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ATYPICAL IRON ACCUMULATION IN FASCICULA NIGRA OF PARKINSON'S PATIENTS: A STUDY IN AN URBAN TERTIARY CARE CENTRE IN SALEM, TAMIL NADU

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Abstract

Background: Individuals diagnosed with Parkinson's disease (PD) exhibit increased concentrations of iron in the brain, particularly in the nigrostriatal dopaminergic pathway. The objective of this study is to compare the pattern of iron deposition in the fascicula nigrale between patients with Parkinson's disease and age-matched controls. This will be achieved by using quantitative susceptibility mapping (QSM) to measure changes in susceptibility. **Methods:** This study included 25 patients diagnosed with Parkinson's disease (PD) and 25 healthy volunteers (HVs) who were matched in terms of age and sex. The HVs served as a control group. Participants performed magnetic resonance imaging (MRI) of the brain and generated quantitative susceptibility mapping (QSM) data. The fascicula nigrale and substantia nigra were delineated using SWI mapping software by investigators who were unaware of the details. Statistical analyses were conducted to ascertain the susceptibility patterns of both of these regions. **Results:** Measurements revealed a notable rise in vulnerability in the substantia nigra among those with Parkinson's disease, as well as an elevated accumulation of iron in the fascicula nigrale extending from the front to the back in all participants. This pattern was magnified, with a notable link shown between increasing age and the Parkinson group. The PD group had higher susceptibility values in the FN, substantia nigra pars compacta (SNc), internal globus pallidus (GPi), red nucleus (RN), putamen, and caudate nucleus in comparison to the HV group ($P < 0.05$). **Conclusion:** The Parkinson group exhibits an increased iron deposition gradient in the fascicula nigrale, which may indicate underlying tract dysfunction. The association between increased iron deposition and rising age is significant and may be a cumulative effect, maybe associated with the duration of the condition. Further investigation is required to determine the origin and process of iron accumulation in the substantia nigra (SN), as well as the connection between iron deposition in the red nucleus (RN) and Parkinson's disease (PD).

Keywords: Parkinson's Disease, Substantia Nigra, Iron Accumulation, Magnetic Resonance Imaging (MRI), Quantitative Susceptibility Mapping (QSM)

INTRODUCTION

Parkinson's disease (PD) is a degenerative neurological condition characterised by a gradual loss of motor function.The underlying cause of Parkinson's disease (PD) is

the degeneration of dopaminergic neurons and the presence of Lewy bodies in the striatum pathway [1–3]. Individuals diagnosed with Parkinson's disease (PD) exhibit elevated levels of iron in their brain, particularly within the nigrostriatal dopaminergic pathway [4]. Both in vivo and postmortem investigations have shown that iron is linked to brain degeneration in Parkinson's disease (PD) [5, 6]. Excessive iron accumulation contributes to oxidative stress and the death of neurons [4]. Within cells, unbound ferrous irons (Fe2+) undergo a reaction with hydrogen peroxide (known as the Fenton reaction). This interaction results in the creation of detrimental ferric irons (Fe3+) and highly reactive oxygen species. These reactive species then proceed to injure cellular components, particularly proteins. Magnetic resonance (MR) quantitative susceptibility mapping (QSM) is an innovative technique that can accurately measure the magnetic susceptibility value of brain tissue using gradient-echo (GRE) MR imaging (MRI) data. This technique offers exceptional contrast between iron-rich deep grey matter nuclei and the surrounding tissues [7].

The fascicula nigrale (FN) is composed of the striatonigral tract and nigrostriatal tract, which were initially identified by Harder et al. as a mineralized structure that extends from the globus pallidus (GP) to the substantia nigra (SN) (Figure 1) [8].This pathway has been theorised to be involved in the transportation of iron between the basal nuclei and midbrain [8, 9]. The susceptibility weighted imaging (SWI) shows a linear area of increased susceptibility that extends from the medial part of the GP to the anterior part of the substantia nigra. This can be seen in Figures 2.

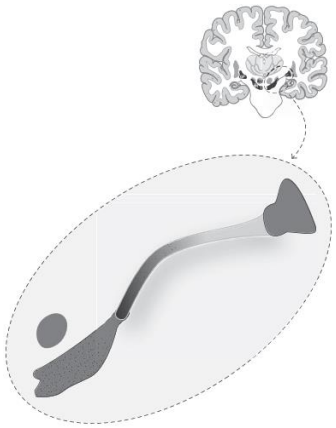

Figure 1: Illustration of the fascicula nigrale, a mineralized midbrain structure extending from the GP to the SN[8,10]

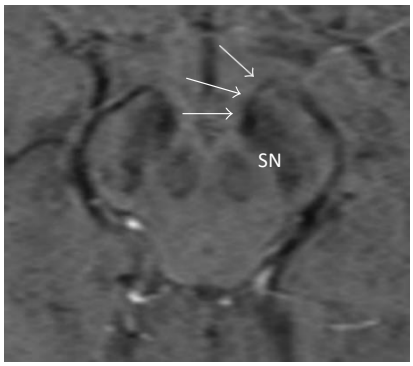

Figure 2: The FN (delineated by white arrows) is shown at its junction with the SN (SWI, 2 mm).[8,9,10]

Multiple scientists have discovered that the substantia nigra (SN) in Parkinson's disease (PD) shows increased buildup of iron. As a result, the mechanism of iron homeostasis in this disease has become a topic of interest for researchers [11, 12]. Lee and Andersen discovered that transferrin, the main protein responsible for transporting iron in the brain, showed elevated amounts in dopaminergic neurons of the substantia nigra in their investigations on rat and monkey models of Parkinson's disease [13]. Olanow and Youdim have hypothesised that transferrin is transported to storage places through axonal transport. This phenomenon has been explored in rats, where the passage of transferrin from the retina to the optic nerve, chiasm, and eventually the supra colliculus has been traced by Moos et al. [14, 15]. In mice models of Parkinson's disease (PD), Hirsch discovered that lactoferrin and DMT1 (divalent metal transporter 1), which are transporters of reactive iron, are excessively expressed in dopaminergic neurons of SN cells [16, 17]. Hirsch discovered a positive correlation between higher levels of DMT1 in the brain and advancing age, which aligns with the documented age-related buildup of cellular iron described by Hallgren and Sourander [16–18]. The presence of a higher number of these transport proteins in the substantia nigra (SN) may contribute to the disturbance of iron balance [13, 16, 17].

As anticipated, the precision of QSM measurements surpasses that of susceptibility weighted imaging (SWI) and R2* mapping [19, 20]. Due to its paramagnetic properties and ability to create local field inhomogeneity, iron (namely ferritin and haemosiderin) can be detected in vivo using GRE sequences [21–23]. Prior research has established a robust and favourable correlation between the susceptibility value and the measured iron level as determined by biochemical analysis [24–26]. Recent autopsy studies have confirmed that the quantitative susceptibility value measured in deep grey matter nuclei is strongly linked ($r = 0.84$) with the iron concentration obtained by inductively coupled plasma mass spectrometry and Perls' iron staining [25, 27].

QSM technology has been utilised in numerous research to investigate iron accumulation in the deep grey matter nuclei of individuals with Parkinson's disease. Multiple investigations have consistently demonstrated an abundance of iron accumulation in the substantia nigra (SN) of individuals with Parkinson's disease (PD), particularly in the substantia nigra pars compacta (SNc) [19, 20, 24, 28–34]. Moreover, there was a strong correlation between the iron concentration in the substantia nigra (SN) of patients with Parkinson's disease (PD) and their Hoehn and Yahr (H&Y) score, Unified Parkinson's Disease Rating Scale (UPDRS), and Hamilton Anxiety (HAMA) Scale [35].

Several researchers have devised noninvasive methods to quantify iron accumulation utilising high-field strength spin-echo T2 weighted MRI sequences, including relaxometry ($R2*$), quantitative susceptibility mapping, and diffusion tensor imaging [36]. SWI was initially created in the mid-1990s, utilising phase to improve contrast in $T2*$ sequences. Quantitative susceptibility mapping originated from the SWI precursor as a technique to utilise phase information for quantifying iron levels in the midbrain, as explained by Haacke et al. [37]. Zhang et al. demonstrated that the mapping of SWI phase shift values was positively associated with Hallgren and Sourander's original autopsy findings in healthy individuals, thereby confirming the use of SWI mapping as a noninvasive method for measuring iron levels [38]. Deistung et al. [39] discovered that quantitative susceptibility mapping provides excellent contrast of brain structures and substructures, revealing details that are not visible on $R2*$, magnitude, or frequency images. Several noninvasive studies utilising SWI and $R2*$ have been

conducted, confirming prior postmortem discoveries of elevated iron accumulation in the brains of individuals with PD [40]. Haacke et al. initially discovered that quantitative susceptibility mapping is more sensitive than R2∗ in detecting changes in iron deposition in patients with multiple sclerosis. Murakami et al. and Barbosa et al. conducted studies comparing these techniques in PD brains and found that quantitative susceptibility mapping is more sensitive, with highly accurate discrimination between patient and control groups [40, 41]. Quantitative susceptibility mapping, the most precise and sensitive measurement approach for midbrain iron deposition, was employed in this investigation to quantify iron deposition in the substantia nigra (SN) and frontal nucleus (FN).

Quantitative susceptibility mapping is more sensitive than R2∗ in detecting changes in iron deposition in patients with multiple sclerosis. Murakami et al. and Barbosa et al. compared both techniques in Parkinson's disease brains, finding quantitative susceptibility mapping more sensitive and precise. This study used quantitative susceptibility mapping to quantify iron deposition in the substantia nigra and frontal nucleus. The study aimed to quantify iron accumulation in the fascicula nigrale among patients with Parkinson's disease, predicting elevated iron accumulation in both the frontal nucleus and the substantia nigra. Further research is needed to examine abnormal iron accumulation in this pathway.

MATERIALS AND METHODS

The Department of Neurology and Department of Radio-Diagnosis at Vinayaka Mission's Kirupananda Variyar Medical College in Salem, Tamil Nadu, conducted a study from November 2022 to May 2024, recruiting 25 patients with a new diagnosis of idiopathic PD. Of these patients, 15 were males and 10 were females, with a mean age of 58.6 years and a range of 50–72 years. The selection criteria for recruitment were based on the UK Parkinson's Disease Society Brain Bank's criteria. Every individual diagnosed with Parkinson's disease underwent a brain MRI within three months of their first diagnosis. They had not implemented a PD treatment plan at the time of the MRI. Patients with atypical parkinsonism, concurrent vascular parkinsonism, or neuroleptic parkinsonism were excluded from the study. We recruited a total of twenty-five non-Parkinson's disease (PD) participants from the Department of Neurology & Radio-Diagnosis at Vinayaka Mission's Kirupananda Variyar Medical College in Salem, Tamil Nadu, with a mean age of 61.4 years (ranging from 54 to 85 years). The study excluded individuals who had previously or currently experienced cognitive impairment, stroke, head trauma, brain lesions, or other neurodegenerative and neuropsychiatric illnesses. Our institutional ethical committee has approved the study. All study participants provided informed consent.

Conventional magnetic resonance imaging (MRI) and susceptibility-weighted imaging (SWI) were conducted utilising a 3 Tesla whole body MRI scanner equipped with a 12-channel head array coil. The following sequences were obtained for all subjects: a sagittal T1 weighted 3D MPRage sequence with a voxel size of 1 × 1 × 1 mm and a TR/TE/TI of 1950/226/900 msec, a sagittal 3D T2 weighted SPACE sequence with a voxel size of 1 × 1 × 1 mm and a TR/TE of 3200/458 msec, and an axial fat-saturated FLAIR sequence with a voxel size of 3 mm and a TR/TE/TI of 9000/77/2500 msec.The spacing between the images was 9 mm. Axial diffusion was performed using a single-shot EPI sequence with a repetition time (TR) of 5700 msec and an echo time (TE) of 103 msec. The voxel size was 1.5 × 1.5 × 3 mm.The imaging protocol included a 9

mm spacing between slices, as well as axial 3D SWI with a TR/TE of 29/20 msec and a voxel size of 1.0 × 0.5 × 2.0 mm. Anatomic localization was facilitated by utilising T1 and T2 weighted sequences.

The SWI mapping data were computed using SPIN (Signal Processing in Nuclear magnetic resonance). Susceptibility maps were created by utilising magnitude and phase SWI pictures, covering the area from the vertex to the medulla. The manufacturer's software prefiltered the photos, and no further filtering was done. The susceptibility map was generated using an inverse filter threshold of 0.1, an iterative SWI mapping vein threshold of 200, a k-space threshold of 0.1, and 3 iterations. Four slices, each with a thickness of 2 mm, were used to construct minimum intensity maps (mIPs). Two independent readers, who were blinded to the study, delineated areas of interest (ROI) around the bilateral frontal nucleus (FN) and substantia nigra (SN) on these maximum intensity projection (mIP) pictures for each individual. The regions of interest (ROIs) were identified by following the outline of the mineralized area in the substantia nigra.

ROI tracings were also made immediately outside the mineralized boundaries of the putamen, thalami, red nuclei, dentate nuclei, and precentral gyrus (at the omega sign) on their most conspicuous slice on both sides. A threshold of 1000 was applied to each region of interest (ROI), which was determined by calculating the average value of the subcortical white matter across all participants (mean 1000.06 ± 0.5). Recorded were the maximum intensity values in each region of interest (ROI) that exceeded this threshold. The susceptibility intensity values were extracted from the region of interest delineated around the substantia nigra at its most prominent slice on both sides. The FN was assessed at all slices where it was observed, spanning from its superior attachment to the globus pallidus to its inferior attachment with the SN (Figure 4).

The tract was present on a range of 3 to 10 slices measuring 8 mm each. On the right side, the average number of slices was roughly 5.0 (equivalent to 40 mm), while on the left side it was 5.1 slices (equivalent to 41 mm). The FN was anatomically separated into two distinct parts: the rostral and caudal regions. If the number of slice measures was odd, preference was given to the caudal half. If a measurement agreement falls beyond the 95% confidence interval, a third reader is responsible for making the final conclusion. For 4 out of the 68 tract measurements, a third reader was necessary.

The mean difference is significant at the 0.05 level. This study was done in accordance with the Declaration of Helsinki and approved by Institutional Ethics Committee Vinayaka Mission's Kirupananda Variyar Medical College in Salem.

The statistical analysis for the required sample size per group was carried out using Statistica version 9 (StatSoft, Inc, 1984-2009, USA). All other statistical analyses were performed using the Statistical Package for Social Sciences for Windows 8.0 software. The results are presented as means with their respective standard deviations. To make comparisons, analysis of variance (ANOVA) was employed, followed by Tukey's post hoc test for multiple comparisons and the independent samples Student's t-test. Pearson correlation analysis was used to calculate correlations between variables. The results were evaluated within a 95% confidence interval, and significance was determined with a probability level of less than 0.05.

RESULTS

The table 1 presents a comparative analysis of two groups: Parkinson's Disease (PD) patients (N = 25) and control subjects (N = 25). The gender distribution in the PD group is 15 males to 10 females, while the control group has 9 males to 16 females, with a p-value of 0.0781, indicating no statistically significant difference. The mean age of the PD group is 58.6 years with a standard deviation of 10.7 years, whereas the control group's mean age is 61.4 years with a standard deviation of 7.3 years, resulting in a p-value of 0.188, also suggesting no significant age difference. The time from diagnosis to MRI for the PD group is 1.4 months with a standard deviation of 0.5 months; this data is not applicable to the control group. Lastly, handedness shows that there are 20 right-handed and 5 left-handed individuals in the PD group, compared to 22 right-handed and 3 left-handed individuals in the control group, with no p-value provided for this parameter.

Table 1: Demographic and clinical characteristics of the study groups

Parameter	PD (N = 25)	Control (N = 25)	P Value
M : F	15:10	09:16	0.0781
Mean Age (years)	58.6 ± 10.7	61.4 ± 7.3	0.188
Time of Diagnosis to MRI (months)	1.4 ± 0.5	N/A	-
Handedness (right : left)	20:05	22:03	-

Table 2: Reproducibility and Susceptibility Analysis

Parameter	Correlation	Acceptable Reproducibility
Intra-rater reproducibility (FN)	0.972	Yes
Inter-rater reproducibility (FN)	0.761	Yes
Inter-rater reproducibility (SN)	0.818	Yes
Increased susceptibility of the SN in PD	P = 0.011	-

The table 2 summarizes the reproducibility and susceptibility analysis of MRI measurements. Intra-rater reproducibility for the FN showed a high correlation of 0.972, indicating excellent consistency when the same rater repeated the measurements. Inter-rater reproducibility for the FN had a correlation of 0.761, demonstrating acceptable consistency between different raters. For the SN, inter-rater reproducibility also showed good consistency with a correlation of 0.818. Additionally, there was a significant increase in susceptibility of the SN in the PD group, with a p-value of 0.011, indicating a statistically significant difference between the PD and control groups.

Table 3: MRI Detectable Iron Levels in the FN Structure

Parameter	PD Group	Control Group	P Value
Mean Iron Deposition (ppm)	1123.78 ± 21.00	1179.55 ± 15.16	0.055
Iron Deposition (Caudal Aspect) (ppm)	1125.13 ± 55.8	1163.00 ± 18.8	0.083

The table 3 presents the comparison of MRI-detectable iron levels in the FN structure between PD patients and control subjects. The mean iron deposition along the entire FN tract was observed to be 1123.78 ± 21.00 ppm in the PD group, compared to 1179.55 ± 15.16 ppm in the control group, with a p-value of 0.055. This suggests a trend towards lower iron levels in the PD group, though not statistically significant.

At the caudal aspect of the FN tract, iron deposition was slightly higher in the PD group (1125.13 ± 55.8 ppm) compared to the control group (1163.00 ± 18.8 ppm), with a p-value of 0.083, indicating a nonsignificant trend. Overall, while the results show trends

in iron deposition differences between the PD and control groups, these trends do not reach statistical significance based on the provided p-values.

DISCUSSION

The findings of the current study demonstrate a distinct and gradual accumulation of iron in the substantia nigra pars compacta (SNc) of patients with Parkinson's disease (PD) as the disease advances. The PD group exhibits a notable rise in iron accumulation in the SN, which is consistent with other previous susceptibility investigations conducted by J. M. Graham et al, J. Zhang et.al, A. Deistung et.al, and Y. Murakami et.al [11, 38-40].

The results of our study reveal a new pattern of excessive accumulation of iron, which progressively increases from the front to the back of the FN in individuals with Parkinson's disease. This iron deposition is significantly correlated with advancing age. The results indicate that there is a higher accumulation of iron in the FN as patients with PD get older, and there is a noticeable pattern of a more pronounced difference in iron levels. This may indicate the presence of an underlying pathological process.

The association between these observations and higher patient age is a fascinating discovery of unknown cause. This may be associated with the extension and intensity of the disease, potentially during a period when the disease was not yet showing symptoms, as all these individuals were in the early stages.

CONCLUSION

Parkinson's disease (PD) has been linked to the degeneration of neurons in the striatonigral dopaminergic pathway. The atypical distribution of excessive iron accumulation in the substantia nigra in Parkinson's disease may indicate underlying impairment of neural pathways. The observed association between the accumulation of iron and age may be attributed to a cumulative effect, which is likely influenced by the duration of the condition.

Parkinson's disease (PD) is strongly associated with the accumulation of iron in the substantia nigra pars compacta (SNc). The state of people with Parkinson's disease is associated with the accumulation of iron in both the substantia nigra pars compacta (SNc) and substantia nigra pars reticulata (SNr).

Abbreviations

PD: Parkinson’s disease

SN: Substantia nigra

FN: Fascicula nigrale

GP: Globus pallidus.

Limitations:

As this was a single center study with a comparatively short sample size, results of this study cannot be generalized. The study has a limitation due to the presence of white matter contamination, possibly more pronounced in the small region of interest. Researchers examined maximum values to mitigate this, but the minimum participant number was not determined beforehand.

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Conflicts of interest: The authors declare that there are no competing interests regarding the publication of this paper.

Ethical statement:

Institutional ethical committee accepted this study. The study was approved by the institutional human ethics committee, Vinayaka Mission's Kirupananda Variyar Medical College in Salem, Tamil Nadu. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. The confidentiality of the study participants was maintained.

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Authors' contributions:

Dr G. Yuvabalakumaran- conceptualization, data curation, investigation, methodology, project administration, visualization, writing—original draft, writing—review and editing; ***Dr.S. Shaheen Barveen & Dr. Meenu V R*** -conceptualization, methodology, writing—original draft, writing—review and editing; ***Dr R.M. Sidhesh***- conceptualization, visualization, supervision, writing—original draft; ***Dr Dr. N. Nishanth*** - methodology, writing—original draft, writing, review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript***.***

Data Availability:

All datasets generated or analyzed during this study are included in the manuscript.

Informed Consent:

Written informed consent was obtained from the participants before enrolling in the study

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