slices, 256×256 matrix, 0.9×0.9×0.9 mm voxel size, and 256×256 mm field of view (FOV).

Processing of structural data

All structural images were processed using VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) and SPM8 (http://www.fil.ion.ucl.ac.uk/) running under Matlab R2014b (Mathworks, Natick, MA, USA). First, the data format was converted from DICOM to NIFTI. Secondly, the image quality was checked, including the integrity of data collection and whether there were serious artefacts. Thirdly, VBM8 was used to segment the three-dimensional images of T1-MPRAGE to obtain GM, WM, and cerebrospinal fluid using the voxel of $0.9\times0.9\times0.9$ mm^3 as the unit, and the segmentation results were modulated using a Jacobian determinant for volume analysis. Then, the GM space was normalized to the Montreal Neurological Institute (MNI) template space using the Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL). Finally, GM partitions were smoothed with an 8-mm full width at half maximum (FWHM) Gaussian kernel.

Statistical analysis

The descriptive data in demographics and clinical characteristics were expressed as mean ± standard deviation or percentage. Differences among categorical data were assessed using Fisher's exact test. The comparisons of group difference in continuous variables were assessed using Student's *t*-test and analysis of variance (ANOVA). These analyses were performed using SPSS, version 22.0.

The comparisons of GM maps that were smoothed among groups were assessed using ANOVA in SPM8. The process of statistical analysis included statistical modelling, model estimation, and contrasts. Statistical parametric mapping was obtained with SPM8, and results were assessed at a threshold of $p<0.001$, uncorrected for multiple comparisons (cluster extent = 60 voxels). The next step was to extract the salient regions with xjView and create a mask. Then, REST was used to extract the signal values of activated brain regions obtained by ANOVA analysis. Finally, the Bonferroni method was used for multiple comparisons, and the threshold was taken to be p-value <0.05 (two-tailed).

Results

Demographics and clinical characteristics are summarized in Table 1. There was no difference among the three groups in terms of age (p=0.915), gender (p=0.922), and education level (p=0.954). The results of regional GM volume analysis among the three groups by ANOVA are summarized in Table 2 and shown in Fig 1. In the comparison of HC, MWoA, and VM, there were positive results in the right medial superior frontal gyrus, the right angular gyrus, the left middle frontal gyrus, and the supplementary motor area (SMA) of right hemisphere (p<0.001, uncorrected, cluster extent = 60 voxels). The results of the Bonferroni multiple comparisons were shown in Table 3. Compared with the other two groups, the group of patients with VM had increased GM volume of the right medial superior frontal gyrus and the right angular gyrus (p<0.05, uncorrected). Compared with patients with MWoA, patients with VM also had increased volume of the left middle frontal gyrus (p<0.05, uncorrected). Patients with MWoA had a lower GM volume of the SMA of right hemisphere than HC (p<0.05, uncorrected).

Discussion

The results of the present study showed a distinctive pattern of GM abnormalities in patients with VM, characterized by increased volume of the right medial superior frontal gyrus and the right angular gyrus compared to patients with MWoA as well as HC. In addition, the volume of the left middle frontal gyrus also increased in patients with VM compared to patients with MWoA. The present findings are not entirely consistent with a previous study, but it was consistently found that there was no area of GM volume reduction in patients with VM compared with the other two groups.[13]

In a previous study, human vestibular areas were described in detail.[14] These areas including the superior frontal gyrus,[15,16] the angular gyrus,[15,17] the middle frontal gyrus,[15,16,18–20] etc., were identified during caloric and galvanic stimulation of the peripheral vestibular organs by functional neuroimaging studies. In another study, functional brain MRI during visual stimulation showed activation of brain regions associated with integration of visual and vestibular cues, with decreased activation in the superior frontal gyrus, which may help to integrate the outcomes of different cognitive operations.[21,22] In the authors' opinion, the different patterns of activated and deactivated brain regions may be due to incomplete central adaptive mechanisms during recurrent vertigo. To date, the causal relationship between recurrent vertigo and changes in GM structure in these areas has not been established.

The complete experience of pain includes perception, emotion, and cognition. The pain pathway, including the emotional and the sensory components, is divided into two parallel ascending pathways.[23] The medial superior frontal gyrus is involved in emotional responses and the participative feelings of pain, as well as memory, attention response, and cognitive reaction related to pain.[24] The inferior parietal angular gyrus and medial superior frontal gyrus are important brain regions that constitute the default network, which is mainly involved in the memory, consciousness, and other advanced functions of the brain in resting state.[25] Although the exact functional role of the default mode network (DMN) is not fully understood, it is considered that DMN plays an important role in conscious experience and in maintaining a general low-level focus of attention on events.[26,27]

The middle frontal gyrus is associated with pain perception and management. The superior, middle frontal gyrus and the angular gyrus are also important parts of the limbic system and represent an important link in the formation of the affective pathway of pain. Brain regions related to the limbic system are involved in both the formation of medial pain pathways that lead to migraine and the modulation of pain perception that increases the pain threshold of migraine patients. Frequent pain may alter the structure of these brain regions.

The prefrontal cortex (PFC) refers to the entire frontal cortex except the primary and the secondary motor cortex, which is the regulatory region associated with pain-relief of opioids and other forms of analgesia and may attenuate the perception of pain signals through cognitive regulation.[28–31] The PFC in humans includes the superior frontal gyrus, the middle frontal gyrus, and the inferior frontal gyrus. A study of pain-induced stimuli found that migraine has more activation in PFC and brain regions associated with pain,[32] and researchers suggested that these brain

Table 1
Demographics and patient characteristics.

	VM	MWoA	HC
Number of participants	18	21	21
Age (years)	36.17±8.65	36.81±11.61	36.15±12.11
Gender (male/female)	3/15	4/17	5/16
education level (years)	12.11±2.47	11.86±2.74	12.00±2.51
VM disease duration (years)	6.56±3.36	NA	NA
Migraine disease duration (years)	12.67±7.62	11.57±7.32	NA
Attack frequency per month	2.72±2.23	1.86±1.20	NA

NA, not applicable; VM, vestibular migraine; MWoA, migraine patients without aura; HC, healthy controls.

Table 2
Regions showing significant grey matter volume differences among VM patients, MWoA patients, and healthy controls (p<0.001, uncorrected, cluster extent = 60 voxels).

Brain regions (AAL)	Cluster extent (number of voxels)	Peak MNI coordinates (x y z)			Peak intensity
Frontal_Mid_L	127	−27	51	19.5	13.3729
Angular_R	99	46.5	−48	30	11.9610
Frontal_Sup_Medial_R	79	9	54	34.5	10.2438
Supp_Motor_Area_R	64	10.5	9	54	11.9308

VM, vestibular migraine; MWoA, migraine patients without aura; AAL, anatomical automatic labelling; L, left; R, right; MNI, Montreal Neurological Institute; Frontal_Mid_L, left middle frontal gyrus; Angular_R, right angular gyrus; Frontal_Sup_Medial_R, right medial superior frontal gyrus; Supp_Motor_Area_R, right supplementary motion area.

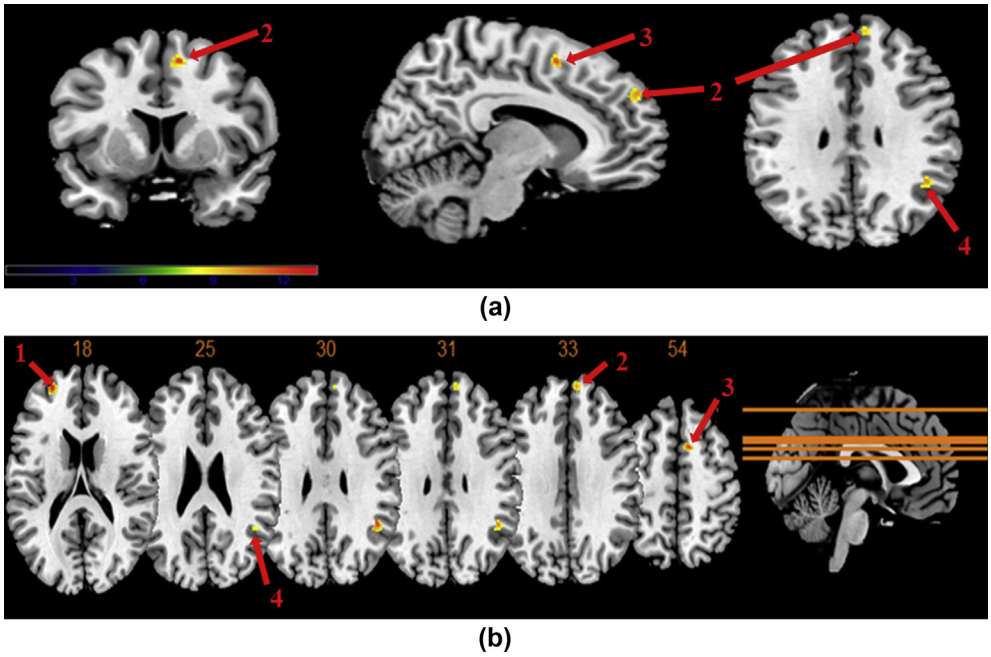

Figure 1 Areas showing significant regional GM volume differences ($p<0.001$, uncorrected, cluster extent = 60 voxels) among VM, MWoA, and HC on a high-resolution T1-weighted template. Right side of the image is the right side of the brain. (a) Regions of increased GM volume were shown according to a yellow-red scale (colour coded according to intensity of activation). (b) The numbers in the figure represented the number of layers in standard template space. 1: left middle frontal gyrus; 2: right medial superior frontal gyrus; 3: right supplementary motion area; 4: right angular gyrus.

regions were involved in cognitive aspects of pain perception, such as memory related to pain. Therefore, the enhancement of cognitive processes may affect brain sensitivity associated with high expectation and high alertness of pain. Increased GM volume of these brain regions in patients with VM may indicate that patients' memory of painful experiences is enhanced.

Mesiofrontal areas, including the PFC, play a vital role for postural balance control. The involvement of the inferior frontal gyrus, the middle frontal gyrus, and the superior frontal gyrus in the integration of somatosensory and vestibular information was confirmed.[33] Two studies have shown that in addition to the cerebellum, dysfunction of the supplementary motor area and PFC may be directly associated with postural instability.[34,35] Frequent pain and dizziness inputs may alter the structure and function of the frontal cortex. The inferior parietal lobule, including the supramarginal gyrus and angular gyrus, plays a major role in the pain response and in the perception of temperature and pressure.[36] The angular gyrus is part of the somatosensory processing regions.[37] The inferior parietal lobule has been shown to be activated by vestibular stimulation.[14] Based on the study of patients with epilepsy, Smith proposed that "the center of vestibulo-psychic region may be located in the angular gyrus" in 1960.[38]

Table 3
Regions showing significant grey matter volume differences between patients and controls as well as between different groups of migraineurs using the Bonferroni multiple comparisons ($p<0.05$, uncorrected).

Brain regions (AAL)	Group 1	Group 2	Mean difference (group 1 − Group 2)	*p*-Value
Frontal_Sup_Medial_R	VM	HC	0.064757367	0.008
Frontal_Sup_Medial_R	VM	MWoA	0.082494577	0.001
Frontal_Mid_L	VM	MWoA	0.106646891	0.001
Supp_Motor_Area_R	HC	MWoA	0 .061021356	0.001
Angular_R	VM	HC	0.104953885	0.009
Angular_R	VM	MWoA	0.105792469	0.008

AAL, anatomical automatic labelling; L, left; R, right; VM, vestibular migraine; MWoA, migraine patients without aura; HC, healthy controls. Frontal_Mid_L, left middle frontal gyrus; Angular_R, right angular gyrus; Frontal_Sup_Medial_R, right medial superior frontal gyrus; Supp_Motor_-Area_R, right supplementary motion area.

The increased GM volume in these brain regions may be related to self-adaptation of the central nervous system. Some of the brain regions identified in the present study are multi-integrative, secondary processing areas that are involved in assessment, integration, and expectations of pain and are strongly related to mood and anxiety. Therefore, these changes could reflect the emotional regulation of pain and vestibular symptoms in patients with vestibular migraine.

Patients with MWoA were more likely to develop VM than those with aura.[39] In the present study, clear migraine patients without aura were selected, which improved the accuracy of the study; however, this study also has limitations. First, the number of study participants is relatively small in each group. In addition, the underlying limitations associated with the VBM methodology should be considered. It is unclear whether GM changes are caused by irreversible mechanisms or whether they simply reflect changes in extracellular space or microvascular capacity. In the next few years, the combination of structural and

functional methods may allow us to better understand the pathophysiology of vestibular migraine.

In future studies, more participants should be recruited to confirm the present results and the control group should include migraine patients with aura (MWA) accompanied by vestibular symptoms in the aura phase. Longitudinal studies have also been shown to be necessary to explore evolutionary dynamics of brain abnormalities.

It is not clear whether these changes are a consequence of the migraine or whether pre-existent or acquired changes in these regions make patients more prone to have VM. The observed changes probably reflect the adaptive mechanism related to the plasticity of cortex in patients with VM.

In summary, the results of neuroimaging studies have shown that there are widespread cortical structural abnormalities in the brain regions related to pain and sensory processing in patients with VM. The results of the present study have shown that GM volume of nociceptive and multisensory vestibular areas is increased in patients with VM compared to controls and VM patients have a different pattern of GM abnormalities compared to patients with MWoA. The changes in main frontal cortex volume reflect a strong emotional component in VM.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

The authors thank Qingdao People's Livelihood Science and Technology Project [17-3-3-18-nsh] for the financial support provided.

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