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Quantitative Assessment of Iron Accumulation in Parkinson's Disease across Discrete Regions of Brain by Susceptibility Mapping

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ABSTRACT

➢ ***Background***

Iron overload has been implicated in the pathology and pathogenesis of Parkinson's disease (PD). Aberrant iron concentrations have been observed in such as substantia nigra, red nuclei, globus pallidus and cortex of PD patients. When neuromelanin-containing organelles accumulate high load of toxins and iron during aging a neurodegenerative process can be triggered. Also, neuromelanin released by degenerating neurons activates microglia and causes neurons death starting a self-propelling mechanism of neuroinflammation and neurodegeneration.

➢ ***Objectives***

To evaluate the accumulation of iron in various deep nuclei of brain and to measure volume of iron accumulated using QSM, and compare with control scale.

➢ ***Methods***

In this study, SWI images of the MRI scans of 45 Parkinson patients within the age group of 45-85 years, were analyzed and the volume of iron in the dentate nuclei, red nuclei, and SN and lentiform nuclei was measured. SWI-MRI images of 54 Non Parkinson patients were also analyzed similarly and volume of iron measured .An average scale of iron accumulation in 43 Non-Parkinson patients control group was also formed.

➢ ***Results***

The volume of iron accumulation clearly proved to be higher in Parkinson patients when compared to the control group. Also data collected from Non Parkinson patients indicated that iron deposition increases with increasing age.

➢ ***Conclusions***

The knowledge of the differences in iron concentration among the deep nuclei in the brain in Parkinson's can help in its early diagnosis as iron promises to be a potential biomarker of PD.

Keywords:- *Iron Overload; Parkinson's Disease; Susceptibility Weighted Imaging.*

CHAPTER 1
INTRODUCTION

Parkinson's disease (**PD**) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. The cause of Parkinson's disease is generally unknown, but believed to involve both genetic and environmental factors. Some of the early signs of Parkinson's disease are pill-rolling tremor, bradykinesia, rigid muscles, impaired posture and balance, loss of automatic movements, speech and writing changes. There is no cure for Parkinson's disease, but medications, surgery, and physical treatment can provide relief. The main families of drugs useful for treating motor symptoms are levodopa , dopamine Agonists and MAO-B inhibitors. [1] Parkinson's disease presents a variable clinical spectrum and symptoms overlap with multiple neurological conditions of various causes, hindering its diagnosis at its early stages, resulting in treatment delays and frequent diagnostic errors. [2]

Iron overload has been implicated in the pathology and pathogenesis of Parkinson's disease (PD). The substantia nigra, where the selective loss of dopaminergic neurons occurs, is the primary region in the brain known to deposit iron. [3] In healthy ageing, selective accumulation of iron occurs in several brain regions and cell types. However, the oxidative stress and cellular damage in neurodegenerative diseases like Parkinson's, leads to the accumulation of iron in specific brain regions, which is greater than that observed in healthy ageing.

Excess iron can cause cell death through reactive oxygen species derived from Fenton's reaction by which iron catalyses hydrogen peroxide [4-8]. Fe (II) takes part in the Fenton reaction is oxidized to Fe (III). Elevated iron level is caused by the iron-chelated neuromelanin that is released from dead neurons injured by aggregation of alpha-synuclein [9]. The iron concentration and iron distribution in deep brain nuclei may work as promising biomarkers in PD. The **characteristic iron accumulation** in the substantia nigra of individuals with Parkinson's disease can be detected in vivo with MRI [10] and also, iron can change the magnetic susceptibility of tissues where it deposits.

Quantitative Susceptibility Mapping (QSM) is a novel technique which allows determination of the bulk magnetic susceptibility distribution of tissues in vivo from gradient echo magnetic resonance phase images. In this study, we will utilize Magnetic Resonance Imaging and Quantitative Susceptibility Mapping to identify and measure the volume of iron in the deep nuclei of Parkinson's patients. By comparing the iron accumulated, with normal subjects of the same age group we aim at improving early diagnosis and treatment of PD.

CHAPTER 2

LITERATURE REVIEW

Bilgic, Berkin et al. (2012) conducted a study using recently-developed Quantitative Susceptibility Mapping (QSM) methodology to estimate the tissue magnetic susceptibility , based on MRI signal phase as a measure of the tissue iron concentration and identified higher iron concentrations in striatal and brain stem nuclei in the older than the young group.

He N, Ling H, Ding B, et al. (2015) conducted a study to assess iron variations in multiple deep grey matter nuclei in early Parkinson's Disease using Quantitative Susceptibility Mapping.

Wang, Y., & Liu, T. (2015) conducted a study to summarize the basic physical concepts and essential algorithmic steps in quantitative susceptibility mapping (QSM) and concluded that The first order solution of QSM can be robustly obtained using the Bayesian approach, and has promising clinical and scientific applications that involve large susceptibility changes by hemoglobin, ferritin, calcification, and contrast agents.

Wang, Zhibin et al.(2016) conducted a study applying susceptibility-weighted imaging (SWI) to find iron-related lesions for the diagnosis and differentiation of PD and concluded that the pathologic alterations of parkinsonism show abnormal brain iron deposition, and therefore in SWI the signal intensity changes in deep brain nuclei, thereby raising the possibility of early diagnosis and differentiation.

Langkammer C, Pirpamer L, Seiler S, et al. (2016) conducted a study on Parkinson's Disease using Quantitative Susceptibility Mapping , and concluded that patients with PD had increased R2* values in the substantia nigra, compared to healthy control subjects and also showed higher susceptibilities in substantia nigra, in the nucleus red nucleus, thalamus, and globus pallidus.

Guan X, Xuan M, Gu Q, et al.(2017) conducted a study to analyse the Regionally progressive accumulation of iron in Parkinson's disease as measured by quantitative susceptibility mapping, and concluded that iron deposition in the substantia nigra is affected exclusively in early stages of the disease, providing objective evidence of the iron-related progression throughout the brain in PD Guan, Xiaojun et al. (2017) conducted a study to identify nigral iron as a potential Biomarker for Parkinson's disease, and concluded that

quantification of nigral iron or qualitative analysis of dorsolateral nigral hyperintensity (DNH) will contribute to recognizing high-risk individuals and possibly aid diagnosis.

Xuan M, Guan X et al.(2017) conducted a study to investigate the patterns of iron deposition and their clinical relevance in early-onset Parkinson's disease (EOPD) and middle-late-onset Parkinson's disease (M-LOPD) patients, using quantitative susceptibility mapping technique and concluded that Both the M-LOPD and EOPD patients showed increased nigral iron content which confirmed the general characteristic pathological changes of PD.

Chen, Qiqi et al. (2019) conducted a study to evaluate the iron deposition in the substantia nigra (SN) and other deep gray matter nuclei of PD patients using quantitative susceptibility mapping (QSM) , the results of which showed a specific and progressive iron deposition in the substantia nigra pars compacta (SNc) and in some deep grey matter nuclei of PD patients during disease progression.

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CHAPTER 3

AIM

- QUANTITATIVE ASSESSMENT OF IRON ACCUMULATION IN PARKINSON'S DISEASE ACROSS DISCRETE REGIONS OF BRAIN BY SUSCEPTIBILITY MAPPING

CHAPTER 4

OBJECTIVES

- To evaluate the accumulation of iron in various deep nuclei of brain in diagnosed cases of Parkinsonism by a retrospective study on MRI scans.
- To measure volume of iron accumulated using quantitative susceptibility mapping
- To compare the evaluated data with the normal scale, measured using Non-Parkinson subjects as control group (age and sex matched with study group)

CHAPTER 5
METHODOLOGY

Type of study: Retrospective Comparative Study

Study size and population:

- 45 patients, both male and female of age group 45-85 years, diagnosed with Parkinson's , by clinical evaluation
- 54 Non Parkinson patients (Subgroup-Control Group)
- Subgroup- 43 Non-Parkinson patients of the same age group and gender as control group

Selection Criteria

Inclusion criteria:

MRI scans included in the study belong to

- Patients diagnosed with Parkinsonism, by clinical evaluation
- Only MRI scans having mag- ii sequence will be included
- Non Parkinson patients with no neurological afflictions similar to Parkinson's (for comparison)

Exclusion criteria:

MRI scans of patients with other neurological infirmities like brain tumors, hematomas, cerebrovascular accidents, etc. Are excluded from study group

Study parameters and methods:

MR brain images of **45 Parkinsonism patients** (admitted in G Block IP of Sri Ramachandra Hospital), done between April to October 2019 were retrospectively studied. Institutional ethical clearance was obtained. They belonged to the age group of **45 to 85 (Mean-65.44, SD-8.795)** and were diagnosed as **Parkinsonism** clinically by Senior Neurologist. **54 Non Parkinson patients** were analysed of which a s**ubgroup of 43 clinically normal subjects in the same age group (45-85 , Mean-58.09 , SD-8.182)** who had come for non-specific complaints like headache, giddiness were used as controls . MR imaging was performed with a **1.5 T superconducting system** (Avanto Siemens, Erlangen, Germany) with a **12 element Head Neck**

coil. The Susceptibility weighted images (SWI) (Magnitude images) were studied [11-12]. A **three-dimensional (3D) SWI sequence** was obtained with **2.5mm slice thickness and 0mm interslice gap.**

The iron containing dentate, red nuclei, substantia nigra, lentiform nuclei of right and left sides were identified in the SWI imaging sequence of the MRI scans of each patient. They were seen as hypo intense areas. [13] SWI has been validated in recent autopsy studies to demonstrate that the susceptibility in deep grey matter nuclei highly correlated with the iron concentration as determined by Perl's iron staining. [14-15]

The longest dimensions of the hypo intense areas were obtained. Exclusion criteria included haemorrhages in the basal ganglionic / midbrain region and studies with non-diagnostic quality images. The intra and inter observer variability was 2%

Volume calculation:

The iron volume was calculated according to the formula ABC***/2,*** as proposed by Rashmi Kothari et al. The MRI section with the largest area of iron was taken into account with A representing the largest diameter, B representing the diameter perpendicular to *A*. *C* value was obtained by the formula: *C*= number of slices the iron is visualized x (slice thickness + interslice gap). All measurements were recorded in centimeter scale and the product obtained was divided by 2, which yielded the iron volume in **cubic centimeter**

The volume of iron in various nuclei in Parkinson's patients as compared to the control patients was statistically analyzed.

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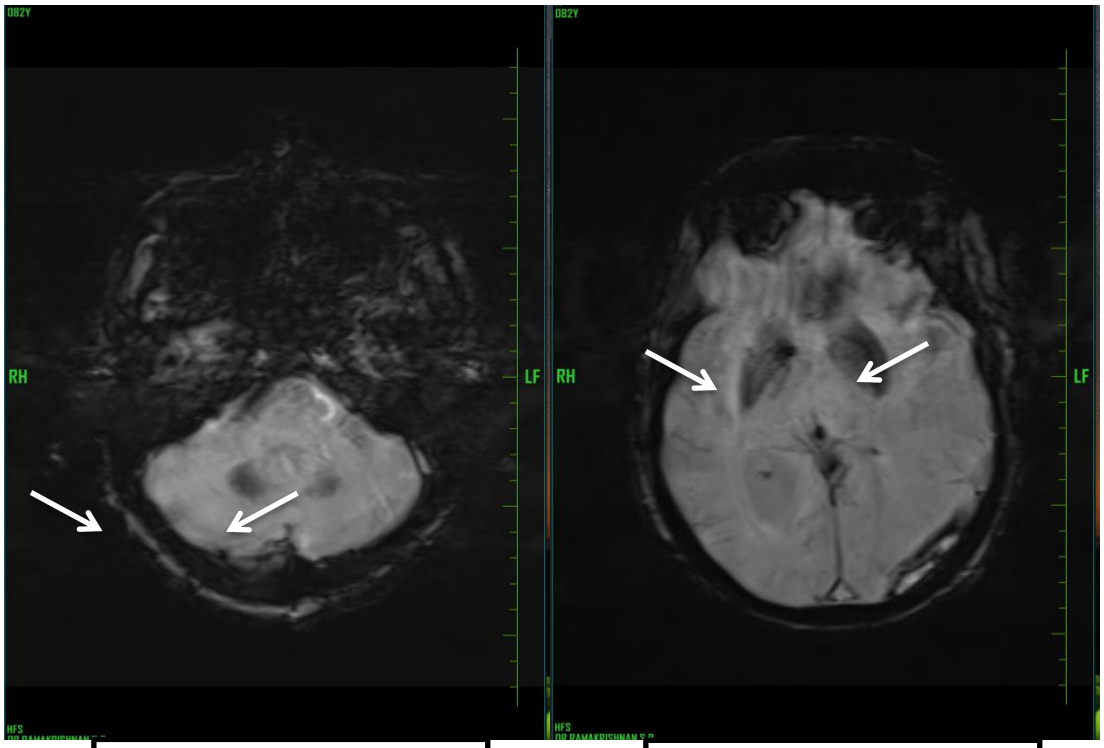
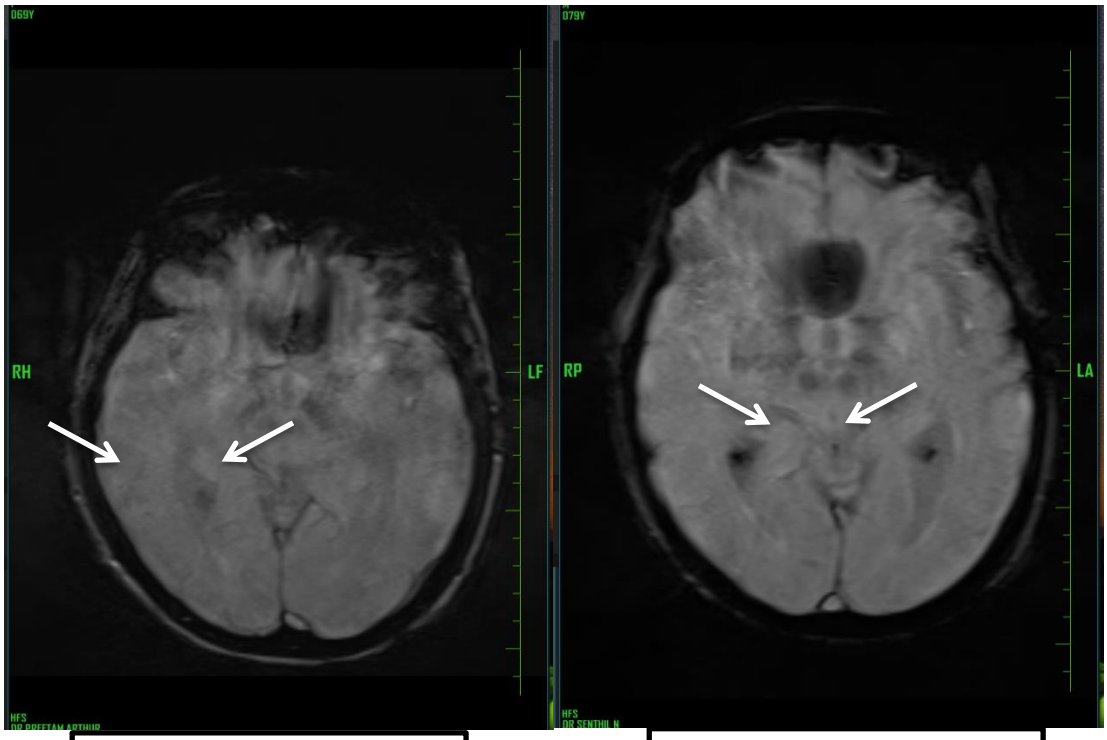


DENTATE NUCLEII

LENTIFORM NUCLEII



SUBSTANTIA NIGRA

RED NUCLEII

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CHAPTER 6

RESULTS

➢ *VOLUME OF IRON MEASURED IN STUDY GROUP (IN CU.CM)*

45 PATIENTS

S. NO	AGE	RIGHT DENTATE	LEFT DENTATE	RIGHT RN	LEFT RN	RIGHT SN	LEFT SN	RIGHT LENTIFORM	LEFT LENTIFORM
1	48	0.23735	0.22525	0.086063	0.063525	0.070688	0.0594	1.947125	1.9656
2	49	0.623	0.71175	0.043463	0.053625	0.15575	0.13545	0.7587	0.603825
3	51	0.105225	0.135975	0.147	0.133	0.09815	0.105975	1.12095	1.2246
4	55	0.28855	0.38485	0.03525	0.0351	0.22165	0.231525	1.4484	1.7372
5	55	0.279225	0.341475	0.064788	0.068438	0.17755	0.1394	1.2996	1.38165
6	56	0.209375	0.3034	0.15355	0.13135	0.07665	0.074613	1.30095	1.3685
7	56	0.163925	0.18135	0.06105	0.0592	0.107725	0.07755	0.6345	0.7028
8	57	0.370125	0.48195	0.153	0.15725	0.341775	0.2709	2.70015	2.27205
9	58	0.358875	0.2584	0.19095	0.188888	0.2613	0.2805	2.6397	2.381063
10	58	0.158025	0.13585	0.224775	0.202125	0.1989	0.2106	2.397	2.38815
11	60	0.06345	0.079888	0.0736	0.07685	0.457275	0.344138	0.577875	0.7169
12	60	0.141	0.12065	0.050525	0.0495	0.121275	0.096938	1.2384	1.2264
13	60	0.2112	0.22425	0.162	0.15015	0.086925	0.0938	0.8174	1.3527
14	60	0.1804	0.162	0.1575	0.13735	0.26565	0.255	1.428375	1.3248
15	60	0.135938	0.1628	0.11715	0.1147	0.111388	0.129575	1.852875	1.78075
16	62	0.193563	0.199675	0.093	0.072025	0.24585	0.1749	2.1291	2.14305
17	62	0.1022	0.144788	0.112	0.075525	0.26825	0.2952	1.030925	1.3209
18	62	0.28875	0.29415	0.11725	0.1463	0.139425	0.1404	1.209075	1.197225
19	63	0.4268	0.38925	0.078	0.0612	0.106163	0.116	0.669125	0.6678
20	63	0.235625	0.3146	0.1209	0.1088	0.1425	0.095175	1.3615	1.5048
21	64	0.192425	0.169113	0.0928	0.081	0.0889	0.121688	2.210513	2.574473
22	64	0.372	0.39375	0.1206	0.0972	0.22785	0.26235	1.24875	1.70625
23	65	0.2701	0.25185	0.1443	0.13125	0.22165	0.25025	2.341163	2.300513
24	65	0.142875	0.135788	0.1295	0.1015	0.135675	0.10125	1.348525	1.27875
25	65	0.346375	0.32465	0.10385	0.12395	0.1932	0.21855	2.22855	2.276438
26	65	0.0855	0.0968	0.1422	0.142	0.164475	0.193875	0.94095	1.1139
27	66	0.234063	0.196875	0.05775	0.0735	0.1577	0.128513	1.430325	1.39125
28	67	0.109725	0.084563	0.023063	0.03055	0.1152	0.1121	1.7415	1.4453
29	68	0.2175	0.2205	0.1036	0.1691	0.0994	0.1273	1.99995	1.8183
30	69	0.130688	0.158175	0.133	0.125125	0.126	0.1408	2.6208	2.05005
31	69	0.496975	0.3772	0.21	0.1785	0.1435	0.1728	2.1726	2.075025
32	70	0.17	0.240075	0.0511	0.055025	0.110688	0.087588	0.668525	1.01835
33	70	0.174	0.223125	0.0403	0.0527	0.1122	0.09585	1.12095	1.18925

34	73	0.234	0.2289	0.11025	0.105525	0.193725	0.1885	2.53485	2.025
35	73	0.130313	0.192375	0.0725	0.05875	0.33735	0.306	2.205225	2.0412
36	73	0.27885	0.2528	0.126	0.09	0	0.2226	1.58925	1.48365
37	73	0.2142	0.31025	0.072875	0.083475	0.1533	0.200075	1.0132	1.0143
38	74	0.35775	0.268125	0.0975	0.09135	0.2635	0.361725	1.96875	2.000325
39	75	0.30015	0.25025	0.09	0.096075	0.174675	0.14555	0.92925	1.02555
40	76	0.34055	0.33075	0.0783	0.0864	0.1353	0.1802	0.576	0.6931
41	79	0.145163	0.14175	0.1332	0.168	0.10695	0.0795	1.612925	1.81675
42	79	0.123	0.130175	0.0364	0.030375	0.057813	0.044175	1.20345	1.3246
43	82	0.2173	0.3392	0.08215	0.064575	0.32195	0.21935	1.5725	1.839225
44	82	0.345825	0.3278	0.13065	0.1575	0.072775	0.094188	3.283125	2.35725
45	84	0.10125	0.107313	0.0455	0.0476	0.081938	0.10065	1.01505	1.09865
AVERAGE VOLUME OF IRON (CU.CM)		**0.233404**	**0.244543**	**0.10376**	**0.100576**	**0.165568**	**0.166277**	**1.558631**	**1.560405**

➢ *VOLUME OF IRON MEASURED IN NON PARKINSON PATIENTS*

(In cu.CM)

54 PATIENTS

S.NO	AGE	RIGHT DENTATE	LEFT DENTATE	RIGHT RN	LEFT RN	RIGHT SN	LEFT SN	RIGHT LENTIFORM	LEFT LENTIFORM
1	7	0	0	0	0	0	0	0	0
2	9	0	0	0	0	0	0	0	0
3	13	0	0	0	0	0.0104	0.129413	0.224475	0.221725
4	14	0	0	0	0	0.025075	0.039	0.28855	0.21125
5	18	0	0	0	0	0.05225	0.069325	0.22425	0.19635
6	28	0	0	0	0	0.027788	0.06045	0.3564	0.238875
7	30	0.0714	0.08555	0.026875	0.02875	0.049875	0.053475	0.26565	0.28575
8	32	0.0767	0.04515	0.015188	0.019688	0.0565	0.03745	0.41925	0.3591
9	34	0.08375	0.09765	0.039	0.0168	0.051188	0.063	0.3136	0.2397
10	39	0.125925	0.119813	0.0377	0.02925	0.048875	0.047638	0.4332	0.42315
11	40	0.11315	0.086938	0.0222	0.02795	0.0595	0.05895	0.3344	0.461825
12	45	0.130488	0.101888	0.0259	0.02475	0.0325	0.064125	0.534375	0.5796
13	45	0.225	0.25625	0.0432	0.0375	0.087313	0.07125	0.5654	0.6344
14	47	0.2044	0.268	0.1073	0.1073	0.112125	0.17685	0.573075	0.502
15	48	0.074925	0.1617	0.0378	0.0325	0.049213	0.052725	0.256725	0.4841
16	48	0.1054	0.108075	0.0464	0.053625	0.043138	0.05775	0.4403	0.37275
17	48	0.175275	0.223125	0.0338	0.03645	0.08	0.072263	0.35145	0.4851
18	49	0.167475	0.150938	0.0464	0.0416	0.0714	0.0714	0.736	0.91425

19	49	0.1131	0.1248	0.015888	0.020963	0.0693	0.06665	0.37045	0.4774
20	49	0.11715	0.107675	0.0234	0.022575	0.069188	0.07	0.5124	0.6201
21	50	0.087075	0.075563	0.02415	0.0246	0.042875	0.047025	0.36115	0.395625
22	52	0.103075	0.151563	0.0464	0.03875	0.080238	0.078725	0.7252	0.94615
23	52	0.1292	0.1241	0.0768	0.054	0.140875	0.1421	0.194025	0.198875
24	53	0.1938	0.238125	0.093	0.1005	0.169575	0.155575	0.704475	0.7854
25	54	0.059925	0.081225	0.029	0.02535	0.04185	0.040238	0.504225	0.432525
26	55	0.108	0.1037	0.05415	0.053625	0.049725	0.06625	0.3179	0.3465
27	55	0.07875	0.085425	0.02475	0.029925	0.05625	0.06435	0.38525	0.276375
28	55	0.1016	0.096313	0.0884	0.084	0.147375	0.12995	0.716625	0.7028
29	55	0.19305	0.171675	0.0864	0.0924	0.1254	0.158625	0.73	0.8178
30	56	0.09455	0.105	0.021275	0.018963	0.0494	0.0495	0.31845	0.294525
31	57	0.07875	0.085	0.022038	0.028188	0.066	0.056813	0.248	0.38325
32	57	0.10065	0.106425	0.0378	0.031725	0.0494	0.0884	0.42175	0.560325
33	58	0.142763	0.1326	0.090113	0.064325	0.06885	0.055875	0.801625	0.65075
34	58	0.11385	0.116413	0.054375	0.051	0.053625	0.04	0.382	0.472725
35	59	0.1566	0.12425	0.0603	0.0729	0.197625	0.1914	0.495725	0.6223
36	59	0.1968	0.214775	0.0435	0.0377	0.12495	0.12285	0.506	0.463275
37	60	0.1184	0.1491	0.045	0.04625	0.102688	0.109888	0.4272	0.56295
38	60	0.094875	0.114063	0.042	0.0432	0.0555	0.06235	0.297825	0.35145
39	60	0.134875	0.137063	0.0496	0.04785	0.04485	0.0516	0.3036	0.39585
40	61	0.049	0.0532	0.03625	0.0378	0.46475	0.091163	0.7371	0.76755
41	62	0.085313	0.097463	0.0377	0.0378	0.070625	0.052725	0.3675	0.331088
42	63	0.096688	0.07625	0.0728	0.0775	0.1134	0.128125	0.9295	0.69
43	64	0.107675	0.102175	0.1095	0.093	0.15625	0.1488	0.423775	0.4588
44	65	0.135675	0.12665	0.0375	0.0325	0.0721	0.08905	0.39895	0.4452
45	65	0.118038	0.1254	0.04725	0.0429	0.060588	0.0515	0.43225	0.425625
46	65	0.2982	0.294275	0.0918	0.06815	0.1394	0.1449	0.837	0.7648
47	65	0.0871	0.086625	0.05175	0.04725	0.1365	0.1885	0.4029	0.46125
48	65	0.068125	0.0812	0.03	0.025625	0.15045	0.196875	0.40905	0.633
49	67	0.124688	0.091413	0.031175	0.0329	0.046638	0.068175	0.30595	0.4725
50	68	0.10115	0.11815	0.062125	0.0578	0.072	0.072563	1.3377	1.4196
51	68	0.285525	0.3196	0.0806	0.07155	0.115025	0.135	0.3765	0.54675
52	73	0.2277	0.2508	0.0432	0.03375	0.085463	0.08645	0.82425	0.8136
53	74	0.224	0.177975	0.034075	0.037625	0.055088	0.07095	0.73255	0.7625
54	80	0.22425	0.21	0.05945	0.0868	0.08505	0.124425	0.8632	0.990075

➢ *Volume of iron measured in control group*

(SUB-GROUP OF NON PARKINSON PATIENTS) (In CU.CM)

43 PATIENTS

S.NO	AGE	RIGHT DENTATE	LEFT DENTATE	RIGHT RN	LEFT RN	RIGHT SN	LEFT SN	RIGHT LENTIFORM	LEFT LENTIFORM
1	45	0.130488	0.101888	0.0259	0.02475	0.0325	0.064125	0.534375	0.5796
2	45	0.225	0.25625	0.0432	0.0375	0.087313	0.07125	0.5654	0.6344
3	47	0.2044	0.268	0.1073	0.1073	0.112125	0.17685	0.573075	0.502
4	48	0.074925	0.1617	0.0378	0.0325	0.049213	0.052725	0.256725	0.4841
5	48	0.1054	0.108075	0.0464	0.053625	0.043138	0.05775	0.4403	0.37275
6	48	0.175275	0.223125	0.0338	0.03645	0.08	0.072263	0.35145	0.4851
7	49	0.167475	0.150938	0.0464	0.0416	0.0714	0.0714	0.736	0.91425
8	49	0.1131	0.1248	0.015888	0.020963	0.0693	0.06665	0.37045	0.4774
9	49	0.11715	0.107675	0.0234	0.022575	0.069188	0.07	0.5124	0.6201
10	50	0.087075	0.075563	0.02415	0.0246	0.042875	0.047025	0.36115	0.395625
11	52	0.103075	0.151563	0.0464	0.03875	0.080238	0.078725	0.7252	0.94615
12	52	0.1292	0.1241	0.0768	0.054	0.140875	0.1421	0.194025	0.198875
13	53	0.1938	0.238125	0.093	0.1005	0.169575	0.155575	0.704475	0.7854
14	54	0.059925	0.081225	0.029	0.02535	0.04185	0.040238	0.504225	0.432525
15	55	0.108	0.1037	0.05415	0.053625	0.049725	0.06625	0.3179	0.3465
16	55	0.07875	0.085425	0.02475	0.029925	0.05625	0.06435	0.38525	0.276375
17	55	0.1016	0.096313	0.0884	0.084	0.147375	0.12995	0.716625	0.7028
18	55	0.19305	0.171675	0.0864	0.0924	0.1254	0.158625	0.73	0.8178
19	56	0.09455	0.105	0.021275	0.018963	0.0494	0.0495	0.31845	0.294525
20	57	0.07875	0.085	0.022038	0.028188	0.066	0.056813	0.248	0.38325
21	57	0.10065	0.106425	0.0378	0.031725	0.0494	0.0884	0.42175	0.560325
22	58	0.142763	0.1326	0.090113	0.064325	0.06885	0.055875	0.801625	0.65075
23	58	0.11385	0.116413	0.054375	0.051	0.053625	0.04	0.382	0.472725
24	59	0.1566	0.12425	0.0603	0.0729	0.197625	0.1914	0.495725	0.6223
25	59	0.1968	0.214775	0.0435	0.0377	0.12495	0.12285	0.506	0.463275
26	60	0.1184	0.1491	0.045	0.04625	0.102688	0.109888	0.4272	0.56295
27	60	0.094875	0.114063	0.042	0.0432	0.0555	0.06235	0.297825	0.35145
28	60	0.134875	0.137063	0.0496	0.04785	0.04485	0.0516	0.3036	0.39585
29	61	0.049	0.0532	0.03625	0.0378	0.46475	0.091163	0.7371	0.76755
30	62	0.085313	0.097463	0.0377	0.0378	0.070625	0.052725	0.3675	0.331088
31	63	0.096688	0.07625	0.0728	0.0775	0.1134	0.128125	0.9295	0.69
32	64	0.107675	0.102175	0.1095	0.093	0.15625	0.1488	0.423775	0.4588
33	65	0.135675	0.12665	0.0375	0.0325	0.0721	0.08905	0.39895	0.4452
34	65	0.118038	0.1254	0.04725	0.0429	0.060588	0.0515	0.43225	0.425625

35	65	0.2982	0.294275	0.0918	0.06815	0.1394	0.1449	0.837	0.7648
36	65	0.0871	0.086625	0.05175	0.04725	0.1365	0.1885	0.4029	0.46125
37	65	0.068125	0.0812	0.03	0.025625	0.15045	0.196875	0.40905	0.633
38	67	0.124688	0.091413	0.031175	0.0329	0.046638	0.068175	0.30595	0.4725
39	68	0.10115	0.11815	0.062125	0.0578	0.072	0.072563	1.3377	1.4196
40	68	0.285525	0.3196	0.0806	0.07155	0.115025	0.135	0.3765	0.54675
41	73	0.2277	0.2508	0.0432	0.03375	0.085463	0.08645	0.82425	0.8136
42	74	0.224	0.177975	0.034075	0.037625	0.055088	0.07095	0.73255	0.7625
43	80	0.22425	0.21	0.05945	0.0868	0.08505	0.124425	0.8632	0.990075
AVERAGE VOLUME OF IRON (CU.CM)		**0.135649**	**0.142465**	**0.051031**	**0.048964**	**0.095455**	**0.094505**	**0.524637**	**0.574686**

	AVERAGE VOLUME OF IRON ACCUMULATED	
	STUDY GROUP	**CONTROL GROUP**
RIGHT DENTATE	0.2334	0.1356
LEFT DENTATE	0.2445	0.1425
RIGHT RN	0.1038	0.0510
LEFT RN	0.1006	0.0490
RIGHT SN	0.1656	0.0955
LEFT SN	0.1663	0.0945
RIGHT LENTIFORM	1.5586	0.5246
LEFT LENTIFORM	1.5604	0.5747

Iron accumulated in different nuclei of the brain (**Dentate Nucleus, Red Nucleus, Substantia Nigra, and Lentiform Nucleus)** was analysed in **45 Parkinsons patients** of age group **(45-85, Mean-65.44, SD-8.795)**. 54 Non Parkinson's patients were also analysed of which **43 Non Parkinson's patients** of the same age group as the study group **(45-85, Mean-58.09, SD-8.182)** were taken as **control group**. The volume of iron accumulated was measured **(in cu.cm)** using **Susceptibility Mapping in Magneting Resonance Imaging** and the results were statistically analysed using SPSS software.

The volume of iron accumulated in regions of interest in the study group was proved to be higher that the volume of iron in the control group.

The volume of iron accumulated in the **right red nucleus** had an **average of 0.1038 cu.cm in the study group**. This was higher when compared to an **average of 0.0510 in the control group**.

The **left red nucleus** had an **average of 0.1006 in the study group and 0.0490 in the control group,** consistent with the study.

Statistical analysis gives p<0.01 for the volume of iron measured in the right and left red nuclei

The average volume of iron accumulated in the **right dentate nucleus (study group-0.2334, control group-0.1356)** and the **left dentate nucleus (study group-0.2445, control group-0.1425)** was also consistent with the study.

Statistical analysis gives p<0.01 for the volume of iron in the right and left dentate nuclei.

The **right substantia nigra** had an average of **0.1656 in the study group and 0.0955 in the control group**. The **left substantia nigra** had an average **of 0.1663** in the **study group and 0.0945** in the **control group.**

Statistical value of p is <0.01 for right and left substantia nigra, which is significant.

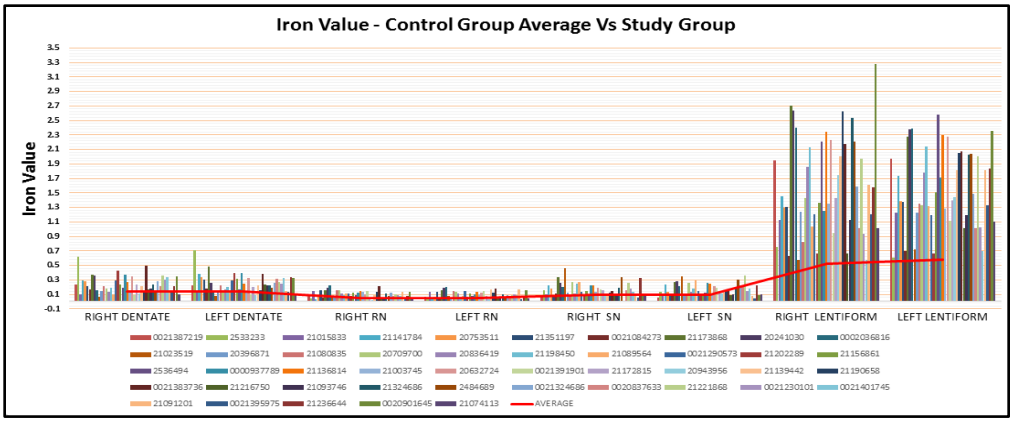
The volume of iron in the **right lentiform (1.5586)** and **left lentiform (1.5604)** in the **study group** was found to be much higher than the average volume of iron in **right lentiform (0.5246) and left lentiform (0.5747) in the control group**.

Statistical analysis gives p<0.01 for the volume of iron calculated in both right and left lentiform nuclei.

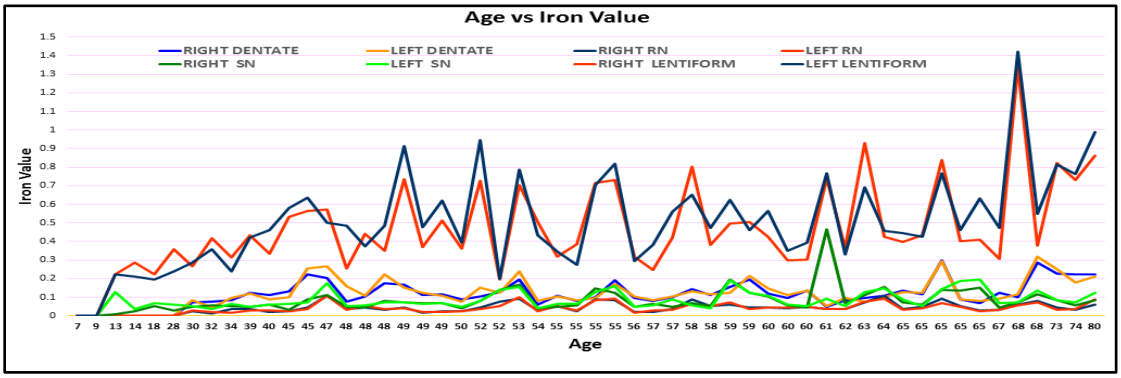
The average iron accumulated for each nucleus in the control group was set as a control scale and findings of the study group were compared to it.

Graph 1 depicts that in Parkinsons patients the iron accumulated is higher when compared to Non Parkinsons patients of the same age group.

The volume of iron accumulated increases with increasing age, depicted by Graph 2. The volume of iron accumulated in the youngest patients was found to be insignificant.



GRAPH 1



GRAPH 2

GROUP STATISTICS				
gp		**Mean**	**Std. Deviation**	**p**
AGE	**STUDY GRP**	65.44	8.795	.000
	CONTROL GRP	58.09	8.182	.000
RIGHT DENTATE		0.2334	.1159	.000
		0.1356	.0595	.000
LEFT DENTATE		0.2445	.1194	.000
		0.1425	.0650	.000
RIGHT RN		0.1038	.0471	.000
		0.0510	.0246	.000
LEFT RN		0.1006	.0454	.000
		0.0490	.0234	.000
RIGHT SN		0.1656	.0892	.000
		0.0955	.0707	.000
LEFT SN		0.1663	.0799	.000
		0.0945	.0456	.000
RIGHT LENTIFORM		1.5586	.6703	.000
		0.5246	.2310	.000
LEFT LENTIFORM		1.5604	.5363	.000
		0.5747	.2298	.000

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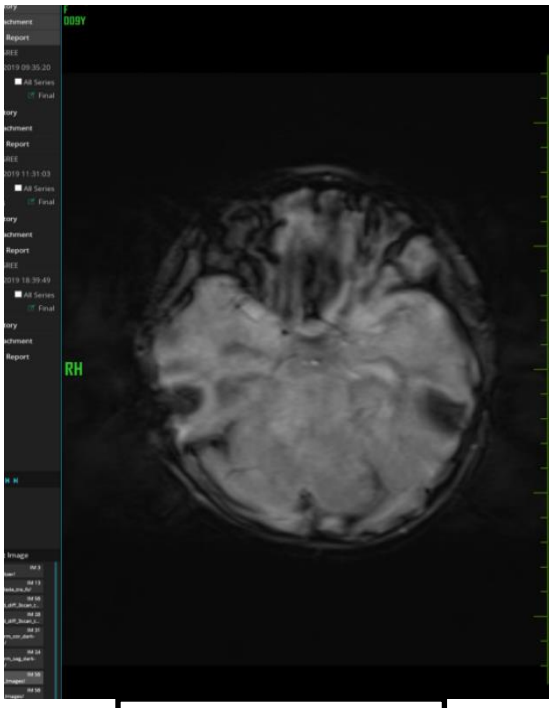
MRI FINDINGS IN NON PARKINSON'S PATIENTS



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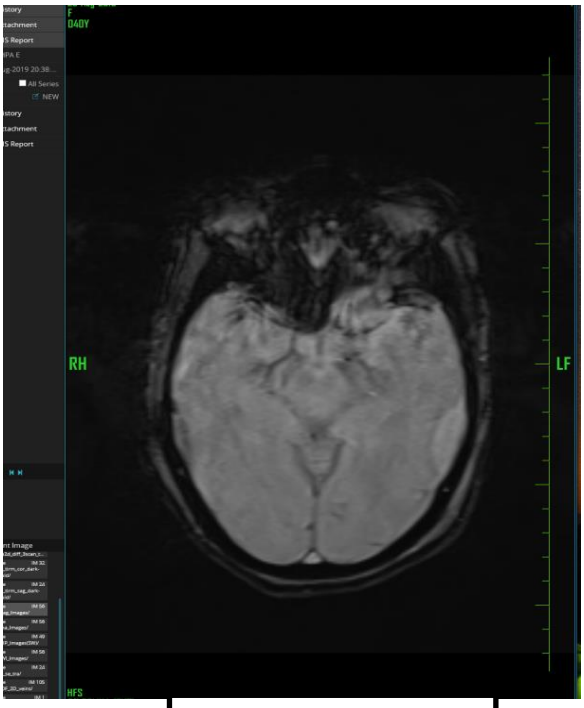

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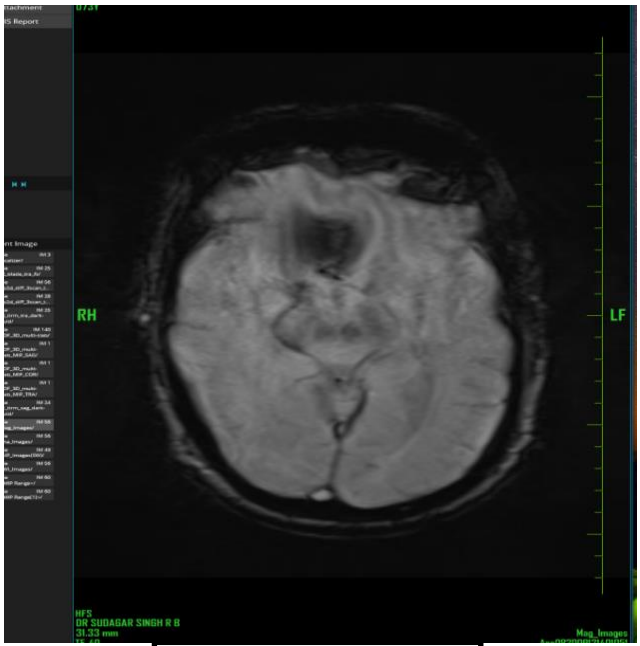

73 Y

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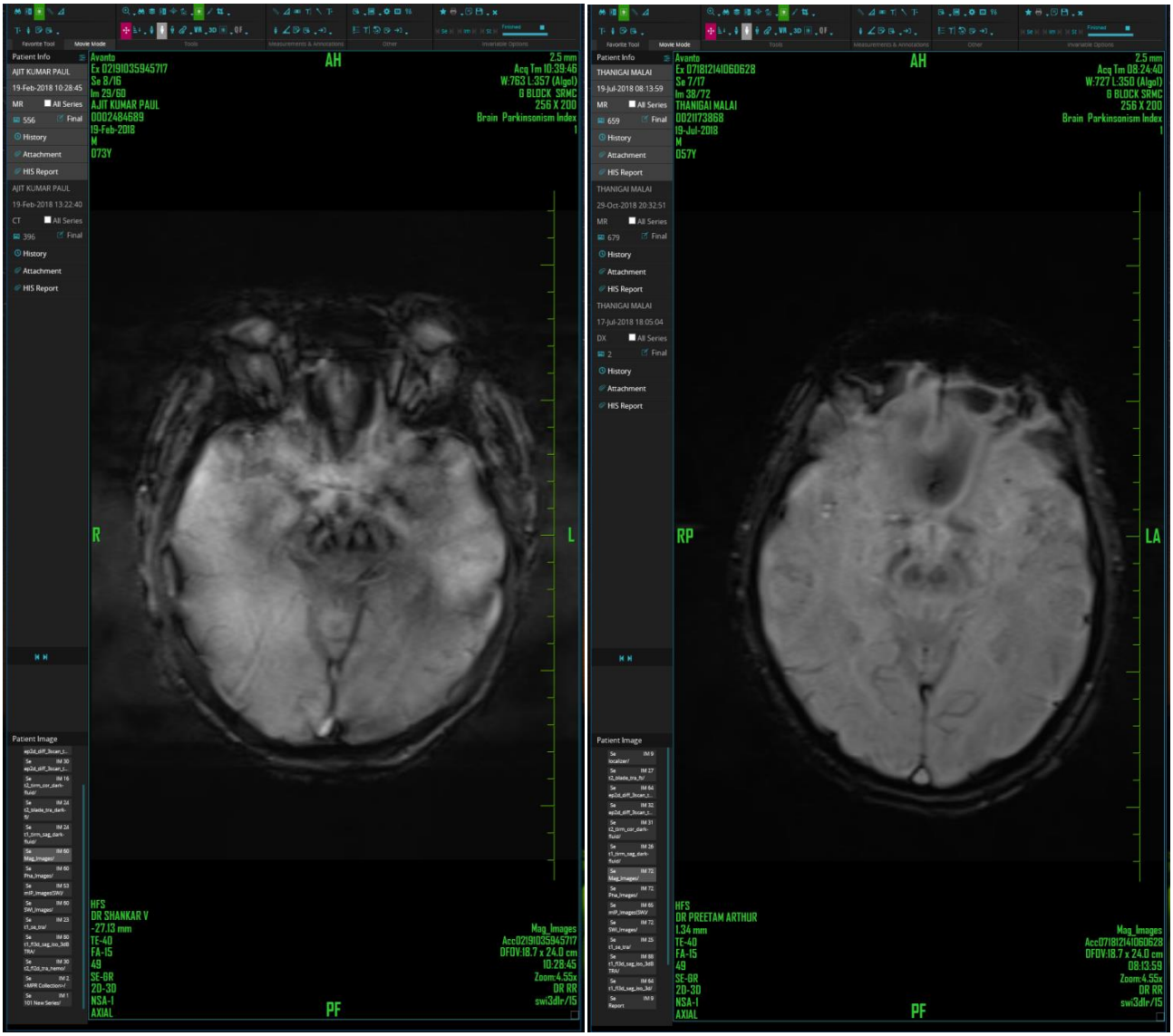
MRI FINDINGS IN PARKINSON'S PATIENTS



INCREASED IRON DEPOSITION IN SUSTANTIA NIGRA AND RED NUCLEUS IS SEEN AS MORE INTENSE AND DARKER REGIONS IN MRI SCANS OF PARKINSON'S PATIENTS WHEN COMPARED TO NON PARKINSON PATIENTS

CHAPTER 7
DISCUSSION

Neuromelanin accumulates during aging and is the catecholamine-derived pigment of the dopamine neurons of the substantia nigra and norepinephrine neurons of the locus coeruleus, the two neuronal populations most targeted in Parkinson's disease. Dopamine accumulation can induce neuronal death; however, excess dopamine can be removed by converting it into a stable compound like neuromelanin, and this process rescues the cell. The main iron compound in dopamine and norepinephrine neurons is the neuromelanin-iron complex, since neuromelanin is an effective metal chelator. Neuromelanin serves to trap iron and provide neuronal protection from oxidative stress. This equilibrium between iron, dopamine, and neuromelanin is crucial for cell homeostasis and in some cellular circumstances can be disrupted. Indeed, when neuromelanin-containing organelles accumulate high load of toxins and iron during aging a neurodegenerative process can be triggered. In addition, neuromelanin released by degenerating neurons activates microglia and the latter cause neurons death with further release of neuromelanin, then starting a self-propelling mechanism of neuroinflammation and neurodegeneration. [16]

Several studies have shown increases of total iron concentration in the substantia nigra of patients with Parkinson’s disease. Our study utilized quantitative susceptibility mapping and concluded that iron deposition in patients suffering from Parkinson’s is higher than non-Parkinson patients. [17] This is in accordance with the findings of Guan X, Xuan M, Gu Q, et al. (2017) The QSM values significantly increased in the SNc for EPD patients compared with those of the normal controls), indicating increased iron content in this region and SNr RN and GP as well. [18]

The findings of Langkammer C, Pirpamer L, Seiler S, et al. (2016) also correlated increase in iron in substantia nigra, globus pallidus, thalamus and the nucleus ruber of patients with PD compared to controls [19], also in accordance with the findings of Chen Q, Chen Y, Zhang Y, et al. (2019) which concluded that, there was more iron deposition in the PD group Along the GP–FN–SN pathway, especially in the FN and SN. [20]

Neuropathological studies that used accurate spectroscopic methods to measure total iron concentrations in specific brain regions, such as substantia nigra pars compacta and reticulata showed that iron concentrations in these regions increase with disease severity. [21-24]

El-Agnaf OM, Irvine GB., and Uversky VN, Li J, Fink AL found that Ferric iron can, in vitro, catalyse the conversion of α-synuclein from the α-helix to the β-sheet conformation that is present in Lewy bodies. [25-26]

In Parkinson's disease, loss of neuromelanin and an increase in iron concentration is noted in the substantia nigra. A positive association between iron and ferritin concentrations, and a negative association of neuromelanin content with the area of echogenicity of the substantia nigra could therefore provide a basis for diagnosis and therapeutic follow-up studies in patients with Parkinson's disease according to Zecca L, Berg D, Arzberger T, et al.(2005)[27]

In healthy ageing, selective accumulation of iron occurs in several brain regions and cell types .The results of our study also proved that iron deposition increases with age in non parkinson's patients.. Bilgic B, et.al(2012) found that the elderly group had significantly more iron than the young group in striatal regions of the putamen and globus using QSM [28], which is in accordance with the results of our study

CHAPTER 7

CONCLUSION

Parkinson's disease (PD) is the second most common degenerative neurological disorder after Alzheimer's disease. Although the incidence of Parkinson's increases with age, only an estimated four per cent of people are diagnosed before the age of 50. Through this study, we measure the volume of iron accumulated in various discrete regions of the brain, apart from the substantia nigra and compare it with normal subjects. This knowledge of the differences in iron concentration and distribution among the deep nuclei in the brain in Parkinson's can help in its early diagnosis and better treatment.

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