Original Article

Quantitative susceptibility mapping to evaluate brain iron deposition and its correlation with physiological parameters in hypertensive patients

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Background: Regional excessive iron overload is pernicious to motor functions and cognitive functioning of the brain. The aim of this research was to utilize quantitative susceptibility mapping (QSM) to inspect brain iron accumulation in patients with hypertension (HP), and to evaluate whether it is correlated with physiological parameters.

Methods: Thirty-one HP and 31 age- and sex-matched healthy controls (HC) were included. All participants underwent brain magnetic resonance imaging (MRI), and QSM data were obtained. Differences in brain iron deposition in deep gray matter nuclei of participants were compared between HP and HC. The correlations between iron deposition, body mass index (BMI), maximum systolic blood pressure (SBP), and diastolic blood pressure (DBP) were analyzed.

Results: The HP group showed increased susceptibility values in the caudate nucleus (CA), putamen (PU), globus pallidus (GP), and dorsal thalamus (TH), compared with the HC group. There was a significant positive correlation between BMI and the susceptibility values in the dentate nucleus (DN); the maximum SBP and DBP were positively correlated with magnetic susceptibility of the CA, PU, GP, and TH, respectively.

Conclusions: These results are indicative of the role of overload brain iron in deep brain gray matter nuclei in HP and suggest that HP is associated with excess brain iron in certain deep gray matter regions.

Keywords: Hypertensive; quantitative susceptibility mapping (QSM); magnetic resonance imaging (MRI); iron deposition; deep gray matter

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Introduction

Along with rapid social and economic development, hypertension (HP) is the most common risk factor related to cardiovascular disease, which is the main source of mortality worldwide (1). The overall estimated prevalence of HP and prehypertension in Chinese adults aged 18 years and over are 27.9% and 39.1%, respectively. The weighted prevalence of HP is 23.2% (≈244.5 million) (2). One of

the most important factors leading to high blood pressure is aging (3). It is estimated that by 2050, the ratio of older adults will stand at 30% of China's total population (4). Among citizens over 65 years old, the prevalence of HP is more than 55%, and it increases with age (2).

Iron plays an important role in maintaining physiological homeostasis in the body. Serum ferritin, transferrin, and hemoglobin are the most widely used biomarkers in epidemiological and clinical studies to evaluate body iron stores. Iron overload induces several health problems including heart disease, neurodegenerative disorders. The risk factor for neurodegenerative diseases is hypertension. Lee *et al.* observed that HP increases as the serum ferritin quartile increases (5). Transferrin and hemoglobin levels are positively associated with blood pressure and incident HP (6). HP may be associated with increases in the content of heme and non-heme iron beyond the normal changes associated with age (7). Iron is involved in the development of normal cognitive functions in the brain. Increased subcortical iron is associated with decreased cognitive and motor functions in the elderly population (8). The neuroradiological markers of hypertension induced cerebrovascular disease include lacunar infarction and microbleeding, which are related to the decline of cognitive ability (9). Some studies have demonstrated that there has been a correlation between hypertension and the high incidence of cognitive impairment and dementias (10,11).

Body mass index (BMI) is a commonly used and recognized method for reporting obesity rates, calculated as the square of weight/height (kg/m^2). A BMI of 24–28 kg/m^2 suggests overweight in Chinese people, and ≥28 kg/m^2 indicates obesity for Chinese people (12). Overweight and obesity are also important risk factors for HP. Developing hypertension was more common among those who became overweight or obese (5).

Quantitative susceptibility mapping (QSM) can quantify the magnetic susceptibility of tissues in the body and is a magnetic resonance (MR) imaging technique of increasing significance (13), and it accurately reflects the spatial distribution of tissue magnetic susceptibility. QSM has been established as noninvasive method for *in vivo* quantification of brain tissue iron. Previous studies using phase imaging or susceptibility-weighted imaging have found that abnormal iron deposition in the brain occurs in some neuropsychiatric diseases (14). Compared with phase imaging, the QSM method provides more accurate measurements of deposited iron. QSM has become a powerful tool in magnetic resonance imaging (MRI) to monitor brain iron (15).

Few studies have yet reported on the relationship between brain iron deposition and HP. Rodrigue *et al.* (7) observed significantly greater iron content in primary visual cortex, hippocampus, entorhinal cortex, superior frontal gyrus, caudate nucleus, and putamen as measured by T2*. Here, the QSM method is used to examine brain iron deposits in clinically hypertensive patients and to test the hypothesis that HP is related to the increase of iron concentration in deep gray matter. We present the following article in accordance with the MDAR reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5170).

Methods

Participants

We recruited two groups of age- and sex-matched participants: 31 hypertensive patients (HP, 16 males, 15 females; mean age =64.5±11.5 years) and 31 healthy controls (HC, 15 males, 16 females; mean age =61.9±11.8 years). The exclusion criteria included the following: (I) history of severe mental or neurological disease or cerebral trauma; (II) participants with secondary HP or medications that increase blood pressure (BP); and (III) contraindications of magnetic resonance examination. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Xi'an Daxing Hospital (Xi'an, China) (No.: DX2021-716[1]) and informed consent was taken from all the patients.

Definition of variables

After the participant had sat still for at least 5 minutes, the blood pressure in the sitting position was measured three times on the right arm supported by the heart level, with a 1-minute interval between each measurement. The average of the three readings was used for subsequent analysis. Severity of HP was based on the average of the three readings at a single time point. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. Patients with SBP ≥140 mmHg or DBP ≥90 mmHg, patients diagnosed as hypertensive according to the 2010 Chinese guidelines, and/or those who had used antihypertensive medicine within the last 2 weeks were considered hypertensive (2).

Weight was measured in light clothing using a calibrated

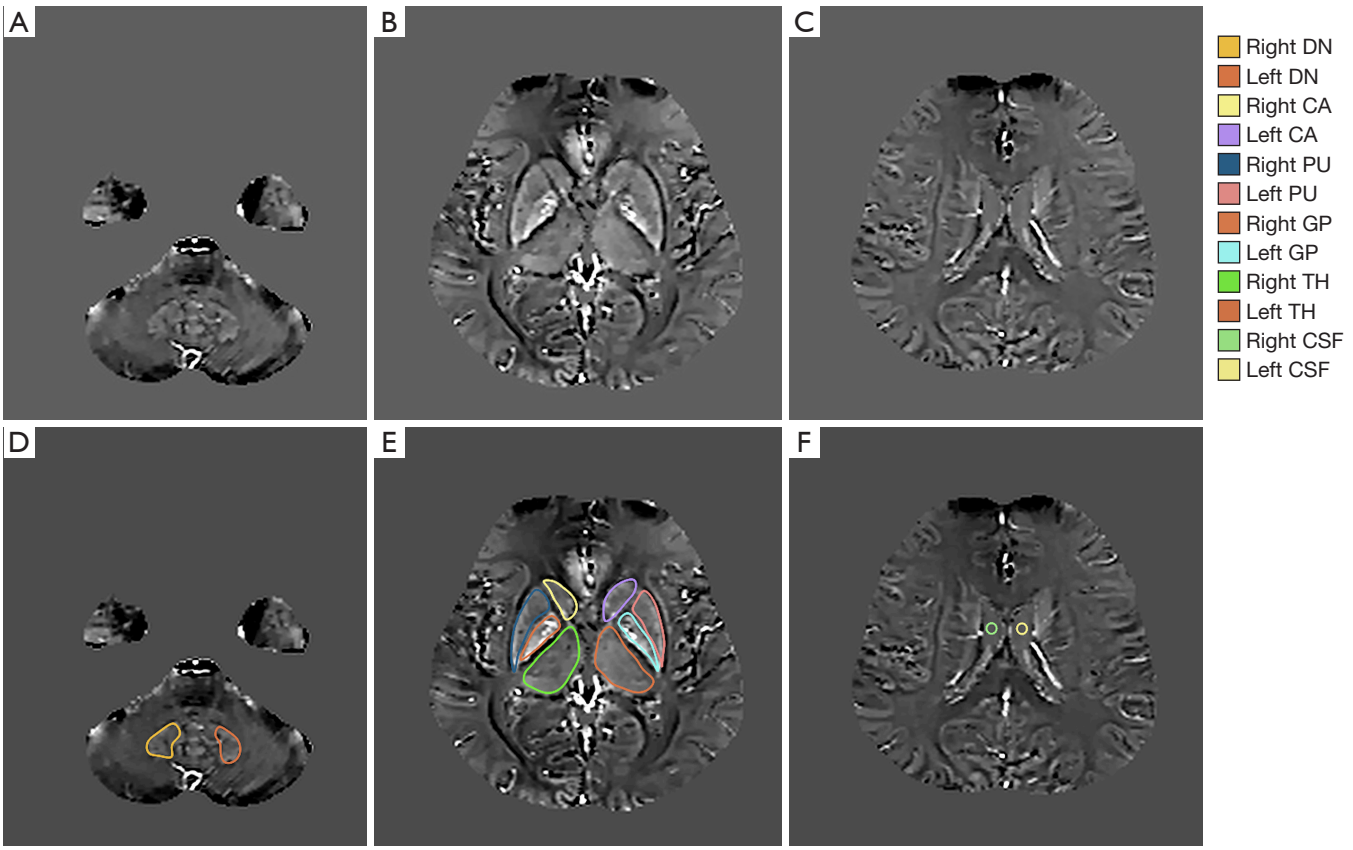

Figure 1 Quantitative susceptibility mapping images of a 62-year-old subject of six selected regions. Regions of interest around the bilateral dentate nucleus (DN), caudate (CA), putamen (PU), globus pallidus (GP), dorsal thalamus (TH), and cerebrospinal fluid (CSF) were drawn manually.(A-C) QSM images of the subject; (D-F) Regions of interest outlined in the QSM images.

beam balance to within 0.1 kg. A portable stadiometer was used to measure height without shoes, accurate to 0.1 cm. BMI was reported as the square of weight (kg) divided by height (m), accurate to two decimal places.

MR image acquisition

MRI data were acquired on a 1.5TSiemens magnetic resonance scanner (MAGNETOM Aera, Erlangen, Germany), using the head coil with 16 channels. A routine T2 sequence was performed to exclude cerebral softening. After that, a multiecho gradient echo (ME-GRE) sequence was applied for QSM acquisition with the following parameters: repetition time (TR) =51 ms, $TE_1/\Delta TE/TE_8$ =8.22 ms/5 ms/43.22 ms, bipolar readout, slice thickness =2 mm, flip angle =20°, FOV =230 mm × 210 mm, matrix size =224×180, bandwidth =200 Hz/Px, and slices =56.

Image processing and data analyses

The magnitude and phase images from ME-GRE acquisition were postprocessed to generate susceptibility maps using the morphology-enabled dipole inversion (MEDI) toolbox in Matlab (R2016b, Mathworks, Natick, MA, USA). The regions of interest covering major structures in deep gray matter included the dentate nucleus (DN), caudate nucleus (CA), putamen (PU), globus pallidus (GP), dorsal thalamus (TH), and cerebrospinal fluid (CSF), which were manually drawn on the susceptibility maps to extract tissue susceptibility values (*Figure 1*). The ventricular CSF was used as reference for QSM reconstruction. The susceptibility values of each structure were calculated as the average of the bilateral sides. Regions of interest (ROIs) were outlined in the layer with the area of nuclei on the susceptibility maps. Multiple ROI slices were used to obtain the average susceptibility value. Two senior physicians

Table 1 Comparison of the magnetic susceptibility of the regions of interest between hypertensive patients and healthy controls (P<0.05 was considered as indicating statistical significance)

ROI	HP (ppb)	HC (ppb)	P	t
LCA	23.7±8.6	17.8±12.0	0.03	−2.23
RCA	24.5±7.5	16.8±9.8	0.001	−3.47
LPU	22.9±6.5	17.3±11.6	0.02	−2.34
RPU	23.6±6.6	18.9±9.0	0.02	−2.31
LGP	38.9±9.2	25.9±11.6	<0.001	−4.89
RGP	37.4±9.5	25.9±13.1	<0.001	−3.93
LTH	13.5±4.8	7.3±5.4	<0.001	−4.79
RTH	14.3±5.7	7.1±5.1	<0.001	−5.26

ROI, region of interest; HP, patients with hypertension; HC, healthy controls; LCA, left caudate; RCA, right caudate; LPU left putamen; RPU right putamen; LGP, left globus pallidus; RGP, right globus pallidus; LTH, left dorsal thalamus; RTH, right dorsal thalamus.

with extensive diagnostic experience in MRI of the nervous system plotted the ROIs and measured magnetic susceptibility on the reconstructed QSM images.

Statistical analysis

Version 19.0 SPSS software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Mean ± standard deviation (SD) was utilized to describe measurement data. The normality of measured data was confirmed using the Kolmogorov-Smirnov (KS) test. The independent sample t test was used to compare patient demographics and susceptibility values of each structure between the two groups. The differences between both sides and genders in the magnetic susceptibility of the DN, CA, PU, GP, TH, and CSF were investigated with the Wilcoxon rank sum test in HP. Correlations between the magnetic susceptibility of brain tissue, BMI, maximum SBP and maximum DBP in HP were examined using the Pearson's correlation test. A value of P<0.05 was considered as indicating statistical significance. The consistency between observers was evaluated by calculating Cohen's kappa statistic (Kappa <0.00: inconsistent, kappa =0.00–0.20: slightly consistent, kappa =0.21–0.40: fair and consistent, kappa =0.40–0.60: moderately consistent, kappa =0.61–0.80: substantially consistent; kappa =0.81–1.00: almost exactly the same).

Results

HC and HP did not differ in age or sex (P>0.05). The susceptibility values of the bilateral CA, PU, GP, and TH in HP were higher than those of the HC (P<0.05) (*Table 1*). The magnetic susceptibility of HP showed no statistically significant differences in bilateral DN, CA, PU, GP, and TH, as well as between sexes (P>0.05). Interobserver agreement was high for both sequences (kappa =0.67). We calculated the correlation between BMI, maximum SBP, maximum DBP, and brain iron deposition. BMI was significantly and positively correlated with susceptibility values in DN (r=0.65, P<0.0001) (*Figure 2A*). The maximum SBP was significantly and positively correlated with the susceptibility values for the CA (r=0.69, P<0.0001), PU (r=0.63, P=0.0002), GP (r=0.40, P=0.02), and TH (r=0.45, P=0.01) (*Figure 2B-2E*). Maximum DBP was significantly and positively correlated with susceptibility values for CA (r=0.41, P=0.02), PU (r=0.37, P=0.04), GP (r=0.56, P=0.001), and TH (r=0.43, P=0.016) (*Figure 2F-2I*).

Discussion

In this research, QSM was used to compare brain iron concentrations between HP and HC of the same age, and we estimated the correlations between HP and physiological parameters. We found that the magnetic susceptibility of subcortical structures of HP, such as the bilateral CA, PU, GP, and TH, were higher than those in HC. These results suggest that the amount of iron deposition in the brains of HP was excessive. This iron overload might be caused by several factors. Cardiovascular and cerebrovascular diseases are the most common complications in patients with HP and cause microbleeding, subcortical lacunar infarctions, and diffuse white matter lesions. The results of Lyu *et al.* provide evidence that microbleed severity is associated with HP grade (16). HP-associated cerebral microbleeds are typically located in the basal ganglia and thalamus (17). Increased iron accumulations have also been detected in the vicinity of cerebral infarction (18). In the brain, iron is found in three forms: heme iron, non-heme iron, most of which is stored in the ferritin protein, and labile iron, which is too dilute to show on QSM (8,19). Ferric heme iron in the hemoglobin molecule creates local inhomogeneity detectable through magnetic resonance imaging (7). Previous research found that the prevalence of hypertension in male increased according to increases in ferritin levels (5). Excessive iron produces free radicals, which can increase

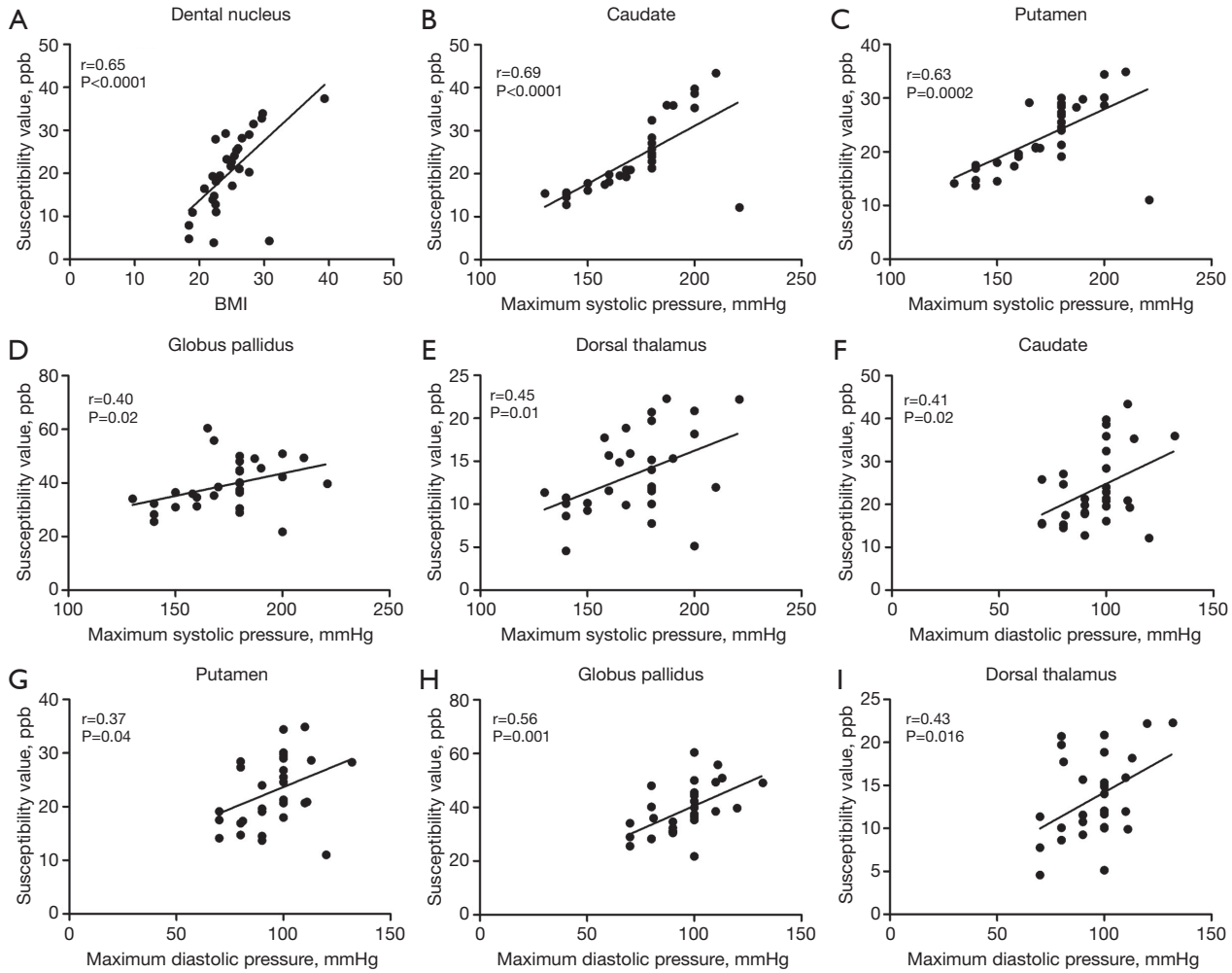

Figure 2 Bivariate scatter plots showing a positive correlation between body mass index and the magnetic susceptibility of the dentate nucleus (A), between maximum diastolic pressure, maximum systolic pressure, and magnetic susceptibility of the caudate nucleus, putamen, globus pallidus, and dorsal thalamus (B-I).

the concentration of reactive oxygen species and lipid peroxidation, causing blood-brain barrier destruction, arteriosclerosis and neuronal death (20).

Our data showed that the correlation between BMI and the susceptibility values of the DN was significantly positive (r=0.65, P<0.0001). Previous studies found that the prevalence of HP increased with increasing BMI (21). The BMI change is associated with avoiding HP versus developing HP (22). A follow-up study (23) is available on Chinese adults, which explored the relationship between overweight or obesity and HP. It found that the risk of high blood pressure and an increase in BMI of overweight or obesity groups was 1.16 to 1.28 times that of the normal body group. Obesity may contribute to increased brain iron deposition, which is associated with HP.

Elevated blood pressure leads to iron overload in the brain (24). Our study also found that the maximum SBP was significantly and positively correlated with the susceptibility values for CA (r=0.69, P<0.0001), PU (r=0.63, P=0.0002), GP (r=0.40, P=0.02), and TH (r=0.45, P=0.01). Maximum DBP was significantly and positively correlated with the susceptibility values for CA (r=0.41, P=0.02), PU (r=0.37, P=0.04), GP (r=0.56, P=0.001), and TH (r=0.43, P=0.016). A global prospective observational study showed that SBP and DBP were positively correlated with stroke risk, incidence of coronary heart disease, and the mortality of cardiovascular disease. Elevated blood pressure has been shown to be associated with

cardiovascular mortality and morbidity (25). The risk of cardiovascular and cerebrovascular disease will increase proportionally to elevated SBP or DBP, and the risk of disease will double for every 20 mmHg increase in SBP or 10 mmHg increase in DBP (26). Cohort studies performed in Asian populations have shown significant associations between SBP and mortality and between SBP and the risk of cardiovascular diseases (27). Controlling blood pressure in HP is considered a key measure for cardiovascular risk management and a cornerstone of preventive strategies (28). Since elevated blood pressure is a risk factor that can be changed by lifestyle changes and relatively cheap medicine, an important strategy to prevent stroke is evidence-based blood pressure management.

This study has certain limitations. First, the number of hypertensive patients was too small to allow reliable generalizations to the general population of HP. Studies with larger sample sizes are required to assess the mechanism of brain iron accumulation in HP. Second, HP is divided clinically into different degrees, whereas in this study, there was no analysis of different degrees of HP. This particular research question will be addressed in future studies with larger sample sizes. Third, the ROIs were manually drawn by researchers, which has inherent errors.

To sum up, we made use of QSM to assess the accumulation of brain iron in hypertensive patients and found that iron accumulation increased mainly in the caudate, PU, GP, and dorsal thalamus. Our results show that excessive iron in the deep gray matter nuclei of the brain plays a role in HP, which suggests HP is associated with excess brain iron in certain deep gray matter regions.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-5170

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-5170

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5170). Dr. SW is from MR Scientific Marketing, Siemens Healthineers. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Xi'an Daxing Hospital (Xi'an, China) (No.: DX2021-716[1]) and informed consent was taken from all the patients.

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