Utility of Imaging of Nigrosome-1 on 3T MRI and Its Comparison with 18F-DOPA PET in the Diagnosis of Idiopathic Parkinson Disease and Atypical Parkinsonism

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ABSTRACT: Background: Loss of nigrosome-1 on 3T and 7T magnetic resonance imaging (MRI) is a recently explored imaging biomarker in the diagnosis of neurodegenerative parkinsonism.

Objectives: This study was undertaken to evaluate the utility of imaging of nigrosome in the diagnosis of neurodegenerative parkinsonism on 3T MRI.

Methods: An institution-based prospective case-control study was conducted at a tertiary care center in North India. 3T venous blood oxygen level-dependent (VenoBOLD) and high-resolution susceptibility-weighted imaging (SWI) imaging sequences in MRI were performed in 100 patients with parkinsonism (56 with idiopathic Parkinson's disease [IPD], 30 with young onset Parkinson's disease [YOPD], 12 with progressive supranuclear palsy, and 2 patients with multiple system atrophy) and 15 controls. Grading of nigrosome was done in both the sequences. Each patient underwent 18F-DOPA positron emission tomography (PET), detailed neurological examination including Hoehn and Yahr (H&Y) staging and Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scoring.

Results: The diagnostic sensitivity and specificity of the detection of loss of nigrosome-1 on VenoBOLD and SWI sequence at 3T MR imaging were 90% and 66.7% and 94% and 80%, respectively. A weak negative correlation was found between the grading of the nigrosome and clinical parameters (H&Y and UPDRS III). There was no correlation between the side of nigrosome loss and clinical asymmetry. However, nigrosome imaging was not able to differentiate between Parkinson's disease and atypical parkinsonism.

Conclusions: The loss of nigrosome-1 on 3T MRI on SWI and VenoBOLD sequences may serve as a potential imaging marker in the diagnosis of degenerative parkinsonian syndromes. However, it cannot differentiate between idiopathic Parkinson's disease and atypical parkinsonian syndromes.

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta resulting in classical motor and a plethora of non-motor symptoms.¹ The diagnosis of Parkinson's disease is mainly clinical and relies on the cardinal motor symptoms of bradykinesia, tremor, and rigidity.² However, the clinical diagnosis can be challenging in 15% to 20% of the cases because of overlap with various atypical parkinsonian syndromes.³

Fluorodopa F18 positron emission tomography (18F-DOPA PET) is a valuable tool to measure the uptake of dopamine precursors for the assessment of presynaptic dopaminergic integrity. Similar to FP-CIT SPECT, 18F-DOPA PET has excellent sensitivity and specificity in differentiating Parkinson's disease from essential or dystonic tremor. However, they are not able to differentiate among various parkinsonian syndromes.^{4,5} They are expensive and may not be available in resource-limited settings.

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The reliable diagnosis of PD remains a challenge in such situations and has been an active field of research for finding more affordable investigations for the diagnosis of these chronic ailments.

In this regard, there has been a recent surge of interest in the field of biomarkers for PD. One such recently studied *in vivo* imaging biomarker is the Nigrosome imaging on 3T and 7T magnetic resonance imaging (MRI) sequences.^{6–8} Based on calbindin D_{28k} immunostaining patterns, the dopaminergic neurons in the substantia nigra pars compacta are divided into calbindin rich regions (matrix) and calbindin poor regions known as a nigrosome. There are 5 different nigrosomes, the largest being nigrosome-1.⁹ Pathological studies have demonstrated a higher degree of neuronal loss in nigrosomes compared to the matrix with the maximum depletion in nigrosome-1 (98%) that is located in the caudal and mediolateral part of substantia nigra pars compacta. The loss of dopaminergic neurons in PD follows a stereotyped temporospatial progression starting from nigrosome-1 and then spreading to other nigrosomes and finally to the matrix.¹⁰

Nigrosome-1 is visible as a linear, comma, or a wedge-shaped hyperintense structure in the dorsolateral region of substantia nigra pars compacta on susceptibility-weighted sequences of MRI. It has been referred to as a “swallow-tail” shaped structure with the tails being formed by the hypointense signal of substantia nigra pars compacta laterally and the medial lemniscus medially.¹¹ Poor visualization of this dorsolateral nigral hyperintensity (DNH) on imaging using 3T and 7T MRI is a fairly consistent imaging feature in patients with PD with high sensitivity, specificity, and diagnostic accuracy.^{12,13}

Therefore, we studied the use of nigrosome imaging on 3T MRI in the diagnosis of PD and compared it with 18F-DOPA PET scanning. We also studied the role of nigrosome imaging in differentiating PD from various atypical parkinsonian syndromes and sought to find its correlation with disease severity.

Methods

One hundred consecutive patients with a possible or probable diagnosis of idiopathic Parkinson's disease (IPD) and atypical parkinsonism (AP) were recruited from the Movement Disorders Clinic of the Department of Neurology in PGIMER, Chandigarh from January 2018 to April 2019. Diagnosis of PD was based on the UK Parkinson's Disease Society Brain Bank diagnostic criteria.¹⁴ AP syndromes were diagnosed according to their respective criteria.^{15,16} Young-onset Parkinson's disease (YOPD) was defined as the age of onset <50 years.¹⁷

The exclusion criteria included the following: (1) vascular parkinsonism;¹⁸ (2) major head injury; (3) history of encephalitis; (4) neuroleptic treatment at the onset of symptoms; (5) presence of structural lesion or hydrocephalus on brain imaging; (6) reversible causes of parkinsonism; and (7) any of the contraindications to MRI because of metal foreign bodies/implants or claustrophobia.

Fifteen healthy subjects were recruited from volunteers who were the attendants of patients and medical staff in our hospital.

This study was approved by the Institutional Ethics Committee. All patients and healthy subjects gave written informed consent.

A detailed clinical and neurological examination was carried out in all the patients. Hoehn and Yahr (H&Y) staging and the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scoring was done for all the cases both in the *off* state (12 hours after the last dose of levodopa/carbidopa [L-DOPA]) and *on* state (1 hour after 250 mg of L-DOPA/carbidopa).

3T MRI brain with special sequences like venous blood oxygen level-dependent (VenoBOLD) and high-resolution susceptibility-weighted imaging (SWI), 3 dimensional (3D) T₁-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence along with routine T₁ axial, T₂ axial, diffusion-weighted imaging (DWI), fluid attenuated inversion recovery sequence (FLAIR), and T₁ and T₂ sagittal MRI sequences were done for all the patients and healthy controls.

The images were assessed by 2 experienced neuroradiologists. The evaluation of nigrosome-1 was done on both the right and the left-sides separately in VenoBOLD and high-resolution SWI sequence. It was graded as 0, 1, and 2 as per the following criteria: 0 = complete loss of nigrosome; 1 = partial loss of nigrosome; and 2 = complete nigrosome is visualized.

A mutual consensus was taken between the 2 neuroradiologists for the interpretation of each MRI. If nigrosome was abnormal even on 1 side, it was taken as abnormal. When abnormal nigrosome was found on both sides; the side with the higher degree of loss was taken as the predominant side.

18F-DOPA PET imaging of the brain was performed using a dedicated Discovery STE 16 PET/computed tomography (CT) scanner. Static images of the brain were acquired in 3D mode 60 minutes after the intravenous administration of contrast containing 185 MBq of 18F DOPA. Images were generated and reconstructed in the transaxial, sagittal, and coronal plane and evaluated qualitatively for striatal uptake. Visual analysis of the scans was done by an experienced Nuclear Medicine expert who was blinded to the radiological and clinical information. The scans were assessed for 18F-DOPA uptake in bilateral basal ganglia with a focus on the caudate and the putamen. Any asymmetry in the uptake was also duly noted. All patients undergoing nuclear imaging were taken off L-DOPA and other dopamine agonists for a minimum duration of 24 hours.

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS version 21.0, IBM, Chicago, IL). Data normalcy was checked by applying the Kolmogorov-Smirnov test. For normally distributed quantitative data, mean, and standard deviation (SD) was calculated, otherwise median and inter-quartile range (IQR) was calculated. Qualitative variables were presented as frequency and percentage. Appropriate parametric and nonparametric tests such as the independent *t* test, Mann-Whitney *U* test, Chi-square or Fisher's exact test were applied between independent variables and 2 disease groups. Correlation coefficients were found out amongst different clinical and neuroimaging parameters using the Spearman's rank test. The sensitivity, specificity, and 95% confidence intervals were calculated using the online MedCalc software. A two-tailed *P* value of <0.05 was considered to be significant.

Results

A total number of 100 patients of PD and atypical parkinsonism were recruited. The mean age of the patients and healthy controls was 56.25 ± 11.29 years and 46.20 ± 8.5 years, respectively. The mean age of onset of symptoms was 53.15 ± 11.5 years, and the duration of illness was 3.09 ± 2.32 years. Males were affected more than females, M:F = 72:28. Motor UPDRS III (*off*) for patients was 42.54 ± 20.16 . The majority of patients had H&Y stage II ($n = 61$) followed by H&Y III ($n = 16$). The clinical and demographic details of patients and controls are given in Table 1.

Out of 100 patients, 56 (56%) were IPD, 30 (30%) were YOPD, and 14 (14%) were atypical parkinsonism (12 PSP and 2 MSA-P). The mean age of onset of disease was 55.35 ± 11.34 years and 61.79 ± 9.53 years in PD and AP group, respectively. There was a significant difference between the mean UPDRS III motor score (*off* state) in PD and AP, being 40.48 ± 19.91 and 55.14 ± 17.48 , respectively, $P < 0.011$ and total UPDRS score in these 2 groups (69.45 ± 30.00 in PD and 109.93 ± 37.06 in AP, respectively, $P < 0.001$), depicting severe parkinsonism and higher morbidity in patients having atypical parkinsonian syndromes (Table 1).

In patients with PD, males were 2.5–3 times more commonly affected than females. Bradykinesia was the predominant symptom in 85 patients whereas tremor was predominant in 15. All patients ($n = 14$) with progressive supranuclear palsy (PSP) and multiple system atrophy (MSA-P) also had bradykinesia as the cardinal symptom. Out of all patients, 90% had bilateral disease, whereas only 10% had unilateral disease.

Visualization of Nigrosome on SWI and VenobOLD Sequences

Using the VenobOLD sequence, 90 out of 100 patients were found to have an abnormal nigrosomal imaging. In the SWI

sequence, however, 4 more patients were rated as having abnormal imaging that the VenobOLD sequence had shown as normal. Grading of nigrosomes was done in both the sequences and is depicted in Table 2. A complete absence of the nigrosome was seen in around 20% of patients (Fig. 1).

The sensitivity and specificity of the VenobOLD sequence in comparison to the clinical diagnosis were found to be 90% and 66.7%, respectively. Concerning the SWI sequence, we found higher values in terms of sensitivity (94%) and specificity (80%) than the VenobOLD sequence.

We correlated clinical asymmetry with the asymmetry noted in the nigrosome scans in the patients diagnosed with IPD (86 patients). On VenobOLD sequences, out of 48 patients with left-sided predominant disease, nigrosome was absent on the right side in only 6 (12.5%) patients and out of 38 patients with right-sided predominant symptoms, nigrosome was absent on left side in only 8 (21%) patients ($P = 0.79$). Similarly, no correlation was found in the SWI sequence ($P = 0.71$) (Supplementary Table S1). Hence, the side of nigrosome loss or abnormality had poor lateralizing value in patients with asymmetrical onset IPD in our study.

Correlation between Clinical Parameters and Grading of Nigrosome

We also correlated various clinical and demographic parameters with the grading of nigrosome on the VenobOLD sequence and SWI sequence separately using the Spearman's rank test.

A weak negative correlation was found between grading of nigrosome on VenobOLD sequence and stage and severity of disease as measured by H&Y staging ($r = -0.236$, $P = 0.018$) and UPDRS III (*off* stage) ($r = -0.281$, $P = 0.005$). A negative correlation was also noted with the duration of disease, for example, as the disease advances in duration with worsening of

TABLE 1 Baseline characteristics: (cases-100, control-15)

Characteristics	Cases				Controls (N = 15)
	Total (n = 100)	Idiopathic PD (n = 86)	Atypical Parkinsonism (PSP and MSA) (n = 14)	P value	
Age	56.25 ± 11.29 (17–82)	55.35 ± 11.34 (17–81)	61.79 ± 9.53 (48–82)	0.047	46.20 ± 8.5
Gender (M:F)	72:28	63:23	9:5	0.384	10:5
Age of onset of disease (years)	53.15 ± 11.5 (15–80)	52.16 ± 11.51 (15–77)	59.29 ± 9.67 (47–80)	0.031	
Duration of illness (onset to presentation in years)	3.09 ± 2.32 (0.5–17)	3.19 ± 2.47 (0.5–17)	2.5 ± 0.85 (1–4)	0.305	
UPDRS motor score III <i>off</i>	42.54 ± 20.16 (3–93)	40.48 ± 19.91 (3–93)	55.14 ± 17.48 (35–87)	0.011*	
UPDRS motor score –III <i>on</i>	29.65 ± 19.47 (0–83)	26.5 ± 17.76 (0–82)	49 ± 18.81 (23–83)	< 0.000*	
UPDRS Total Score	75.12 ± 33.95 (11–163)	69.45 ± 30 (11–143)	109.93 ± 37.06 (58–163)	< 0.000*	
Overall H&Y stage	2.39 ± 0.93 (1–5)	2.18 ± 0.72 (1–4)	3.64 ± 1.08 (2–5)	< 0.000*	
Stage 1		9	0		
Stage 2		59	2		
Stage 3		11	5		
Stage 4		7	3		
Stage 5		0	4		

Results are expressed in mean $\pm$ SD (range). UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoen and Yahr; PD, Parkinson's disease.

*Significant P-values are highlighted with bold font.

TABLE 2 Grading of nigrosomes in different sequences in patients with Parkinson's disease and atypical parkinsonism (N = 100)

Grades of Nigrosomes	Right	Left	Bilateral	Total
VenoBOLD				
0 = complete loss	2	9	10	21
1 = partial loss	13	6	50	69
2 = normal				10
SWI				
0 = complete loss	2	9	11	22
1 = partial loss	7	2	63	72
2 = normal				6

motor symptoms, there was an increase in the loss of nigrosome, but it was not statistically significant. Similar findings were also observed in the SWI sequence (Supplementary Table S2).

F18 DOPA PET Results

Abnormal F18-DOPA PET with reduced uptake on either or both sides was present in 96 patients (Fig. 1). Four patients in the PD group had normal tracer uptake in bilateral putamen and

FIG. 1. 3T VenoBOLD and transaxial images of 18F DOPA PET/CT. (A) VenoBOLD image of a healthy control shows normal nigral hyperintensity in bilateral substantia nigra (grade 2). (B) Transaxial images of 18F-DOPA PET/CT showing bilaterally symmetrical comma-shaped normal uptake in striatum. (C) IPD patient with right-sided predominant symptoms. 3 T MRI (VenoBOLD sequence) showing grade 1 nigrosome (partially present) on both sides in axial section of midbrain. (D) 18F-DOPA PET/CT showing reduced uptake in bilateral putamen (left > right). (E) 3T MRI showing completely absent nigrosome (grade 0) on both sides. (F) 18F-DOPA PET/CT showing reduced uptake in bilateral striatum (right > left).

TABLE 3 Diagnostic accuracy of MRI sequences (VenoBOLD and SWI) for patients with Parkinson's disease, atypical parkinsonism, and healthy controls: PD = 86, AP = 14, HC = 15

	PD vs. HC (95% CI)	AP vs. HC (95% CI)	PD + AP vs. HC (95% CI)
MRI_VenoBOLD			
Sensitivity	88.4 (79.6–94.2)	100 (76.8–100)	90 (82.4–95.1)
Specificity	66.7 (38.4–88)	66.7 (38.3–88.2)	66.7 (38.4–88.2)
MRI_SWI			
Sensitivity	93 (85.4–97.4)	100 (76.8–100)	94 (87.4–97.8)
Specificity	80 (51.9–95.6)	80 (51.9–95.7)	80 (51.9–95.7)

All measures of sensitivity and specificity are given in % (95% CI).
PD, Parkinson's disease; AP, atypical parkinsonism; HC, healthy controls.

caudate. These 4 patients had normal nigrosome on VenoBOLD and SWI sequences.

In patients with IPD, the predominant side of the clinical disease was correlated with the predominant side of reduced tracer uptake in F18-DOPA PET. Out of 48 patients with left-sided predominant disease, predominantly right-sided reduced tracer uptake was seen in 31 (64.5%) patients and out of 38 patients with the right-sided predominant disease, left-sided predominantly reduced tracer uptake was seen in only 24 (63.1%) patients with $P < 0.001$ showing the significant lateralizing value (Supplementary Table S1).

Table 3 summarizes the diagnostic accuracy measures among the 3 groups (PD vs. AP vs. controls).

Discussion

Loss of dorsolateral nigral hyperintensity on MRI is a recently explored imaging biomarker in the diagnosis of neurodegenerative parkinsonism inclusive of PD, PSP, and multiple system atrophy.^{19–22} Various sequences including 3D FLAIR, SWI, and VenoBOLD have been studied in various studies in this regard.^{21–24} The results of our study reiterate the fact that loss of dorsolateral nigral hyperintensity occurs in patients with PD and AP.

The most significant finding of our study was the higher sensitivity and specificity of the SWI sequence on 3T MRI in comparison to the VenoBOLD sequence in the detection of the loss of nigrosome. However, the specificity values have to be handled with caution because of small number of controls in our study.

Our results have been reflected in few comparable studies. Schwarz and colleagues¹¹ in 2014 reviewed 114 scans in 3T high-resolution SWI in a prospective and retrospective case-control study and found out that 3T SWI scans had a sensitivity of 100%, specificity of 95%, and accuracy of 96% in diagnosing PD. Similarly, Gao and colleagues²⁰ in 2015 studied 54 patients with SWI sequence and found sensitivity and specificity to be 100% and 96.08%.

A majority of the studies have used the SWI sequence in the analysis of nigrosomes. However, Stezin and colleagues²³ used the VenoBOLD sequence and found a sensitivity of 98.5%, and specificity and positive predictive values of 93.6% and 94.3%, respectively. A meta-analysis of 10 studies comprising 364 PD

patients and 231 controls published in 2017 found an overall sensitivity and specificity of loss of nigrosome to be 94.6% and 94.4%, respectively, on 3T MRI.²⁵

Our study did not show any lateralizing value of nigrosome abnormality with the predominant side of clinical disease whereas, in a study done by Stezin and colleagues,²³ poorly visualized nigrosome-1 was demonstrated to be significantly associated with a higher clinical motor asymmetry on the contralateral side in 64.8% of subjects. A study by Noh and colleagues¹³ also showed good agreement between clinical asymmetry and contralateral loss of nigrosome. This lack of correlation in our study may be explained by 2 reasons. First, the majority of the patients in our study had bilateral disease at the time of presentation. Second, our study involved a visual assessment of nigrosome based on the relative asymmetry of loss of hyperintensity rather than a quantitative estimation that could have affected the results.

In F18-DOPA PET imaging, 4 patients out of 86, with a clinical diagnosis of PD had normal tracer uptake in bilateral putamen and caudate. These 4 patients also had completely normal nigrosome on the VenoBOLD sequence. All these patients were in the early stage of the disease with a disease duration of 1 year. These patients may fit into the category of scans without evidence of dopaminergic dysfunction (SWEDDs).²⁶ Out of these 4 patients, 1 died of cardiac failure and 1 was lost to follow-up. The diagnosis was revised in 2 patients at 1 year follow-up. One was diagnosed as dystonic tremor and the other was diagnosed as cervical and lumbar spondylosis.

We also studied whether nigrosome imaging helped in differentiating between PD and AP. An interesting, although not statistically significant, observation was that no patient with AP had completely normal nigrosome in our study, whereas 10 patients out of 86 in the PD group had completely normal nigrosome. No conclusions could be drawn owing to the sample size. However, we are hopeful that further studies with a larger sample size may be able to demonstrate whether imaging of nigrosome can differentiate between PD and AP.

Reiter and colleagues²¹ studied 148 patients with neurodegenerative parkinsonism (104 = PD, 22 = MSA, and 22 = PSP) and 42 healthy controls. They also demonstrated that loss of dorsolateral nigral hyperintensity on high-field SWI could not differentiate between PD and AP.²¹ A prospective observational cohort study by Meijer and colleagues²⁷ found the diagnostic accuracy of the swallow-tail sign to differentiate between typical and atypical parkinsonism was only marginal. Calloni and

colleagues²⁸ also showed poor specificity (0%) of nigrosome-1 in discriminating IPD from AP disorders with a sensitivity of 96.4%. They suggested the use of multiparametric MRI using midbrain atrophy and putaminal hypointensity in addition to nigrosome imaging to differentiate among various parkinsonian disorders.

However, the major advantage of the nigrosome imaging remains that it can be done without incurring any additional cost to the patient. Additionally, PET studies are not available or affordable to patients in smaller healthcare centers and in these settings, imaging of nigrosomes can assist in reliably proving the diagnosis of PD.

The major limitation of our study was the small sample size especially in the AP group compared to PD. We have used only the clinical criteria of PD as the gold standard for diagnosis and there was no pathological confirmation of the cases. A clinico-pathological overlap, though seen in a minority, is always a possibility in degenerative parkinsonian disorders. Second, the lack of agreement between the clinical asymmetry and lateralization on nigrosome imaging further underlines the importance of the requirement of imaging protocols in interpreting these scans. Optimization and standardization of a sequence for visualization of nigrosome-1 could have improved the diagnostic values further but our resource limited settings prevented us from designing that into our methodology in the current study. Imaging protocols have been suggested using susceptibility-weighted imaging and quantitative susceptibility mapping especially to look at nigrosome-1 (N1) territory of substantia nigra pars compacta. Cheng and colleagues²⁹ chose a resolution of 0.67 mm × 0.67 mm × 1.34 mm with good signal-to-noise with echo times of 11 ms and 20 ms.

Bae and colleagues³⁰ found a high concordance rate of 86.2% between loss of nigral hyperintensity on 3T SWI and nigrostriatal dopaminergic degeneration indicated by SPECT. However, we could not correlate findings on MRI with 18F-DOPA PET because of a lack of PET imaging in healthy controls.

Further studies with a large sample size are needed to confirm the use of the nigrosome-1 detection in the routine clinical diagnosis of IPD and their ability to discriminate between typical and AP disorders. Moreover, the importance of these scans in diagnosing PD in the premotor stage cannot be overemphasized.

To conclude, we highlight the clinical usefulness of nigrosome imaging in the diagnosis of PD. The loss of nigrosome on 3T MRI on SWI and VenoBOLD sequences may serve as a potential imaging marker in the diagnosis of degenerative parkinsonian syndromes. Additional expensive PET studies can be avoided if the loss of nigrosome confirms the diagnosis of PD on routine 3T SWI or VenoBOLD imaging.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution,

C. Review, and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review, and Critique.

H.K.: 1C, 2A, 3A

S.M.: 1A, 1B, 2C, 3B

C.K.A.: 1B, 1C, 3B

K.C.: 1A, 1B, 1C, 3B

S.R.: 2A, 3B

B.R.M.: 1B, 1C

P.S.: 1B, 1C

V.L.: 1B, 1C, 3B

Ethical Compliance Statement: This study was approved by the Institutional Ethics Committee (INT/IEC/2019/000149). All patients and healthy subjects gave written informed consent. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1 Relationship between clinical asymmetry and nigrosome imaging and PET sequences (only IPD; n = 86)

Table S2 Correlation between visualization of nigrosome on VenobOLD sequence and SWI sequence with various clinical parameters