□原著論文□

Brain iron deposition analysis in Parkinson's disease using quantitative susceptibility mapping

HTWE Khin Moh Moh[1], MUROI Kenzo[2] and MARUYAMA Sumito[2]

Abstract

Background and Purpose: Iron deposition in specific regions of the brain is found in multiple neurodegenerative diseases, including Parkinson's disease (PD). The purpose of the study presented here was to estimate the susceptibility values of basal ganglia (BG) due to iron deposition using quantitative susceptibility mapping (QSM) in correlation with patients' motor functions and to differentiate PD from normal controls.

Material and Methods: Twelve patients with PD, and 8 patients with essential tremor (ET) and other atypical parkinsonism (APS) and, 17 control subjects were recruited. QSM maps were generated from a conventional 3D gradient echo sequence using a 3T-MRI scanner. Susceptibility values (S-values) of anatomic regions of BG were measured on QSM images using Image J software.

Results: Among the deep gray matter nuclei, the mean normalized susceptibility values (Sn-values) of right substantia nigra pars compacta (SNpc), right dentate nucleus (DN), and right and left globus pallidus (GP) were determinant values for discrimination of the parkinsonian disorders from normal control. Moreover, the discriminative Sn-values in the right DN region were differentiating between PD and other APS. PD and ET group had obvious Sn-values' difference in right GP region. In addition, the Sn-values differences in left DN and left GP were also usable in differentiation of PD from other APS.

Conclusion: QSM is a valuable tool for indirect quantification of iron deposition in deep gray matter nuclei, and right SNpc is the remarkable biomarker to distinguish PD from normal controls.

Keywords：Parkinson's disease, brain iron, susceptibility, basal ganglia, substantia nigra, MRI

定量的磁化率マッピングを用いたパーキンソン患者の脳内鉄沈着解析

HTWE Khin Moh Moh[1]　　室井　健三[2]　　丸山　純人[2]

抄　録

目的：脳内の鉄沈着は，パーキンソン病（PD）を含むいくつかの神経変性疾患にみられる．本研究では，鉄沈着に起因する大脳基底核（BG）の磁化率を，定量的磁化率マッピング（QSM）を用いて患者の運動機能と関連づけて評価することにより，PD と健常人とを区別できるかを確かめる．

方法：12 人の PD および 8 人の本態性振戦（ET）を含む他の非定型パーキンソニズム（APS）の患者と 17 人の健常人を対象とした．3T-MRI の 3D gradient echo sequence で QSM を作成し，BG 内各領域で磁化率平均値（S-value）を測定した．

結果：右側の黒質緻密部（SNpc），歯状核（DN）と左右の淡蒼球（GP）の正規化した S-value（Sn-value）はパーキンソン障害と健常人とを区別する決定因子となる．また右側の DN の Sn-value は PD と他の APS を識別する可能性を示した．右側の GP は PD と ET，左側の DN と GP は PD と他の APS とを区別する Sn-value を示す．

結論：QSM は PD の評価に BG 内の鉄沈着を間接的に定量化するに有効なツールで，右側の SNpc での Sn-value 測定で PD と健常人とを区別できうる．

キーワード：パーキンソン病，脳内鉄分，磁化率，大脳基底核，黒質，MRI

受付日：2017 年 8 月 30 日　受理日：2017 年 11 月 4 日

[1] 国際医療福祉大学大学院　医療福祉学研究科　保健医療学専攻　放射線・情報科学分野　博士課程
Division of Radiological Sciences, Doctoral Program in Health Sciences, Graduate School of Health and Welfare Sciences, International University of Health and Welfare
peachmomo75@gmail.com
[2] 国際医療福祉大学　保健医療学部　放射線・情報科学科
Department of Radiological Sciences, School of Health Sciences, International University of Health Sciences

Ⅰ. Introduction

Parkinson's disease (PD) is a progressive degenerative neurological disorder of the central nervous system. Additionally, it is characterized by an asymmetric onset of resting tremor or shaking hands while other limbs are at rest, bradykinesia, rigidity or postural dysfunction and loss of balance[1]. Disease progression is associated pathophysiologically with dopaminergic cell loss and iron accumulation in the substantia nigra pars compacta (SNpc)[2]. An accurate early diagnosis is important as the prognoses and therapeutic plans vary among distinct Parkinsonian disorders[3].

Several molecular compounds found in brain tissue, including nonheme iron, iron in deoxyhemoglobin, myelin, and iron containing proteins like ferritin and hemosiderin, may significantly affect tissue susceptibility and the resultant resonance frequency shift[4]. Nonheme iron, especially that in the iron storage protein ferritin, may present the primary source of magnetic susceptibility in the basal ganglia (BG)[5]. Brain iron plays an essential role in numerous neurophysiologic functions, including neurotransmitter biosynthesis, the myelination process, oxygen transport, protein and DNA synthesis, and mitochondrial respiration[6,7]. Several neurodegenerative disorders, including Alzheimer's disease, PD, and multiple sclerosis, present with abnormally high iron concentrations in neurons and microglia/microphages[8].

Quantitative susceptibility mapping (QSM) is a novel MRI technique used to evaluate and quantify the magnetic susceptibility of iron for assessing the midbrain changes of PD[9]. QSM has several advantages over other iron quantification methods, such as the $R2^*$ and phase methods. For example, QSM can detect bulk magnetic susceptibility within a voxel, thereby providing high accuracy and sensitivity for the estimation of iron concentration, which is significantly correlated with the brain's iron content[10]. Further, QSM allows actual size evaluation of iron-containing structures due to reduction of the blooming artifacts that are inherent in $R2^*$ and phase and also allows detection of both paramagnetic iron and diamagnetic molecular susceptibilities[11].

Many studies have investigated whether iron deposition in the substantia nigra (SN) and BG could function as a diagnostic marker of PD. These studies have found that increased nigra iron levels in the SN and abnormal iron accumulation in the deep gray matter nuclei occurred in patients with other APS such as Progressive Supranuclear Palsy (PSP), parkinsonian subtype Multiple System Atrophy (MSA-P), and essential tremor (ET)[3,12–14]. Interestingly, iron deposition in the BG varies among different parkinsonian-related disorders. Therefore, in the study presented here, we used QSM to assess whether the spatial variation of iron deposition in deep brain nuclei could be used to differentiate PD from normal controls.

Ⅱ. Materials and Methods

1. Subjects

The study included 17 normal controls (61 ± 10 years, 7 males and 10 females) and 20 patients (74 ± 6 years, 11 males and 9 females) that had been assessed via the neuropsychological assessments according to the criteria of the United Kingdom Brain Bank[15]. The 20 patients with symptoms of parkinsonism group, in which of 12 (73 ± 6 years, 6 males and 6 females) were PD, 3 ET (79 ± 7 years, 3 males) and 5 other APS (76 ± 5 years, 2 males and 3 females), which was assessed by experienced neurologists' diagnostic results of patient clinical history in an electronic health record. The inclusion criteria were symptoms of resting or postural tremor or shaking hands, bradykinesia, rigidity or postural instability, and no other dementia. The exclusion criteria were neurologic or psychiatric disease, brain injury, or contraindication to MRI.

This study was approved by the ethical committees of the International University of Health and Welfare (IUHW) and IUHW hospital with approval numbers of 16-Io-2 and 13-B-182 respectively. Written informed consent was

obtained from all subjects prior to their participation. The demographic and clinical data of patients with symptoms of parkinsonism are summarized in Table 1.

2. MR image acquisition

All participants underwent brain MRI on a 3T MRI system (Philips, Achieva 3T) with a 32-channel phased-array head coil. We used a 3D gradient echo sequence (3D-T2* FFE, Fast Field Echo) with the following imaging parameters: TR/TE = 50/20.719 ms, small field of view = 200 × 170 mm^2, matrix size = 256 × 170, slice thickness = 2 mm, spacing = 0.67 mm, voxel size = 0.39 × 0.39 × 2 mm^3, slice numbers = 50−80, and acquisition time = 4 min 51s.

3. Data processing of quantitative susceptibility mapping and image analysis

The processing tasks for QSM reconstruction were executed in the MATLAB (2015b) environment (Mathworks Inc., Natick, MA, USA), and QSM reconstruction software was downloaded from STI Suite. QSM maps were generated by processing data using a basic Bayesian algorithm comprised of 3 steps; (1) estimate the total magnetic field in each voxel from phase data and phase unwrapping was performed using Laplacian-based[16] unwrapping algorithms, and brain mask from magnitude data (2) remove the background field from the total magnetic field was performed using iterative HArmonic (background) PhasE REmovaL using the LAplacian operator (iHARPERELLA) algorithm[17], (3) recovery of a susceptibility map from a local tissue field map, deconvolved with the unit dipole kernel, corresponding to a point-wise division in k-space and iLSQR algorithm was used to perform inverse dipole calculation[16].

Regions of interest (ROIs) settings were done manually on the axial QSM images (Figure 1) of BG, including caudate nucleus (CN), globus pallidus (GP), putamen (PT), red nucleus (RN), dentate nucleus (DN), and SN which was segmented by previous studies[18–20] into SNpc, substantia nigra reticulata (SNr), whole substantia nigra (SNw), and caudal substantia nigra (SNcd). In order to normalize the susceptibility values (S-vaules) of the measured location, we subtract the S-values of white matter of the same slice from the measured S-values for each ROI. Thereafter, normalized susceptibility values (Sn-values) from all participants were analyzed. The average mean and standard deviation (SD) were calculated. Because the parkinsonism group was older than the control group, age-matched groups were created by selecting 10 relatively younger subjects (70 ± 4years, 5 males and 5 females) from the parkinsonism group and 10 relatively older subjects (68 ± 6 years, 4 males and 6 females) from the control group. Further, the

Table 1　Demographic and clinical characteristics of participants.

Participants	Parkinsonism group	No. of Participants	Female, Male (F) (M)	Age (years) mean ± SD
Patients with symptoms of parkinsonism (n = 20)	PD (H&Y1 = 4 patients) (H&Y2 = 3 patients) (H&Y3 = 4 patients) (H&Y4 = 1 patient)	12	6F, 6M	73 ± 6
	Other APS	5	3F, 2M	76 ± 5
	ET	3	3M	79 ± 7
Control (n = 17)		17	10F, 7M	61 ± 10

SD: standard deviation, H&Y: Hoehn and Yahr, PD: Parkinson's disease, APS: Atypical Parkinsonism, ET: essential tremor.

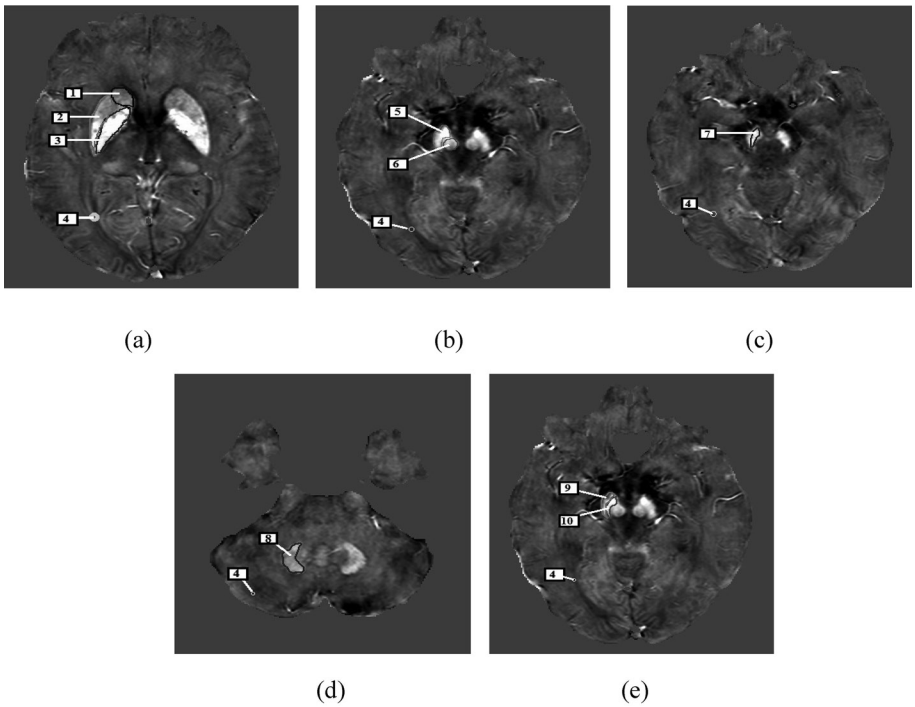

Figure 1　QSM axial images of 64years old woman with Parkinson's disease; ROIs delineated: (a) (1) caudate nucleus, (2) putamen, (3) globus pallidus, (4) occipital white matter, (b) (5) substantia nigra, (6) red nucleus, (c) (7) caudal substantia nigra, (d) (8) dentate nucleus, (e) (9) substantia nigra reticulata, (10) substantia nigra pars compacta.

parkinsonism group was divided into subgroups (PD, ET and other APS) were compared against the control group and then among parkinsonism group.

4. Statistical Analysis

Statistical analyses were performed using SPSS (Windows version 23.0, SPSS Inc., Chicago, IL, USA), and *P*-values <0.05 were considered statistically significant. A Mann-Whitney *U* test was applied in comparison of the Sn-values between the parkinsonism group and control group. To determine the significant Sn-values among the parkinsonism group, the Bonferroni multiple comparison test was used. For the reliability of ROIs measurements, intra-class correlation coefficient was calculated.

Ⅲ. RESULTS

The mean Sn-values and *P*-values were measured on both sides of the hemibrain in the following regions: CN, GP, PT, RN, SNpc, SNr, SNwhole, SNcd, and DN. The SN regions in both hemispheres had higher mean Sn-values than other BG regions; GP also showed increased iron accumulation, but this difference did not reach significance. The mean Sn-values of CN were lower in the parkinsonism group than the control group ($P = 0.02$; Table 2). The intra-class correlation coefficient values for interobserver agreement of ROI measurements in both hemibrains of SN and BG regions for parkinsonism and control groups were 0.78 and 0.67 respectively.

When comparing between the patients with symptoms of parkinsonism including PD, ET and other APS and, 17 control subjects, the right side SNpc, SNr, and SNw structures showed increased iron deposition in the parkinsonism group than in the control group (*P*-values = 0.02, 0.06 and 0.04, respectively) (Table 2). The same significant result was seen in SN region when comparing the age-controlled parkinsonism and control groups (10 subjects from each group) (*P*-values = 0.01, 0.04 and 0.05, respectively) (Table 3).

Table 2　Comparison of mean Sn-values ($\Delta\chi$) and standard deviation in bilateral deep gray matter nuclei between full subjects in control and parkinsonism group (not age-matched).

Structures	Right	Left	*P*-value	
	(mean ± SD)	(mean ± SD)	Right	Left
CN	0.065 ± 0.028	0.061 ± 0.029	0.31	0.02*
GP	0.164 ± 0.039	0.153 ± 0.041	0.74	0.27
PT	0.109 ± 0.024	0.114 ± 0.027	0.33	0.80
RN	0.144 ± 0.036	0.145 ± 0.034	0.67	0.33
SNpc	0.171 ± 0.044	0.176 ± 0.038	0.02*	0.26
SNr	0.131 ± 0.039	0.155 ± 0.036	0.06	0.25
SNw	0.153 ± 0.042	0.165 ± 0.035	0.04*	0.22
SNcd	0.183 ± 0.047	0.191 ± 0.044	0.84	0.63
DN	0.146 ± 0.038	0.136 ± 0.038	0.82	0.07

$\Delta\chi$ values are in parts per million (ppm). Statistics analyzed by Mann-Whitney *U* Test.
*: $P<0.05$. CN: caudate nucleus, GP: globus pallidus, PT: putamen, RN: red nucleus, SNpc: substantia nigra pars compacta, SNr: substantia nigra reticulata, SNw: whole substantia nigra, SNcd: caudal substantia nigra, DN: dentate nucleus.

Table 3　Comparison of mean Sn-values ($\Delta\chi$) and standard deviation in bilateral deep gray matter nuclei between age-matched control and parkinsonism group.

Structures	Right	Left	*P*-value	
	(mean ± SD)	(mean ± SD)	Right	Left
CN	0.073 ± 0.030	0.066 ± 0.026	0.73	0.79
GP	0.177 ± 0.044	0.171 ± 0.040	0.31	0.52
PT	0.112 ± 0.025	0.119 ± 0.025	0.57	0.21
RN	0.152 ± 0.038	0.155 ± 0.033	0.27	0.85
SNpc	0.182 ± 0.049	0.190 ± 0.038	0.01**	0.21
SNr	0.135 ± 0.041	0.165 ± 0.037	0.04*	0.19
SNw	0.162 ± 0.047	0.176 ± 0.032	0.05*	0.23
SNcd	0.191 ± 0.056	0.198 ± 0.048	0.26	0.43
DN	0.162 ± 0.040	0.153 ± 0.037	0.52	0.29

$\Delta\chi$ values are in parts per million (ppm). Statistics analyzed by Mann-Whitney *U* Test.
**: $P<0.01$, *: $P<0.05$. CN: caudate nucleus, GP: globus pallidus, PT: putamen, RN: red nucleus, SNpc: substantia nigra pars compacta, SNr: substantia nigra reticulata, SNw: whole substantia nigra, SNcd: caudal substantia nigra, DN: dentate nucleus.

To estimate whether Sn-values could be used to discriminate the control from different parkinsonism groups (PD, ET and other APS) we compared the Sn-values from the age-matched control group with those from each sub-parkinsonism group (Table 4) and multiple comparison among these groups (Figure 2, 3). Right DN (RDN) regions had significant Sn-values in other APS (*P*-value = 0.01) and discriminated from the control. The Sn-values of right SNpc showed the obvious difference from control group but not significant ($P = 0.07$). The Sn-values of the ET group showed no significant difference from those of the control group in any structures of BG. However, in the ET group Sn-values did trend lower than those of the control group bilaterally in GP (*P*-values = 0.08 and 0.09, right

Table 4　The mean Sn-values ($\Delta\chi$) and standard deviations of bilateral deep gray matter nuclei for discriminating patients with symptoms of parkinsonism from age-matched control subjects.

Comparison		Structure	Mean ± SD	*P*-value
PD	Vs. Control	RSNpc	0.178 ± 0.05	0.07
Other APS	Vs. Control	RDN	0.139 ± 0.03	0.01*
		LGP	0.148 ± 0.037	0.07
ET	Vs. Control	RGP	0.155 ± 0.026	0.08
		LGP	0.154 ± 0.033	0.09

$\Delta\chi$ values are in parts per million (ppm). Statistics analyzed by Mann-Whitney *U* Test.
*: $P<0.05$. PD: Parkinson disease, APS: Atypical Parkinsonism, ET: essential tremor, RSNpc: right substantia nigra pars compacta, RDN: right dentate nucleus, RGP: right globus pallidus, LGP: left globus pallidus.
LGP: left globus pallidus.

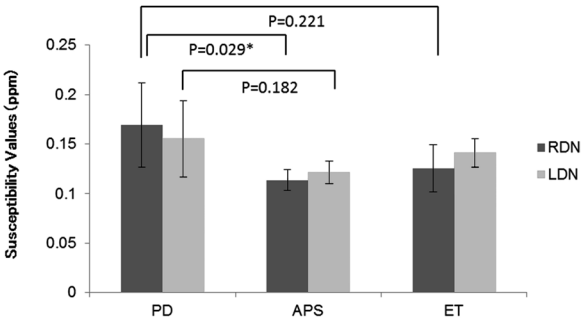

Figure 2　Comparison of mean Sn-values and standard deviation of right and left dentate nucleus region among parkinsonism groups.
Statistics analysed by Bonferroni's multiple comparison test.*: $P<0.05$. PD: Parkinson's disease, APS: other Atypical Parkinsonism and ET: Essential tremor, RDN: right dentate nucleus, LDN: left dentate nucleus

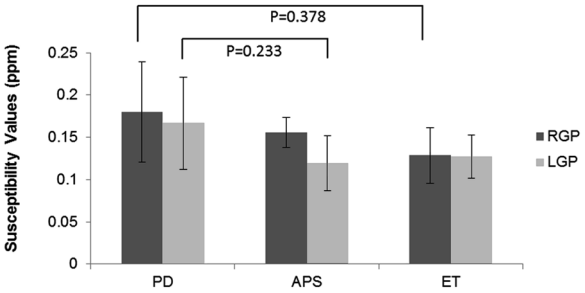

Figure 3　Comparison of mean Sn-values and standard deviation of right and left globus pallidus region among parkinsonism groups.
Statistics analysed by Bonferroni's multiple comparison test.*: $P<0.05$. PD: Parkinson's disease, APS: other Atypical Parkinsonism and ET: Essential tremor, RGP: right globus pallidus, LGP: left globus pallidus

and left respectively). The multiple comparison among the parkinsonism groups, the measured Sn-values in the RDN determined the discrimination of PD from other APS (*P*-value = 0.029) and from ET (*P*-values = 0.221). Similarly, Sn-values for right GP (RGP) region were obvious differences comparing other BG structures between PD and ET (*P*-value = 0.378) and those in left GP (LGP) had a variation between PD and other APS (*P*-value = 0.233) but did not reach the significant (Figure 2, 3).

Ⅳ. Discussion

In early stage of disease, the other parkinsonian disorders resemble PD, making differentiation between diseases at the earliest stages challenging[3]. Of note, deep brain nuclei show abnormal iron deposition in patients with parkinsonian disorders. Previously, histochemical studies have reported increased iron deposition in the SN in PD and have shown a significant correlation between disease severity and iron accumulation[11,21,22]. The study presented here indirect assess of regional iron deposition in the deep gray matter nuclei using QSM to quantify the susceptibility values differences in patients with PD, ET and other APS. Several postmortem studies have reported increased iron accumulation in the SN of patients with PD compared with that in unaffected control subjects; we obtained a similar result with the mean Sn-values of SNpc in our patients with

PD tended to be higher than those in the controls. Although there was no significant result ($P = 0.07$) which in trend and we may collect more patients, it may possible to reach the significant value.

However, Aquino et al. reported that iron depositions in the GP, PT, CN, and SN could be related to the age of the patient and were different in each structure[23]. In the study presented here, there was a significant age difference between participants in the two groups. Thus, we created age-matched subgroups to determine whether the increased iron accumulations in the SN regions were due to disease or age-related changes. Interestingly, the SN regions from the right hemispheres still showed significantly higher iron accumulation in the parkinsonism group than in the control group. Therefore, these Sn-values difference findings in this study were accordance with the disease severity and it seems to be normalization counteract the influence effect of ageing. Furthermore, the mean Sn-values from all BG structures of the parkinsonism group were higher than those of the control group and the study results are compatible with other researchers' findings. Azuma et al[24]., reported previously that the mean S-values of the posterior portions of the more affected hemibrain SNs were significantly higher than those of the less affected hemibrain SNs of PD patients and healthy controls. Although we were not able to compare Sn-values between the more and less affected hemibrains of patients and controls, the bilateral difference of significant results were observed, especially in the right hemibrain, which may relate with the disease severity of affected side. Moreover, we found that the iron deposition in CN was lowered in both hemispheres in brains from the patients with parkinsonism group compared with that from the control group, which is compatible with the findings of Guan et al[22].

Regarding with the differentiation of the symptoms of parkinsonian disorder, the autopsy study investigated about the macroscopic features of three parkinsonian disorders, PD, MSA and PSP, pigment loss in SN in all three disorders which correlate with the other APS however the atrophy of posterior PT and dark discoloration in MSA is prominent but the two not. In PSP, remarkable atrophy and pigment loss in cerebellum white matter and subthalamic nuclei. Another finding was asymmetry is an important supportive feature in PD while the two others are usually symmetrical[25]. Moreover, basal ganglia iron deposition was useful in differentiation of PD from APS, increased iron deposition of GP and CN observed in PSP compared with PD and, while compared with MSA, more prominent iron deposition of GP, RN and SN observed in PSP[14,26].

We found to mention or imply as a possibility that DN, GP and PT regions has abnormal iron deposition due to susceptibility differences between PD and other APS groups in this study. The significant result of susceptibility RDN value was discriminated the PD from other APS with $P = 0.029$ after correction of Bonferroni's multiple comparison test. The rest of the Sn-values in left side of GP, PT and DN were also obvious among the BG structures between these two groups but not statistically significant, if we collected more subjects that may possible to reach the significant value. Furthermore, in the RDN and RGP and, LGP structures had obvious Sn-values between PD and ET groups while comparing other BG structures and thus the DN and GP Sn-values may be possible to use to differentiate the PD from ET. Jin L et al. found that significant brain iron level difference in GP between ET and tremor-dominant PD using susceptibility weighed imaging[27]. These results are compatible with our study results of bilateral GP Sn-values differences. In addition, in assessing the distinguishing of the ET from other APS, the Sn-value differences were observed only in the left PT region and while no other BG structures different. Therefore, as far as we were concerned, the measured Sn-values in the RDN region are able to discriminate the PD from other APS and the susceptibility SN, GP and PT values are also useful to distinguish PD from other parkinonian disorders.

The study presented here has a few limitations. First,

the number of participants was relatively small, and, therefore, apparent differences between PD and other APS including ET need to be studied in a larger sample. Second, the participants in our study were age difference between the parkinsonism and control groups. In order to attain the more reliable results, we need to study with large population of age-matched subjects. Third, although the control subjects have no signs or symptoms of PD or other movement disorders, some presented other symptoms of disease, such as cerebral infarct, hypertension, numbness of limbs, and headache. Finally, ROIs measurements were performed with manual setting and QSM images cannot produced directly from MR image acquisition and require post-processing that lasts approximately 20 minutes.

In conclusion, our data suggest that PD patients exhibit increased iron accumulation in the SNpc region than patients with other parkinsonism. Further, the susceptibility values measured in the RSNpc structure may discriminate the PD from normal controls. QSM is a valuable tool for indirect quantification of iron deposition in deep gray matter nuclei, and RSNpc is the remarkable biomarker to distinguish PD from normal controls.

Acknowledgements

The author thanks: Prof. Kenichiro Katsumata, Prof. Shigeru Nawano, from Department of Radiological Sciences, IUHW, Dr. Hitoshi Yamagata, from Toshiba Medical System, Dr. Makoto Tamari, from Department of Physical Therapy, IUHW, Fukuoka and for patient recruitment; Prof. Hiroyuki Katoh from the Department of Neurology, IUHW Hospital, Mr. Mitsuo Narita, Mr. Masayuki Harada, Mr. Makoto Konishi, and the radiographers from Department of Radiology, IUHW Hospital, and all participants who made this research possible. There is no conflict of interest to report.

References

1）Jankovic J. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry. 2008; 79(4): 368-376
2）Liu C, Wei H, Gong NJ, et al. Quantitative susceptibility mapping: contrast mechanisms and clinical applications. Tomography. 2015; 1(1): 3-17
3）Holtbernd F, Eidelberg D. The utility of neuroimaging in the differential diagnosis of Parkinsonian syndromes. Semin. Neurol. 2014; 34(2): 202-209
4）Duyn JH. Study of brain anatomy with high-field MRI: recent progress. Magn. Reson. Imaging. 2010; 28(8): 1210-1215
5）Haacke EM, Cheng NY, House MJ, et al. Imaging iron stores in the brain using magnetic resonance imaging. Magn. Reson. Imaging. 2005; 23(1): 1-25
6）Sian-Hulsmann J, Mandel S, Youdim MB, et al. The relevance of iron in the pathogenesis of Parkinson's disease. J. Neurochem. 2011; 118(6): 939-957
7）Eskreis-Winkler S, Zhang Y, Zhang J, et al. The clinical utility of QSM: disease diagnosis, medical management, and surgical planning. NMR Biomed. 2017; 30(4)
8）Berg D, Youdim MB. Role of iron in neurodegenerative disorders. Top. Magn. Reson. Imaging. 2006; 17(1): 5-17
9）Du G, Liu T, Lewis MM, et al. Quantitative susceptibility mapping of the midbrain in Parkinson's disease. Mov. Disord. 2016; 31(3): 317-324
10）Wu B, Li W, Guidon A, et al. Whole brain susceptibility mapping using compressed sensing. Magn. Reson. Med. 2012; 67(1): 137-147
11）Langkammer C, Schweser F, Krebs N, et al. Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study. Neuroimage. 2012; 62(3): 1593-1599
12）Boelmans K, Holst B, Hackius M, et al. Brain iron deposition fingerprints in Parkinson's disease and progressive supranuclear palsy. Mov. Disord. 2012; 27(3): 421-427
13）Novellino F, Cherubini A, Chiriaco C, et al. Brain iron deposition in essential tremor: a quantitative 3-tesla magnetic resonance imaging study. Mov. Disord. 2013; 28(2): 196-200
14）Han Y-H, Lee J-H, Kang B-M, et al. Topographical differences of brain iron deposition between progressive supranuclear palsy and parkinsonian variant multiple system atrophy. J. Neurol. Sci. 2013; 325(1-2): 29-35
15）Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J. Neurol. Neurosurg. Psychiatry. 1992; 55(3): 181-184
16）Li W, Wu B, Liu C, et al. Quantitative susceptibility mapping of human brain reflects spatial variation in tissue composition. Neuroimage. 2011; 55(4): 1645-1656
17）Li W, Avram AV, Wu B, et al. Integrated Laplacian-based phase unwrapping and background phase removal for quantitative susceptibility mapping. NMR Biomed. 2014; 27(2): 219-227
18）Lotfipour AK, Wharton S, Schwarz ST, et al. High resolution magnetic susceptibility mapping of the substantia nigra in Parkinson's disease. J. Magn. Reson. Imaging. 2012; 35(1): 48-55
19）Barbosa JH, Santos AC, Tumas V, et al. Quantifying brain iron deposition in patients with Parkinson's disease using quantitative susceptibility mapping, R2 and R2. Magn. Reson. Imaging. 2015; 33(5): 559-565
20）Foster ER, Black KJ, Antenor-Dorsey JA, et al. Motor asymmetry and substantia nigra volume are related to spatial delayed response performance in Parkinson disease. Brain Cogn. 2008; 67(1): 1-10

21）Martin WR, Wieler M, Gee M, et al. Midbrain iron content in early Parkinson disease: a potential biomarker of disease status. Neurology. 2008; 70(16 Pt 2): 1411-1417
22）Guan X, Xuan M, Gu Q, et al. Regionally progressive accumulation of iron in Parkinson's disease as measured by quantitative susceptibility mapping. NMR Biomed. 2017; 30(4): e3489
23）Aquino D, Bizzi A, Grisoli M, et al. Age-related iron deposition in the basal ganglia: quantitative analysis in healthy subjects. Radiology. 2009; 252(1): 165-172
24）Azuma M, Hirai T, Yamada K, et al. Lateral asymmetry and spatial difference of iron deposition in the substantia nigra of patients with Parkinson disease measured with quantitative susceptibility mapping. AJNR Am. J. Neuroradiol. 2016; 37(5): 782-788
25）Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb. Perspect Med. 2012; 2(8)
26）Lee J-H, Han Y-H, Kang B-M, et al. Quantitative assessment of subcortical atrophy and iron content in progressive supranuclear palsy and parkinsonian variant of multiple system atrophy. J. Neurol. 2013; 260(8): 2094-2101
27）Jin L, Wang J, Fei G, et al. Different features of iron deposition in subcortical nuclei between essential tremor and tremor-dominant Parkinson's disease [abstract]. Mov. Disord. 2015; 30 Suppl 1: 4188