



Original Article

Volumetric analysis of subthalamic nucleus and red nucleus in patients of advanced Parkinson's disease using SWI sequences

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ABSTRACT

Background: Parkinson's disease is associated with significant changes in morphometry of subthalamic nucleus (STN); however, not much is known as the disease progresses. The aim of present study was to investigate the volume of STN and Red nucleus (RN) on 3T-magnetic resonance imaging (MRI) and its possible correlation with disease progression in advanced Parkinson's disease patients.

Methods: Patients of advanced Parkinson's disease were prospectively followed for clinical details, motor severity scores, and radiological evaluation. Volumes of the STN and RN were measured on susceptibility weighted imaging, coronal sections in 3T MRI and were correlated with demographic and clinical features.

Results: A total of 52 patients were included in our study. There were 42 (80.77%) males and 10 (19.23%) females. Mean age of onset of Parkinson's disease was 49.48 + 10.90 years. Average duration of disease in the present cohort was 7.65 + 4.31 years. Average STN and RN volume were 103.46 + 21.17 mm³ and 321.73 + 67.66 mm³. Age of onset, disease duration and Unified Parkinson's Disease Rating Scale Part III scores were not found to be associated with changes in STN Volumes. Weak positive trend was noted between RN volume and disease duration (Pearson cor. 0.204, $P = 0.14$). Patients in early-onset Parkinson's disease group had significantly more volume of RN than patients in late-onset Parkinson's disease group ($P = 0.014$).

Conclusion: Disease duration and early age of onset in Parkinson's disease can be associated with increased RN volume. Volume of STN shows relatively no change even with disease progression.

Keywords: Disease duration, Parkinson's disease, Red nucleus, Subthalamic nucleus, Volumetric analysis

INTRODUCTION

Parkinson's disease (PD) manifests clinically with varying combinations of tremor, bradykinesia, rigidity, and other non-motor symptoms. Subthalamic nucleus (STN) has a major role in the pathophysiology of PD.^[3] Deep brain stimulation (DBS) can be helpful in PD particularly for those in advanced stages. Precise targeting of STN has been identified as one of the major factors for the successful outcome of DBS surgery.^[29] Apart from the normal anatomical variations, PD is associated with significant changes in metabolic state and morphometry of STN.^[4] However, not much is known as the disease progresses.

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The aim of the present study was to investigate the volume of STN and Red nucleus (RN) on 3T MRI susceptibility weighted imaging (SWI) sequences and its possible correlation with disease progression in patients with advanced PD.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Neurosurgery, Neurology and Radiology from February 2019 to February 2020. Approval from Institutional Ethics Committee was taken. All consecutive patients admitted and undergoing STN-DBS for advanced PD were included in the study. Motor severity assessment was performed in all patients using Unified Parkinson's Disease Rating Scale Part III (UPDRS III) scores in OFF state by a qualified UPDRS III specialist after depriving the patient of his dopaminergic medications for at least 12 h. Radiological evaluation included volumetric SWI sequences acquired in 3T MRI as a routine protocol. MR Scanner, image acquisition protocol, and methodology were uniform and were done in ON phase without any need for general anesthesia.

Data acquisition

SWI-Acquisitions

Gradient echo sequences, using the following parameters: 80 slices, Field-of-view (FoV) = 240 mm, FoV phase 88%, Repetition time/Echo time = 28/20 ms; flip angle of 15°, with fat suppression and flow compensation, resolution matrix of 352 × 248 with a slice thickness of 0.6 mm, AP and RL phase-encoding direction for axial and coronal orientation, respectively, were used for the acquisition. Acquisition time was 7 min and 14 s for acquiring each SWI dataset. The volumes of the STN and RN were measured on SWI coronal images by tracing the borders of the STN and RN manually on each slice and then were interpolated to calculate the volume. Use of axial sections and axial minimum intensity projection images was made, in cases, where margins of the nuclei were not clearly delineated on coronal images [Figure 1].

Volumes of the nuclei were correlated with demographic and clinical features. Statistical analysis was done using IBM Statistical Package for the Social Sciences trial version 22. $P < 0.05$ was considered significant.

RESULTS

Demography

A total of 52 patients were included in our study. There were 42 (80.77%) males and 10 (19.23%) females. Mean age of the patients was 57.13 + 9.81 years (Median = 59, Range 39–83 years). Maximum number of patients ($n = 24$, 46.15%) was

in the age group of 60–70 years of age. There were 15 patients (28.85%) in the age group of 50–60 years of age. Mean age of onset of PD was 49.48 + 10.90 years. Average duration of disease in present cohort was 7.65 + 4.31 years. There were 14 (26.92%) patients who presented to us within 5 years of onset of disease. Twenty-three patients (44.23%) had disease duration of 6–10 years. There were 15 (28.85%) patients who presented with disease duration of more than 10 years. Twenty-four (46.15%) patients had disease onset before 50 years of age qualifying them for Early Onset Parkinson's Disease (EOPD) group and 28 (53.85%) patients had disease onset after 50 years of age, integrating them into Late Onset Parkinson's disease (LOPD) group. Mean UPDRS III score in OFF state was 55.61 + 9.99 [Table 1].

Volumetric analysis of STN

Volume of the right and left STN and RN was calculated from SWI sequences. None of the patients required any form of anesthesia for image acquisition. Average of volumes of nucleus from both sides was calculated. Mean right and left subthalamic volume was 106.15 + 23.60 mm³ and 100.76 + 21.76 mm³, respectively. Average STN volume was 103.46 + 21.17 mm³ with a range of 65–155 mm³ [Figure 2 and Table 1].

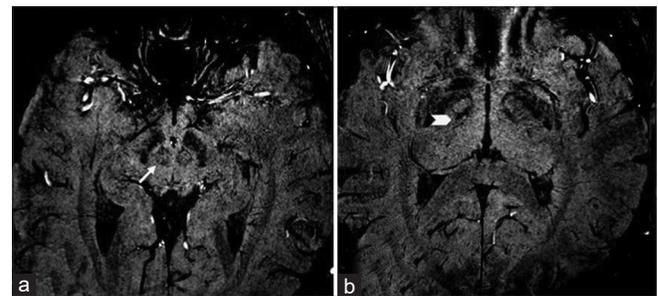


Figure 1: Magnetic resonance imaging susceptibility weighted imaging sequence Axial Sections showing delineation of (a) red nucleus and (b) subthalamic nucleus.

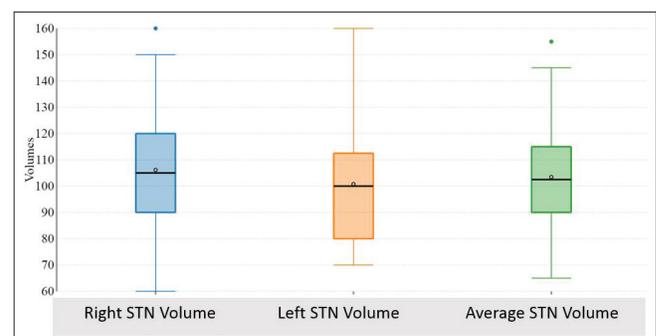


Figure 2: Box and whisker plot showing median and interquartile range of the right, left, and average STN volumes. STN: Subthalamic nucleus.

Volumetric analysis of RN

Mean right and left RN volume were $321.73 + 65.16 \text{ mm}^3$ and $321.73 + 73.39 \text{ mm}^3$. Average RN volume was $321.73 + 67.66 \text{ mm}^3$ with a range of $160\text{--}480 \text{ mm}^3$ [Figure 3].

Table 1: Demographic and clinical parameters of patients included in study.

Parameter	Means/ Frequency
Age	57.1346 + 9.81 years
Gender	Males- 42 (80.77 %) Females- 10 (19.23 %)
Age of Onset	49.48 +10.90 years
Duration of disease	7.65 + 4.31 years
UPDRS III On	15.41 + 5.60
UPDRS III Off	55.61 + 9.99
Right STN volume	106.15 +23.60 mm ³
Left STN Volume	100.76 + 21.76 mm ³
Average STN Volume	103.46 + 21.17 mm ³
Right RN Volume	321.73 + 65.16 mm ³
Left RN Volume	321.73 + 73.39 mm ³
Average RN volume	321.73 + 67.66 mm ³

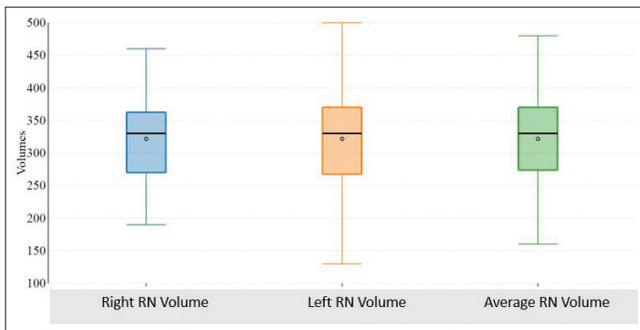


Figure 3: Box and whisker plot showing median and interquartile range of the right, left, and average RN volumes. RN: Red nucleus.

Correlation of STN Volume with demography and clinical features

Parameters acquired through the volumetric analysis were compared with demographic and clinical features. Hemispherical UPDRS III was compared with contralateral STN and RN Volumes. No correlation was noted between age of patient and volume of RN. Disease duration was found to be positively correlated with STN volume but statistical significance was not seen. Overall, no difference related to gender was noticed, except in cases with disease duration of <5 years, males had significantly less STN volume than females ($P = 0.046$). STN volume did not differ in early and late onset PD group. No statistical significance was noted between UPDRS III in off state and STN volumes [Figure 4]. On multivariate analysis as well, age of onset, disease duration, and UPDRS III scores were not found to be associated with any changes in STN Volumes.

Correlation of RN Volume with demography and clinical features

Weak positive trend was noted between volume of RN and disease duration (Pearson cor. 0.204, $P = 0.14$) [Figure 5]. In patients with disease duration of 5–10 years the average RN volume was significantly more in males ($P = 0.018$); however, no overall gender related differences were noted. Patients with EOPD had significantly more volume of RN as compared to patients in LOPD group ($P = 0.014$) [Table 2]. UPDRS III scores in off period did not correlate with nuclei volumes. On multivariate analysis between age of onset, disease duration and UPDRS III Score, only disease duration was associated with increased relative risk; however, significance was not reached (OR 2.076, $P = 0.40$).

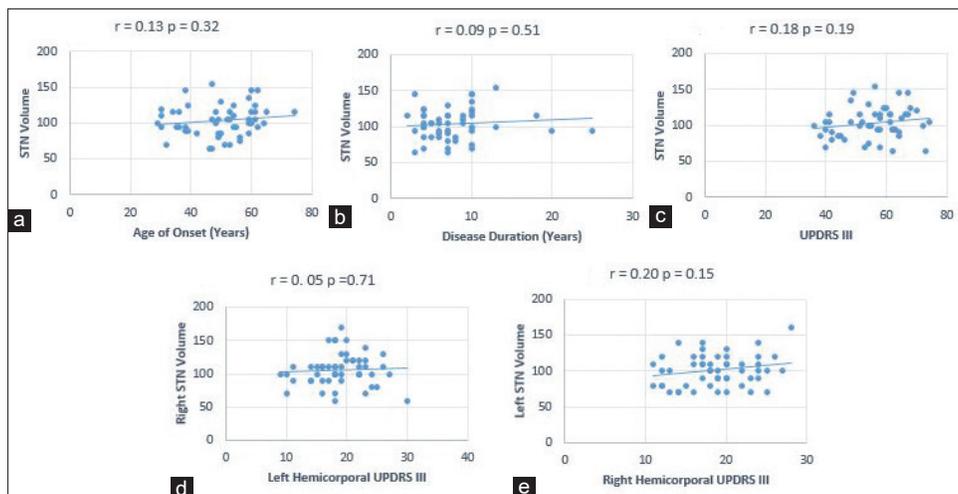


Figure 4: Scatter plot showing correlation between STN Volume and (a) Age of onset, (b) Disease Duration, (c) UPDRS III, and (d) right STN Volume and Left Hemispherical UPDRS III, (e) Left STN Volume and Right Hemispherical UPDRS III. STN: Subthalamic nucleus, UPDRS III: Unified Parkinson’s disease rating scale part III.

DISCUSSION

PD, a progressive neurologic disorder which is known to affect more than 1% of the population over 65 years of age, is characterized by the varying intensity of tremor, rigidity, and bradykinesia.^[19,13] Increasing age plays a strong role for lifetime risk for occurrence of PD.^[8] A peak is noted at 70 years of age and incidence has been noted to be less in cases with age more than 80 years.^[22] STN, a subcortical structure plays an important role in execution of motor events in human body. Degeneration of dopaminergic neurons in substantia nigra has been implicated in the pathogenesis of PD.^[3] Long-term benefits of STN DBS are well established now. Detection of the neurodegenerative changes in STN is also beneficial for diagnosing the progression of disease. Before evolution of advanced imaging techniques, most of the data related to volume and morphometry of brain structures were interpolated from neuropathological brain sections. However, postmortem analysis of volume of subcortical structures can be associated with inconsistent results due to variable shrinkage rate. Schaltenbrand *et al.* Wahren Atlas was often used previously to localize STN in surgical procedures.^[25] Generalizability of the information acquired

from this atlas was not possible, since only three brain sections were utilized for illustration of Basal Ganglia. Moreover, the age of individuals from whom the specimens were taken were <50 years.^[25] Age related changes in morphometry and location of STN are well known to occur.^[9] Hence, precise localization using an atlas with a limited data is questionable. While other atlas for localization of STN are still available, most of them are limited by similar drawbacks of restricted sample size, age range, and non-consideration of pathological changes affecting the cortical and subcortical structures.^[16]

Targeting the STN in DBS can also be done based on AC-PC relations and relation with RN. On comparison of MR and atlas based targeting methods Ashkan *et al.*^[2] demonstrated that T2W imaging has more accuracy in localization of STN as compared to atlas based targeting methods. In spite of the advances in imaging techniques, localization of STN is still difficult due to its smaller size, biconvex shape and oblique orientation. Anatomical approximation with substantia nigra makes delineation of all borders of STN difficult.^[2] Higher clinical benefits are also noticed by performing MR sequences in an anesthetized patient.^[21] However, distortion, particularly at the periphery can be a major significant challenge in imaging and localization of STN. A technical error of up to 2.4 mm in T2 fast SE sequences has been noticed due to distortion. This ultimately results in reduced accuracy of MRI in delineation of anatomy.^[30] SWI sequences have been found to have significant superiority over T2W imaging with an increase in Contrast to noise ratio even at low field strengths.^[20] There has been a surge in the interest in using SWI as it is better for structures with rich iron content like STN and visualization of parenchymal vessels, which in future, may obviate the need for Gadolinium contrast MRI while deciding the trajectory.^[23] Vertinsky *et al.* in their study of localization of STN concluded that good

Table 2: Comparison of STN and RN Volumes in Early and Late Onset Parkinson's disease group.

	STN Volume			RN Volume		
	Mean	Std Dev	p Value	Mean	Std Dev	p Value
EOPD (24)	100.8	22.24	0.41 (ANOVA)	346.04	64.28	0.014 (ANOVA)
LOPD (28)	105.7	20.35		300.89	64.43	

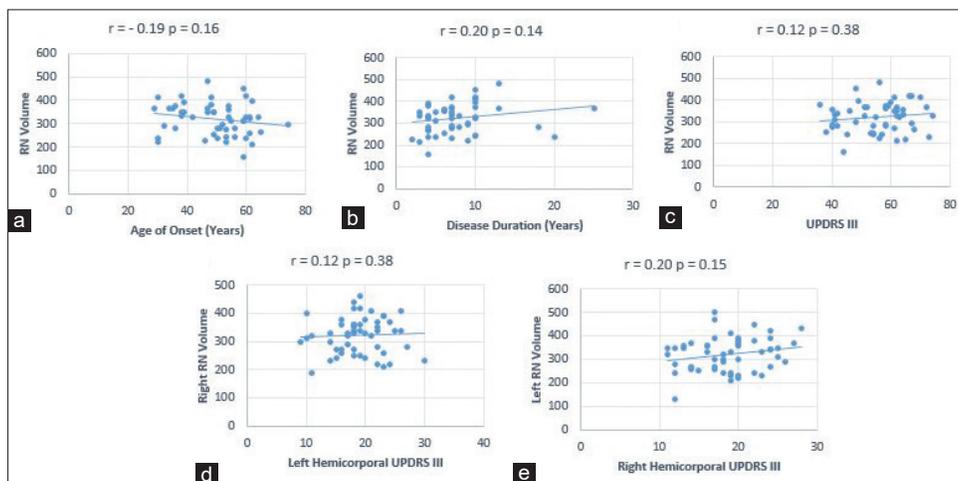


Figure 5: Scatter plot showing correlation between RN volume and (a) age of onset, (b) disease duration, (c) UPDRS III and (d) right RN volume and left hemicorporal UPDRS III, (e) left RN volume and right hemicorporal UPDRS III. RN: Red nucleus, UPDRS III: Unified Parkinson's disease rating scale part III.

Table 3: Comparison of various studies on Volumetric analysis of STN and RN and their findings.

Sr No	Author	Year	Sample Size	MRI Sequence	Findings
1	Colpan et al ^[22]	2008	12 Cases 12 Controls	3T T2W MRI	Parkinson's disease is associated with smaller STN volume. RN Volume is more in cases with increased duration of disease.
2	Camlidag et al ^[26]	2013	20 Cases 20 Controls	1.5 T T2W MRI	Parkinson's disease is associated with increase in Volumes of STN and RN.
3	Shah et al ^[23]	2019	30 Cases	3T SWI	Disease duration has positive correlation with Volumes of STN and RN.
4	Present Study	2020	52 Cases	3T SWI	Volume of STN stays consistent as disease progresses. Longer disease duration and early age of onset in Parkinson's disease is associated with increased RN volume.

visualization of STN can be achieved using SWI sequences and can omit the requirement for intraoperative microelectrode recording.^[28] However, SWI sequences are associated with few disadvantages like signal distortion particularly at high field strength which can make the edges of the nucleus blur.^[10] On comparison of magnetic field strength of MRI, 3 T sequences have superiority over 1.5 T sequences in delineation of STN.^[6] In experimental studies, higher strengths such as 7 T and 9.4 T have been found to be more superior in localizing and delineating the STN anatomy.^[1,17]

Volumetric analysis of STN plays an important role in planning of target in DBS. Motor and cognition disturbances can occur after DBS. These changes can be attributed to suboptimal placement of electrodes or to spread of current to surrounding structures.^[18] Volumetric and morphometric discrepancies of the STN should be taken into consideration while planning and programming the therapy in cases of PD. Smaller the size and volume of the STN, less is the scope for error of placement of electrodes for optimal outcome. However, the results of volumetric analysis have been found to be variable in different studies. Differences are even seen in volumes of right and left subthalamic nuclei. Colpan and Slavin in their study of correlation of STN Volume and PD progression noted an average STN Volume of $0.13 + 0.01 \text{ cm}^3$ which was less than results from age matched controls.^[7] In a similar recent study of volumetric assessment of STN on SWI images by Shah *et al.*, average STN Volume of 118.66 mm^3 with a range of $80\text{--}170 \text{ mm}^3$ was noted.^[26] Average STN volume noted by Massey *et al.* was 106 mm^3 .^[17] Morphological heterogeneity of STN has been noted in histological studies also.^[14] In our study, there were no significant variations in the volume of STN in relation to age and gender [Table 3].

We did not notice any statistical correlation between STN volumes and disease duration. In neuropathological case-control studies, similar observations were noted, leading to an inference that the volume of STN does not change with disease duration and severity.^[12] In a similar study of volumetric analysis on SWI, no degenerative changes were noted in STN volume, also, they observed a positive correlation with an

increase in disease duration.^[26] Camlidag *et al.*^[5] noticed an increase in size of STN volume with progression in disease. Firing rate of neurons in STN is known to increase along with progression in disease duration^[24] and this was implicated as a cause for compensatory hypertrophy and resultant increase in size of STN. Few studies have noticed degenerative changes in STN as per disease progression.^[7] Age dependent decrease in STN Volumes have also been noted.^[27] Since PD is particularly seen in elderly population, age can be implicated in degeneration process and can be a confounding factor particularly in elderly patients.

We noticed a positive trend between disease duration and volume of RN. Patient with early onset PD had more volumes than late onset PD which are consistent with findings from previous studies.^[5,7,26] Such volume changes can be attributed to compensatory role played by RN by acting as an intersecting point between primary and cerebellar motor pathways.^[11] RN mediated PD-related compensatory changes and increase in its iron content in PD might reflect these changes.^[15] Such compensatory plasticity can be attributed to increase in RN volume.

CONCLUSION

Longer disease duration and early age of onset in PD can be associated with increased RN volume. Volume of STN stays consistent as the disease progresses.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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