Short Communication

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Relationship between Primary Dysmenorrhea and Gray Matter

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ABSTRACT

Aim To investigate the structural changes of gray matter in women with primary dysmenorrhea and discuss the potential relationships between the changes and etiology of the disease. Methods We used an optimized Voxel-Based Morphometry (VBM) approach to compare total and regional volumetric changes of gray matter in 20 primary dysmenorrhea patients with 20 healthy age and menstrual cycle matched controls. All testee are patients of the outpatient department of Tongji hospital in 2015. Results Abnormal volumetric decreases of gray matter were found in regions involved in pain transmission, pain modulation and somatic sensation. Conclusion Abnormal gray matter volume changes are present in PDM patients even in the absence of pain.These changes may underpin a combination of impaired pain inhibition, increased pain facilitation.

Keywords: Dysmenorrhea; Cerebral Cortex; Voxel-Based Morphometry; Magnetic Resonance Imaging

Introduction

Primary Dysmenorrhea (PDM) refers to dysmenorrhea caused by non-pelvic organic lesions. It is one of the most common gynecological diseases in women of childbearing age, presenting as spastic abdominal pain [1]. Epidemiological studies show that 90% adolescent women have experienced dysmenorrhea, and nearly 15% of women have a severe history of dysmenorrhea [2]. With Functional Magnetic Resonance Imaging (fMRI) technology being more and more widely applied, there are more and more fMRI studies in chronic pain confirmed that patients with chronic pain have changes in structure and function of central nervous system3. Studies have shown that [4,5] PDM patients may experience generalized hyperalgesia, which may be associated with peripheral and central nervous sensitization. Therefore, PDM, as a specific chronic pelvic pain disease, should also have some structural or functional changes in the brain of the patient. The purpose of this study is to compare the differences in cerebral cortical MRI morphology between primary dysmenorrhea group and normal control group, to clear the changes of cerebral cortex structure in PDM patients, to provide a solid foundation for further study of the relationship between brain functional changes and PDM patients.

This study selected 20 PDM patients from Jan. to Dec. 2015 in Tongji Hospital Affiliated to Tongji University Gynaecology and Obstetrics Clinic outpatient and emergency department, as experimental group. Average age (23.75 + 3.26) years old, the average menarche (11.60 + 2.64) years old, the average duration of the disease (10.37 + 3.06) years. Experimental group

Inclusion Criteria:

1. Diagnosed by an experienced deputy chief physician through history and physical examination, the degree of the pain in the lately half year is moderate dysmenorrhea, menstrual painkiller is required;

2. Duration of the disease over 1 year;

3. menstrual cycle is regular, menstruation period lasts 27~33d;

4. exclusion criteria: physical examination and ultrasound examination found that uterine fibroids, endometriosis and other adnexal masses pelvic organ disease. In addition to recruit 20 volunteers without a history of chronic pain as a

normal control group, the average age (24.25 + 3.54) years old, the average menarche (11.15 + 3.28) years. The basic conditions such as age, menstruation history, and cultural level between the two groups there are not statistically significant (P>0.05), and they are comparable. In addition, all subjects are married or have sexual experience, but without abortion or childbirth history, and use contraceptive tools. Also need to exclude patients with pituitary diseases, psychiatric disorders, and metal implants or pacemakers in the body. All patients have not been treated with analgesics and antidepressants within 24h prior to MRI examination.

Method

Pain and psychological assessment: all the pain and psychological assessments in this study are evaluated by a deputy chief psychiatry physician. PDM group patients need to use digital pain score (NRS) to evaluate the degree of pain. Patients use numbers from 0-10 according to their perception of pain, 0 means no pain and 10 indicates unimaginable pain, intolerable pain, 1 ~ 3 represents mild pain, 4 ~ 6 for moderate pain, 7 to 10 points severe pain. If the degree of pain of all members of the PDM group in the lately half year are over moderate pain, then NRS score ≥4. All patients are assessed for anxiety and depression by the Hamilton Anxiety Scale (HAMA) and the Hamilton Depression Scale (HAMD-17) before receiving the MRI examination.

MRI Scanning:

All MRI data mining are completed in Tongji Hospital Affiliated to Tongji University Imaging department, scanned by Trio 3.0T MRI SIEMENS, 32 channel head coil matrices, using MPRAGE sequence sagittal images of whole brain structure. MRI scans are performed at the 10~20d of the menstrual cycle in which the patients have no pain. During the scan, the patients lie on their back and lie flat on the scanning bed, relax, close their eyes, breathe quietly, restrict head movements with extended cushions, and reduce noise by using elastic earplugs. The subjects are kept silent at the head and other places. Scanning parameters: TR, 2530ms, TE, 2.34ms, reverse angle 7 degrees, FOV 256 * 224mm, matrix 256

* 256, layer thickness 1mm, interval 0.5mm, layer number 192, voxel size 1 * 1 * 1mm.

MRI Data Processing:

All data processing in Matlab 2008a platform, voxel-based morphometry (VBM) optimization based on SPM8 software application analysis of MRI image preprocessing and statistical parameter method. The main steps include;

1. Create a whole brain template;
2. Create a suitable ectocinerea template for this study;
3. Segmentation from the original image;
4. The original gray image with gray template standardization, use the standardization parameters in the original image in order to obtain the whole brain image as final standardization;
5. Using SPM8 software image normalized segment into gray and white matter, cerebrospinal fluid, and then use the three-dimensional Gauss kernel convolution full width at half height of the gray image the spatial smoothing, improve the SNR of the images, the image comparison can be gray density;
6. Segmented Gray images obtained on the fifth step need to be corrected, and finally do gray matter volume comparison.

Statistical Analysis: statistical analysis of data using SPM double sample t test. First, the results of preprocessing and index calculation are analyzed by SPM8 software, then the statistical results are presented in the XJVIEW software, and the threshold is set to correct the result. P 0.05 (FDR correction), block size greater than 30 of the voxel brain regions is consider as statistically significant difference, so that we can obtain statistical difference map. Overlay brain areas with differences in the MNI coordinate with three-dimensional structure and display with pseudo color. Observe and record the statistical significance of the brain region, voxel activation volume size (body prime), the maximum activation point t value ("t" test, statistic value is greater, the higher the strength) and MNI coordinates. Statistical analysis of other general data is carried out by using SPSS20 statistical analysis software. The measurement data was expressed by X + s standard deviation; the average of two samples is compared by independent sample t test; $P < 0.05$ is statistically significant.

Results

1. Morphological Changes in the Whole Brain: the MRI images of the two groups of patients are read by the same experienced radiologist, and no visible abnormalities are observed. And the image processing and analyzing the data from the experimental group of whole brain gray matter volume (662.26 + 31.74) ml, the control group (674.17 + 29.69) ml, the difference between the two groups after statistical test shows no statistical significance (P>0.05).

2. The Changes in Brain Areas Between 2 Groups: VBM analysis revealed that compared with normal control group, PDM patients showed gray matter volume atrophy in brain areas including the left and right parahippocampal gyrus the left and right middle temporal gyrus (MTG) right temporal gyrus; left and right parietal lobule, left inferior parietal lobule; left after the central gyrus.

Discussion

A number of previous studies showed that primary dysmenorrhea may cause structural and functional changes in brain areas related to pain processing (the pain matrix) [3]. The pain matrix is defined by the brain and the feeling of pain, pain conduction ,pain processing and pain emotion related brain regions consisting of a relatively discrete but mutual influenced pain

management closely related cluster, including thalamus, amygdala, Insula (IC), posterior parietal cortex, Prefrontal Cortex (PPC) PFC), Anterior Cingulate Cortex (ACC), Cingulate Gyrus (MCC), Posterior Cingulate (PCC), Periaqueductal Gray (PAG), basal ganglia, cerebellar cortex, primary Somatosensory Cortex (S1), the second Somatosensory Cortex (S2), Sensorimotor Auxiliary Area (SMA). The complex network consist of brain areas and nucleus is the main place to deal with the pain, emotional, cognitive and other senior central activities [6,7]. May and other morphological studies of patients with chronic pain found that the anterior cingulate gyrus, thalamus, insula and prefrontal cortex were generally thinning of the cortex [8]. This study also found that PDM patients with left and right parahippocampal gyrus, left and right Middle Temporal Gyrus (MTG), right middle temporal gyrus, left and right superior parietal lobule, left inferior parietal lobule, left postcentral gyrus gray matter volume atrophy thinning.

The parahippocampal gyrus and MTG are already well-known areas of pain, sensation, and processing, whereas the superior parietal lobule, the inferior parietal lobule, and the posterior central gyrus are associated with pain perception and pain emotion, [9,10]. It is confirmed that even though PDM is a specific recurrent intermittent attack of chronic pain, it can still cause changes in the volume of grey matter in the brain. Studies have shown that when the body is unable to adapt to chronic pain, there will be emotional and anxiety disorders, and also cause changes in biochemical reactions in the brain and affect the central nervous system processing external information [11]. At the same time, animal model experiments also showed that PFC region atrophy occurred under repeated stress stimulation [12]. This study also found a reduction in the volume of gray matter in many brain regions and found that the reduced volume of brain function is mainly related to pain transmission, visceral sensation, and pain emotion regulation. The mechanism is not completely clear, we speculate may be associated with a direct neurotoxic response, following recurrent chronic pain, will cause recurrent neuronal atrophy or apoptosis of neurons, changes in the metabolism of neurons, neurotoxicity of painkiller, depression and anxiety [3,13].

The results of this study confirmed our assumption, that changes in cortical structures not only appear in persistent chronic pain patients, but also prevalent in dysmenorrhea, such an intermittent episode's pain. This also shows that central nervous system has plasticity. It is easily to be interfered by chronic disease changes, and these changes in central nervous system further affects the healing of chronic disease. Studies have shown that patients with a chronic pain disorder are more likely to suffer from another chronic pain disorder [14], than those with normal or other diseases. Considered the relationship between changes in PDM and other chronic pain and central nervous system structure and function, some scholars suggest that all clinical symptoms of dysmenorrhea patients, especially with multiple pain and highly plastic nervous system in adolescent patients should be given corresponding clinical treatment [15]. In addition, it is worth noting that the research above including this study, is an instant "snapshot", we cannot clarify the causality between chronic pain such as PDM and central nervous changes through those studies, we need further longitudinal studies to define the relationship between these changes and PDM, and further to prove that those changes in the central nervous system whether are reversible or not.

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Disclosure

Each author declares that competing financial interests have been appropriately disclosed according to the policy of the Journal. The authors further declare no personal or professional conflict of interest, whether they are actual or potential.

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