Altered Cerebral Iron Over the Whole Brain in Chronic Migraine Using Voxel-Based Quantitative Susceptibility Mapping

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Abstract

Background: The previous documents demonstrated that iron deposition was identified in brain deep nuclei and periaqueductal gray matter region in chronic migraine (CM), and less is known about the cerebral iron deposition in CM. The aim of this study is to investigate the cerebral iron deposition in CM using an advanced voxel-based quantitative susceptibility mapping.

Methods: A multi-echo gradient echo MR sequence was obtained from 14 CM patients and 28 normal controls (NC), and quantitative susceptibility mapping images were reconstructed and voxel-based analysis was performed over the whole cerebrum. The susceptibility value of all the positive brain regions was extracted and correlation was calculated between the susceptibility value and the clinical variables.

Results: The brain regions with increased susceptibility value in CM patients located in right precuneus, dorsolateral superior frontal gyrus, postcentral gyrus, cuneus, insula and left postcentral gyrus compared with NC. The correlation analysis demonstrated that a positive correlation was identified between susceptibility value of all the positive brain regions and VAS score.

Conclusion: The current study demonstrated increased cerebral iron deposition presented in chronic patients, which suggested that increased cerebral iron deposition might play a role in the migraine chronicization.

Introduction

Chronic migraine (CM) is defined as at least 15 days of headache per month for more than 3 months, including at least eight days a month on which the headache feature and associated symptoms are fully developed migraine attacks[1]. It is estimated that CM affects 1.4–2.2% of the general population globally[2] and around 3% of episodic migraine (EM) patients evolve to CM each year[3]. The etiopathogenesis of migraine are hypothesized to be various processes and mechanisms involving activation of the trigeminal nerve system, abnormality of brain structure and function, vasoconstriction and vasodilation, and cortical spreading depression[4], among which the cerebral cortices serve a vital role. Structural and functional alterations of cerebral cortices have been widely reported in migraine patients[5]. Cortical hyperexcitability and aberrant resting-state brain activity may underlie the cascade of migraine attacks[6]. Interfering with cortical activity can affect pain perception, while pain-related cortical regions undergoing changes in synaptic plasticity can generate pain perception even with no detectable sensory input from the periphery[7].

Increased iron deposition in the brain has been described in migraine patients. Different MRI techniques have been used to measure brain iron concentrations in migraine, including susceptibility weighted imaging (SWI), T2 gradient echo imaging, T2 turbo spin echo sequence, transverse relaxation rates R2, and quantitative T2*[8–12]. Quantitative susceptibility mapping (QSM) is a noninvasive MRI technique that measures spatial distribution of magnetic susceptibility using phase images of gradient-recalled

echoes[13]. It is validated that susceptibility measured by QSM is linearly correlated with concentration of iron in brain nuclei[14] and thus provides us an effective way to detect iron deposition in the brain.

Among the studies probing into the iron deposition in migraine brain, increased iron deposition level has been described in periaqueductal gray matter (PAG), red nucleus, globus pallidus and putamen in migraine patients compared to controls using MRI[9–12]. While most of these researches focus iron deposition on the deep brain nuclei and PAG regions, cerebrum has been randomly studied. In our study we aim to investigate cerebral iron deposition in CM using voxel-based QSM.

Methods

Subjects

The written informed consents were obtained from all subjects according to the approval of the ethics committee of local institutional review board. Fourteen chronic migraine patients [4 males and 10 females, mean age 41.71 ± 8.87 years] and 28 normal controls [10 males and 18 females, mean age 42.36 ± 11.10 years] were sequentially recruited from Headache Clinic and the staffs of Chinese PLA General Hospital.

All the patients should meet the International Classification of Headache Disorders, 3rd Edition (ICHD-III) criteria of chronic migraine without aura[15]. The inclusion criteria was fulfil the following: (1) the diagnosis of migraine and CM refers to 1.1 Migraine without aura and 1.3CM in ICHD-III, respectively; (2) without migraine preventive medication in the past 3 months; (3) absence of other subtypes of headache, chronic pain other than headache, severe anxiety or depression, and psychiatric diseases; (4) absence of alcohol, nicotine, or other substance abuse. The exclusion criteria should meet the following: cranium trauma, the cerebrovascular disease, long-standing hypertension, diabetes mellitus, tumor history and brain surgery. All the subjects should have no MRI scan contraindications such as metal clips within the body and claustrophobia.

All the patients were performed with the Visual Analog Scale (VAS), Migraine Disability Assessment Scale (MIDAS), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD) and Montreal Cognitive Assessment (MoCA) evaluation.

MR data acquisition

All MRI data was acquired using a conventional eight channel phased-array head coil on a GE three-tesla MR scanner (DISCOVERY MR750, GE Healthcare, Milwaukee, WI, USA). A multi-echo gradient echo sequence was used to reconstruct QSM images with the following parameters: first echo time (TE) = 4.72 ms, the last TE = 22.96 ms, deltaTE = 3.648 ms, repetition time (TR) = 26.7 ms, flip angle (FA) = 15°, field of view (FOV) = 22 × 22 cm and matrix = 416 × 320, slice thickness = 1.2 mm, slice gap = -0.6 mm, number of averages = 1. The brain structural images were obtained from a 3D T1 gradient echo sequence with the following parameters: TE = 3.0 ms, TR = 7.0 ms, inversion time = 400 ms, FA = 12°, FOV = 25.6 ×

25.6 cm and matrix = 256×256 , slice thickness = 1.0 mm, slice gap = -0.6 mm, number of averages = 1. All the MR imaging protocols were identical for two 3.0T MR scanner.

Imaging analysis

Imaging analysis was performed under MATLAB R2013b (version 8.2.0.701) (The Mathworks, Natick, MA, USA) environment. The QSM images were reconstructed by STI Suite (V3.0) software (STI.SUITE.MRI@gmail.com). The imaging coregister, normalization and voxel-based analysis were performed with Statistical Parameters Mapping (SPM) (v12.0) software (<https://www.fil.ion.ucl.ac.uk/spm/software/>).

The image processing steps included as following: (1) The e images and phase images were imported into the STI software and then automatically generated magnetic susceptibility images; (2) 3D T1 images (Fig. 1A) were coregistered with the magnitude images (TE = 4.72 ms) (Fig. 1B), and then generated the warped T1 images (Fig. 1C); (3) The warped T1 images were normalized with the T1 template (provided by the SPM software) (Fig. 1D), and then generated the normalized parameters; (4) The normalized parameters were applied with the quantitative susceptibility images (Fig. 1E), and then generated the normalized susceptibility images (Fig. 1F), and then all the normalized images were smoothed by 8 mm full width at half maximum(FWHM); (5) voxel-based analysis was performed using two-sample t-test between CM patients and NC. Significance difference was set at a *P* value of < 0.001 without false discovery rate (FDR) correction; (6) all the positive clusters were saved as a binary regions of interest (ROI) to extract the susceptibility value.

Statistical analysis

The data with normal distribution was described as mean $\pm$ standard deviation. Correlation analysis was performed between susceptibility value of all the positive brain regions and the clinical variables, *P* value of < 0.05 was considered to indicate a statistically significant correlation.

Results

Voxel-based QSM over the whole cerebrum in chronic migraine patients

Figure 2 presented that the brain regions with increased susceptibility value located in right supramarginal gyrus, precuneus, dorsolateral superior frontal gyrus, postcentral gyrus, cuneus, insula and left postcentral gyrus (Table 1). There were no brain regions with decreased susceptibility value over the whole cerebrum.

Table 1
The brain regions with increased susceptibility value over the whole cerebrum in chronic migraine patients

Anatomic region	MNI-space			Cluster size	T value
	X	Y	Z		
Right supramarginal gyrus	50	-26	39	250	4.268
Left postcentral gyrus	-53	-6	22	105	4.260
Right precuneus	3	-54	69	22	3.897
Right dorsolateral superior frontal gyrus	21	62	19	28	3.792
Right postcentral gyrus	40	-19	50	61	3.778
Right dorsolateral superior frontal gyrus	19	0	54	22	3.770
Right insula	39	-20	12	22	3.687
Right cuneus	9	-78	30	14	3.678
Right cuneus	6	-87	32	13	3.633

Correlation analysis between the susceptibility value of all the positive brain regions and the clinical variables

Table 2 presented that there was a significant positive correlation between the susceptibility value of all the brain regions with increased iron (0.010 ± 0.004) and VAS score ($r = 0.0555$, P value = 0.039). The other clinical variables, including MIDAS, diseased duration, headache frequency, HAMA, HAMD and MoCA socre, showed no significant correlation with the susceptibility value (P value > 0.05).

Table 2

Correlation analysis between the susceptibility value of all the positive brain regions and clinical variables

Variables	Mean $\pm$ SD	r	P value	95%CI for r
VAS	7.930 $\pm$ 1.439	0.555	0.039	0.035–0.086
MIDAS	101.357 $\pm$ 56.291	0.226	0.438	-0.347-0.675
DD(years)	11.714 $\pm$ 9.507	0.183	0.532	-0.385-0.650
HF [†]	25.929 $\pm$ 5.717	-0.456	0.102	-0.794-0.099
HAMA	23.429 $\pm$ 10.353	-0.353	0.215	-0.744-0.218
HAMD	17.714 $\pm$ 10.484	-0.082	0.781	-0.587-0.469
MoCA	23.357 $\pm$ 4.684	-0.472	0.088	-0.802-0.078
[†] The number of headache attack per month				
VAS, Visual Analog Scale; MIDAS, Migraine Disability Assessment Scale; DD, disease duration; HF, headache frequency; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MoCA, Montreal Cognitive Assessment; r, correlation coefficient; CI, confidence interval				

Discussion

In this study, we used QSM to analyze 14 CM patients and 28 normal controls, and confirmed elevated iron deposition in several cortical regions in CM patients. There is a positive correlation between susceptibility value of all the positive brain regions and VAS score of CM patients.

To the best of our knowledge, we are the first to use QSM for evaluation of cerebral iron concentration in migraineurs. QSM may provide an effective as well as noninvasive way of revealing iron deposition in the brain in vivo. Previous studies usually used phase imaging or susceptibility weighted imaging for iron evaluation. These phase methods have high spatial resolution and take less scanning time. On the other hand, these methods may yield to nonlocal field influence that caused by calcifications and vessels[16]. Some researches were performed on 1.5T MR scanner and the low field strength may as well result lower sensitivity to local susceptibility effects caused by iron[17].

Iron is a key nutrient for normal central nervous system development and function, including oxygen transportation, DNA and myelin synthesis, mitochondrial respiration and neurotransmitter[18]. Physically there are high levels of iron in the basal nuclei due to the synthesis and metabolism function in dopamine[19]. Meanwhile iron can generate reactive oxygen species, and both iron and reactive oxygen species are indicated to be important initiators and mediators of cell death[20]. Excessive accumulation of iron has been associated with aging and neurodegenerative diseases such as Huntington's disease, Alzheimer's disease, and Friedreich's ataxia[18].

Iron deposition in the migraine brain has been studied in the past 20 years. Welch et al[12] revealed increased iron level in PAG in EM and chronic daily headache patients compared with healthy ones, and the iron increment was correlated to the illness duration. In CAMERA-study, Kruit et al[9] evaluated 138 migraineurs and 75 controls and showed higher iron level in putamen, globus pallidus and red nucleus in migraineurs under age of 50, and the migraine history was positively correlated with iron accumulation. Follow-up study of CAMERA nine years later showed no difference in iron level in deep brain nuclei between groups, and the authors assumed that aging might obscure the migraine-induced iron changes[8]. Tepper et al[10] investigated iron deposition in deep brain nuclei and indicated that T2 imaging in globus pallidus can be used to distinguish between EM and CM patients. Dominguez et al[11] revealed elevated iron deposition in red nucleus and PAG in CM patients compared with EM and controls.

Previous studies have focused on PAG as a key center in the generation and regulation of migraine. And these results referring to PAG and deep brain nuclei, iron accumulation indicates sensory dysregulation in migraine. Our findings revealed elevated iron deposition in the cerebral cortical regions in CM patients compared to normal subjects, which indicated that the impaired iron homeostasis in migraine was not limited to the deep brain nuclei and PAG. The elevated iron deposition areas in this study were in right precuneus, dorsolateral superior frontal gyrus, postcentral gyrus, cuneus, insula and left postcentral gyrus. Among these areas, the precuneus has been indicated to be associated with cognitive modulation of pain sensitivity[21], and the insula is involved in pain experience and expectation[22, 23]. Meanwhile the insula and precuneus both take part in pain catastrophizing on mild pain[24]. The postcentral gyrus and supramarginal gyrus are part of the somatosensory associated cortex. The postcentral gyrus consists of the first somatosensory cortex which is responsible for recognizing the localization and intensity of pain[25]. While the supramarginal gyrus interprets tactile sensory information[26]. A recent functional MRI study focused on the pain matrix network which includes the anterior insula, precuneus, supramarginal gyrus, thalamus, and several other regions, showed that the increased connectivity of the pain matrix may play a role in migraine chronicization[27]. Our result of the iron deposition in the cerebral cortex as well added more support of cortical dysfunction in the pathogenesis mechanism of migraine chronicization. Moreover, higher VAS scores were associated with increased iron deposition or accumulation in cerebral cortex in migraine patients, which suggested that the iron accumulation levels in CM are related to the severity of headache attacks. It remains unclear whether iron accumulation in the cortex has a causative role in the development of chronic migraine headache or the consequence of repetitive of migraine attack.

This study was limited by the modest number of CM patients. And we are not able to draw the causative conclusion of the iron deposition in cortex and migraine chronicization.

In the future, more details of connectivity between cerebral cortex, deep brain nuclei and PAG may be performed and follow-up study is as well necessary to indicate the dynamic change of iron deposition in migraine patients with age.

Abbreviations

QSM, quantitative susceptibility mapping; CM, chronic migraine; NC, normal controls; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MoCA, Montreal Cognitive Assessment; EM, episodic migraine; PAG, periaqueductal gray matter; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Chinese PLA General Hospital approved the research protocol, and the procedures conformed to the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and material

All the data supporting our findings is contained within the manuscript.

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Authors' contributions

LM and SY Y contributed the conception and design of the study. ZYC and MQL contributed to MR data acquisition, and XY C contributed the clinical data acquisition. ZYC contributed the image analysis, ZYC and WD contributed to the interpretation and draft. LM and YSY contributed to the revision for important intellectual content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The flow chart of voxel-based quantitative susceptibility mapping

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Figure 2

The brain regions with increased susceptibility value over the whole cerebrum in chronic migraine patients.

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