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 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 mm$^3$ and 100.76 ± 21.76 mm$^3$, respectively. Average STN volume was 103.46 ± 21.17 mm$^3$ with a range of 65–155 mm$^3$ [Figure 2 and Table 1].

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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 mm$^3$ and 100.76 + 21.76 mm$^3$, respectively. Average STN volume was 103.46 + 21.17 mm$^3$ with a range of 65–155 mm$^3$ [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.](image1)

![Figure 2: Box and whisker plot showing median and interquartile range of the right, left, and average STN volumes. STN: Subthalamic nucleus.](image2)
Volumetric analysis of RN

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

| 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$^3$ |

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

**Correlation of STN Volume with demography and clinical features**

Parameters acquired through the volumetric analysis were compared with demographic and clinical features. Hemipcorporal 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 3: Box and whisker plot showing median and interquartile range of the right, left, and average RN volumes. RN: Red nucleus.

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 Hemipcorporal UPDRS III, (e) Left STN Volume and Right Hemipcorporal 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.\[8\] 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

![Figure 5](https://example.com/figure5.png)

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. 5e) left RN volume and right hemicorporal UPDRS III. RN: Red nucleus, UPDRS III: Unified Parkinson’s disease rating scale part III.

### 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   | 346.04       | 64.28   | 0.014  |
| LOPD (28)        | 105.7         | 20.35   |        | 300.89       | 64.43   |        |

\[ANOV A\]
Visualization of STN can be achieved using SWI sequences and can omit the requirement for intraoperative microelectrode recording. 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. On comparison of magnetic field strength of MRI, 3 T sequences have superiority over 1.5 T sequences in delineation of STN. 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. 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. 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 cm³ which was less than results from age matched controls. In a similar recent study of volumetric assessment of STN on SWI images by Shah et al., average STN Volume of 118.66 mm³ with a range of 80–170 mm³ was noted. Average STN volume noted by Massey et al. was 106 mm³. Morphological heterogeneity of STN has been noted in histological studies also. 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. 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. Camlidag et al 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 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. Age dependent decrease in STN Volumes have also been noted. 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. Such volume changes can be attributed to compensatory role played by RN by acting as an intersecting point between primary and cerebellar motor pathways. RN mediated PD-related compensatory changes and increase in its iron content in PD might reflect these changes. 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.
REFERENCES

1. Abosch A, Yacoub E, Ugurbil K, Harel N. An assessment of current brain targets for deep brain stimulation surgery with susceptibility-weighted imaging at 7 tesla. Neurosurgery 2010;67:1745-56; discussion 1756.
2. Ashkan K, Blomstedt P, Zrinzo L, Tisch S, Yousry T, Limousin-Dowsey P, et al. Variability of the subthalamic nucleus: The case for direct MRI guided targeting. Br J Neurosurg 2007;21:197-200.
3. Benazzouz A, Piallat B, Ni ZG, Koudsie A, Pollak P, Benabid AL. Implication of the subthalamic nucleus in the pathophysiology and pathogenesis of Parkinson's disease. Cell Transplant 2000;9:215-21.
4. Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of Parkinsonism. J Neurophysiol 1994;72:507-20.
5. Camlidag I, Kocabicak E, Sahin B, Jahanshahi A, Incesu L, Aygun D, et al. Volumetric analysis of the subthalamic nucleus based on magnetic resonance imaging in patients with Parkinson's disease. Int J Neurosci 2014;124:291-5.
6. Cheng CH, Huang HM, Lin HL, Chiou SM. 1ST versus 3T MRI for targeting subthalamic nucleus for deep brain stimulation. Br J Neurosurg 2014;28:467-70.
7. Colpan ME, Slavin KV. Subthalamic and red nucleus volumes in patients with Parkinson's disease: Do they change with disease progression? Parkinsonism Relat Disord 2010;16:398-403.
8. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology 2009;72:432-8.
9. den Dunnen WF, Staal MJ. Anatomical alterations of the subthalamic nucleus in relation to age: A postmortem study. Mov Disord 2005;20:893-8.
10. Gasparotti R, Pinelli L, Liserre R. New MR sequences in daily practice: Susceptibility weighted imaging. A pictorial essay. Insights Imaging 2011;2:335-47.
11. Habas C, Cabanis EA. Cortical projections to the human red nucleus: A diffusion tensor tractography study with a 1.5-T MRI machine. Neuroradiology 2006;48:755-62.
12. Hardman CD, Halliday GM, McRitchie DA, Morris JG. The subthalamic nucleus in Parkinson's disease and progressive supranuclear palsy. J Neuropathol Exp Neurol 1997;56:132-42.
13. Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 1998;121:451-7.
14. Lévesque JC, Parent A. GABAergic interneurons in human subthalamic nucleus. Mov Disord 2005;20:574-82.
15. Lewis MM, Du G, Kidacki M, Patel N, Shaffer ML, Mailman RB, et al. Higher iron in the red nucleus marks Parkinson's dyskinesia. Neurobiol Aging 2013;34:1497-503.
16. Lucerna S, Salpietro FM, Alafaci C, Tomasello F. In Vivo Atlas of Deep Brain Structures: With 3D Reconstructions. Berlin, Heidelberg: Springer-Verlag; 2002. Available from: https://www.springer.com/gp/book/9783540425618. [Last accessed on 2020 Dec 25].
17. Massey LA, Miranda MA, Zrinzo L, Al-Helli O, Parkes HG, Thornton JS, et al. High resolution MR anatomy of the subthalamic nucleus: Imaging at 9.4 T with histological validation. Neuroimage 2012;59:2035-44.
18. McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. Clin Neurophysiol 2004;115:589-95.
19. Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 1999;53:85-90.
20. O'Gorman RL, Shmueli K, Ashkan K, Samuel M, Lythgoe DJ, Shahidiani A, et al. Optimal MRI methods for direct stereotactic targeting of the subthalamic nucleus and globus pallidus. Eur Radiol 2011;21:130-6.
21. Plaha P, Ben-Shlomo Y, Patel NK, Gill SS. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. Brain 2006;129:1732-47.
22. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Mov Disord 2014;29:1583-90.
23. Rauscher A, Sedlack J, Barth M, Haacke EM, Reichenbach JR. Noninvasive assessment of vascular architecture and function during modulated blood oxygenation using susceptibility weighted magnetic resonance imaging. Magn Reson Med 2005;54:87-95.
24. Remple MS, Bradenham CH, Kao CC, Charles PD, Neimat JS, Konrad FE. Subthalamic neuronal firing rate increases with Parkinson's disease progression. Mov Disord 2011;26:1657-62.
25. Schaltenbrand G. Atlas for Stereotaxy of the Human Brain. Germany: Georg Thieme; 1977. Available from: https://www.ci.nii.ac.jp/naid/10029743082. [Last accessed on 2020 Dec 25].
26. Shah V, Alugolu R, Arora A, Kandadai RM, Mudumba V, Borghoin R. 3T MRI-SWI based volumetric analysis of the subthalamic and red nuclei in advanced Parkinson's disease. J Neurosurg Sci 2020. doi: 10.23736/S0390-5616.20.04935-8. Epub Ahead of Print.
27. Shen W, Wang H, Lin Z, Shen H, Chen X, Fu Y, et al. Stereotactic localization and visualization of the subthalamic nucleus. Chin Med J (Engl) 2009;122:2438-43.
28. Vertinsky AT, Coenen V A, Lang DJ, Kolind S, Honey CR, Li D, et al. Localization of the subthalamic nucleus: Optimization with susceptibility-weighted phase MR imaging. Am J Neuroradiol 2009;30:1717-24.
29. Welter ML, Schüpbach M, Czernecki V, Karachi C, Fernandez-Vidal S, Golmard JL, et al. Optimal target localization for subthalamic stimulation in patients with Parkinson disease. Neurology 2014;82:1352-61.
30. Zonenshayn M, Rezai AR, Mogilner AY, Beric A, Sterio D, Kelly PJ. Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. Neurosurgery 2000;47:282-92; discussion 292-4.

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