Journal of Taibah University Medical Sciences (2022) 17(1), 87–95

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com

Original Article

Comparative morphometric evaluation of the brainstem in neurodegenerative diseases with healthy individuals using magnetic resonance imaging

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Received 15 May 2021; revised 17 June 2021; accepted 21 June 2021; Available online 11 August 2021

الملخص

أهداف البحث: قياسات المكون ضمن القيمة المرجعية هي عامل مستخدم على نطاق واسع في العلوم الطبية الحيوية. وتؤكد هذه الدراسة على قيمة التغيرات الشكلية في بنية جذع الدماغ عند الأشخاص الأصحاء وتطبيقها في اكتشاف وتشخيص الاضطرابات التنكسية العصبية.

طرق البحث: تضمنت هذه الدراسة وبأثر رجعي صورا بالرنين المغناطيسي لـ ٥٠ فردا سليما بدون أمراض عصبية، و٣٥ حالة تم تشخيصها سريريا لمرض باركنسون و١٢ حالة من الشلل فوق النوى المترقي. تم النظر في قياسات منطقة الدماغ المتوسط، ومنطقة الجسر، ونسبة الدماغ المتوسط إلى منطقة الجسر، والمتفوق للدماغ المتوسط، وسمك المادة السوداء، وعرض الساق الدماغية، والمسافة بين السويقات، وتقعر الساق الدماغية وفقا للبروتوكولات القياسية.

النتائج: كان متوسط القطر الأمامي الخلفي للمرضى الذين يعانون من مرض باركنسون ١.١١ ±٠.١سم، وهو أكثر من مجموعة التحكم ومرضى الشلل فوق النوى المترقي. بالإضافة إلى ذلك، أظهر المرضى الذين يعانون من الشلل فوق النوى المترقي أقل مساحة للدماغ المتوسط والجسر هي ١.٠٦ ±٠.٣٤و٤.٠١ ± ١.٢سم مربع، على التوالي، مقارنة بالمجموعات الأخرى. كانت نسبة الدماغ المتوسط إلى منطقة الجسر هي الأقل بين مرضى الشلل فوق النوى المترقي (٠.٢١ ±٠.٠٦ سم) مقارنة بمجموعتي مرض باركنسون ومجموعةالتحكم. كما تم العثور على متوسط سماكة ساقي المخيخ الأيمن والأيسر الأوسطين (١.٢٥ ± ٠.١٩و ١.٢٤ ±٠.١٧ سم) أقل في مجموعةمرضى باركنسون. وكان قياس عرض المادة السوداءيقل تدريجيا في مرضى باركنسون وأكثر في المرضى الذين يعانون من الشلل فوق النوى المترقي. وكان المظهر الجانبي المحدب للدماغ المتوسط سمة ثابتة في جميع المجموعات.

الاستنتاجات: تؤكد هذه الدراسة على قيمة القياسات الشكلية لملف جذع الدماغ في التمييز بين الأمراض التنكسية العصبية لدى الأفراد الأصحاء المسنين عند دمجها مع بياناتهم السريرية.

الكلمات المفتاحية: قياس شكل جذع الدماغ؛ الأمراض التنكسية العصبية؛ مرض باركنسون؛ الشلل فوق النوى المترقي؛ جذع الدماغ

Abstract

Objective: Measurement of a component within the reference value is a widely used parameter in Biomedical Science. This study highlights the value of morphometric changes in healthy individuals' brainstem structure and their application in the detection and diagnosis of neurodegenerative disorders.

Methods: This retrospective study included magnetic resonance (MR) images of 50 healthy individuals without neurological diseases, 35 clinically diagnosed individuals with Parkinson's disease (PD), and 12 individuals with Progressive Supranuclear Palsy (PSP). Measurements of midbrain area, pons area, ratio of midbrain to pons area, superior profile of midbrain, thickness of substantia nigra (SN), cerebral crus width, interpeduncular distance, and concavity of the crus were analysed as per the standard protocol.

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Peer review under responsibility of Taibah University.

Production and hosting by Elsevier

 https://doi.org/10.1016/j.jtumed.2021.06.012

Results: Patients with PD had mean anteroposterior diameter of 1.11 ± 0.1 cm, which was more than the control group and PSP patients. Additionally, PSP patients showed the least midbrain and pons area of 1.06 ± 0.34 and 4.01 ± 1.2 sq.cm, respectively, compared to other groups. The ratio of midbrain to pons area was the least among PSP patients (0.21 ± 0.06 cm). Mean thickness of the right and left middle cerebellar peduncles (1.25 ± 0.19 and 1.24 ± 0.17 cm) was less in the PD group. The width of the SN gradually reduced in PD and more so in PSP patients. The convex superior profile of the midbrain was a consistent feature in all groups.

Conclusion: This study highlights the value of morphometrics of the brainstem profile in differentiating neurodegenerative diseases among aged, healthy individuals when combined with their clinical data.

Keywords: Brainstem morphometry; Brainstem profile; Neurodegenerative diseases; Parkinson's disease; Progressive supranuclear palsy

Introduction

The term neurodegenerative disease encompasses a wide variety of slowly progressive disorders associated with progressive loss of neurons typically affecting the functionally related group of neurons.[1] Most neurodegenerative diseases commonly manifest in later years of adulthood. This creates some kind of disparity for the clinicians to attribute certain set of symptoms to normal ageing process or presence of a neurodegenerative disease.[2]

Brainstem is composed of the medulla oblongata, pons, and midbrain parts with various tracts and several nuclear masses in it. It is part of the neural axis extending between the caudal end of diencephalon to the exit of upper rootlets of the first pair of cervical spinal nerves. Brainstem activities may be divided into three types: conduit functions (through ascending and descending tracts), cranial nerve functions (sensory and motor nuclei related to cranial nerve functions at various brainstem levels), and integrative functions (cardiovascular and respiratory activity and regulation of consciousness). Magnetic resonance (MR) imaging provides reliable morphometric data about the brainstem region both in healthy individuals and in those with neurodegenerative diseases. Such data also provide accurate reference points on the brainstem that helps reach their internal neural structures. Thus, it helps neurosurgeons to formulate intervention strategies to treat neural structures within the brainstem. Further, it can be used to monitor the progression of disease and its treatment.[3,4]

In Parkinson's disease (PD), the earliest neural degeneration proceeds from the dorsal nucleus of vagus medulla to serotonergic raphe nucleus and nucleus coeruleus of pons and pars compacta of substantia nigra (SN). Pars compacta of substantia nigra (SNc) is the high signal intensity area situated between dorsally-placed red nucleus and ventral low signal areas of pars reticularis of substantia nigra (SNr).[5,6] The diagnostic markers in PD are the diminution and depigmentation of dopaminergic neurons in pars compacta of SN and noradrenergic neurons in locus coeruleus.[7,8]

Though the diagnosis of Progressive Supranuclear Palsy (PSP) is based mainly on the clinical criteria, the imaging marker of PSP is the midbrain atrophy. In patients with PSP, brain appears grossly normal or shows mild atrophy. Atrophy is the most prominent in posterior fossa structures. The SN can be mildly hypopigmented. Most characteristic visual symptom is difficulty in voluntary vertical movement of eye, often downward, but sometimes only upwards.[9–11]

Analysis of the morphometric measurements of superior cerebellar peduncle (SCP), middle cerebellar peduncle (MCP), pons (P), midbrain (M), and infratentorial structures revealed them to be sensitive and specific in more than 80% of cases. MCP/SCP and P/M ratios were significantly higher in PSP patients than PD patients. Among parameters like the midbrain area, the ratio of pons versus midbrain area, and the midbrain area are the most accurate and diagnostic markers in terms of distinguishing between PSP and PD. There is ample evidence in the literature which highlights decrease in the thickness of SN in PD and atrophy of midbrain in PSP.[12,13]

The accurate clinical diagnosis of PD based on motor symptomology alone is subjected to errors because of the wide spectrum of associated neurodegenerative diseases. Thus, the crucial morphometric details of brain by neuroimaging in association with clinical symptomatology help to differentiate various neurodegenerative diseases. The present study highlights brainstem morphometric differences between a few PD patients and healthy control individuals using standard MR imaging. It emphasises on the value of morphometric changes in brain structure in normal individuals and their application in the detection and diagnosis of neurodegenerative disorders.

Materials and Methods

Source and collection of data

Our Institutional ethical clearance committee (wide reference no. IEC 512/2014) approved the study proposal. Departments of Anatomy and Neurology were permitted to retrospectively access the medical records of patients diagnosed with PD and PSP from 2011 to 2015.

MR images of 100 patients were considered for the evaluation of midbrain profile. Control group comprised of 50 patients with normal brain parameters (37 men and 13 women aged between 50 and 70 years) but admitted for diseases other than neurological problems. Another 47 cases include, clinically diagnosed patients of classical PD and PSP. Images of patients with head injuries, cerebrovascular accidents, and any space occupying in brain were excluded from the study.

MRI analysis of the midbrain

All cases were studied with 1.5-T units (GE Medical Systems, Milwaukee). In the study, 4- or 5-mm thick

midsagittal images were obtained with the field of view measuring 24 cm. T1-weighted images (repetition time; TR = 1000/echo time; TE = 30) were obtained. For quantitative planimetric evaluation of areas, we used an image analyser and a computerised interpretation programme. While acquiring the sagittal images, the midsagittal image was taken from an axial image at the level of the midbrain that passed through the centre of the interpeduncular cistern and the centre of the aqueduct. Images were transferred to the workstation belonging to the MR unit. Axial images of the midbrain at the centre mammillary body were considered for the measurement of SN thickness. In the axial plane, the SN appeared as a crescent-shaped region. The area of the midbrain was traced by plotting the broken lines above the inferior and superior pontine notch. The measurements were analysed thrice for each image, and the mean values of those measurements were used in the statistical analysis.

MR images were analysed and evaluated retrospectively under a radiologist's guidance. The following six parameters were evaluated in the MR images:

1. Figure 1 illustrates the reference points taken to measure the anteroposterior diameter of the midbrain at superior colliculus level (measured from the interpeduncular fossa to the anterior margin of the cerebral aqueduct), and maximum antero-posterior diameter of pons was measured at mid-pontine level (measured on the ventral surface of the pons midway between the midbrain and medulla oblongata to the floor of the fourth ventricular).
2. Areas of midbrain and pons were calculated on midsagittal images as the area enclosed by the polygon drawn around their boundaries (Figures 2 and 3).
3. The superior profile of midbrain was observed from the midsagittal MR images and classified as convex, concave, or flat (Figure 4).
4. Thickness of SN – pars compacta measured as a hyperintense band anterior to red nucleus (Figure 5).
5. Interpeduncular distance (Figure 6A), width of cerebral crus (Figure 6B), concavity of lateral border of tegmentum (Figure 6C), and width of middle cerebellar peduncle (Figure 6D) were measured on axial sections.
6. Images were also observed for hyperintensities in pons and atrophy in cerebellum. Hyperintensities appeared as bright areas. Two most common patterns of cerebellar atrophy were sought.

Results

Table 1 depicts the demographic details of the study groups. The average age of MR image examination among the control group was higher among the males. Nearly half of the male patients with PD belonged to the age group of 61–70 years, while the 42% of female patients were between 51 and 60 years. Most patients with PSP belonged to advanced ages (more than 70 years).

Table 2 shows the measurement of various parameters of brainstem profile. The mean anteroposterior diameter was highest among the patients with PD (1.11 ± 0.1 cm) and least in PSP patients (0.98 ± 0.2 cm). Among the three disease groups, the area of midbrain was the least in the PSP group. Thus, PSP patients had the least anteroposterior diameter as well as area of midbrain. The average anteroposterior diameter and the mean area of pons was more in PD patients. The ratio of the midbrain to that of pons was the least in PSP patient. A gradual increase was observed in PD patients and in the control (healthy) individuals. Thus, the ratio of the midbrain area versus pons area increases with the decrease in the area of pons (see Table 3).

The midbrain superior profile in midsagittal section of MR images are sensitive and specific in midbrain atrophy. In

Figure 1: Reference points taken to measure the anteroposterior diameter of the midbrain at superior colliculus level; maximum antero-posterior diameter of pons was measured at mid-pontine level.

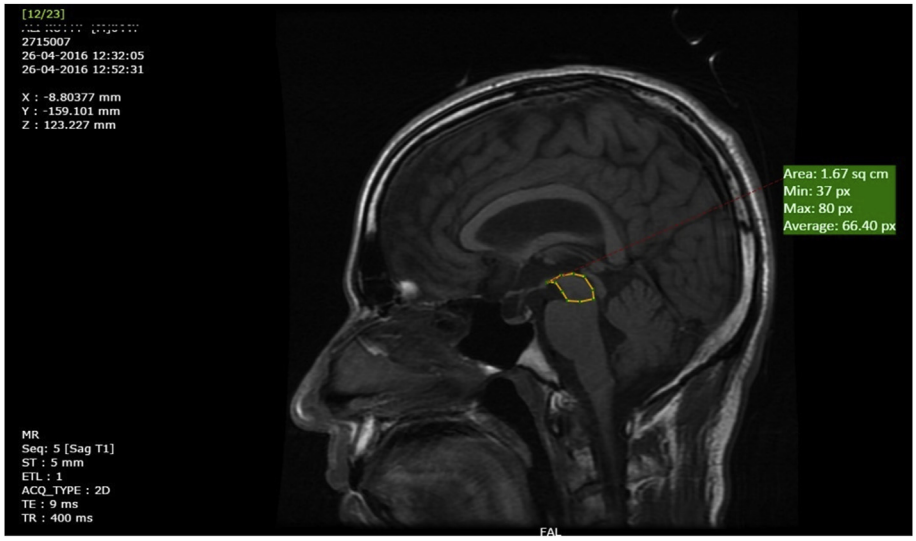

Figure 2: Areas of the midbrain in midsagittal images as the area enclosed by the polygon drawn around their boundaries.

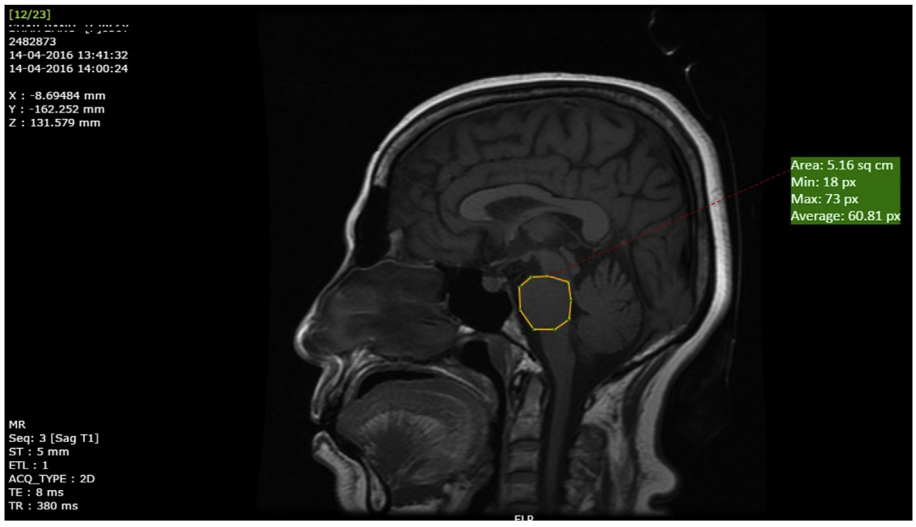

Figure 3: Areas of pons in midsagittal images as the area enclosed by the polygon drawn around their boundaries.

control individuals, the superior profile was convex (78% of patients) to flat (20% of patients), but the superior profile was flat in most of the cases of PD and PSP (Graph no 1).

Mean thickness of pars compacta was more among the control group individuals on both sides when compared to those with neurodegenerative diseases (Right side: 0.49 ± 0.33 cm and left side 0.52 ± 0.35 cm). Compared measurement of the thickness of pars compacta on the right side in PD and PSP groups showed that the width of SN gradually reduced in PD patients and more so in PSP patients.

Midbrain tegmentum has an important diagnostic value in differentiating PSP and PD as the tegmentum is composed of fibres and numerous nuclear masses. As the degeneration begins from the tegmentum, measurement of the concavity on right and lateral sides of tegmentum of midbrain is considered the most important. The concavity on the sides of midbrain tegmentum was more in patients with PD. Mean interpeduncular distance was the least among control individuals (0.8 ± 0.06 cm) and maximum among patients with PSP (0.86 ± 0.1 cm). The width of the right and left crura of midbrain was significantly reduced in size in PSP than in PD patients. The mean thickness of right and left side middle cerebellar peduncle was larger in PD patients than other groups.

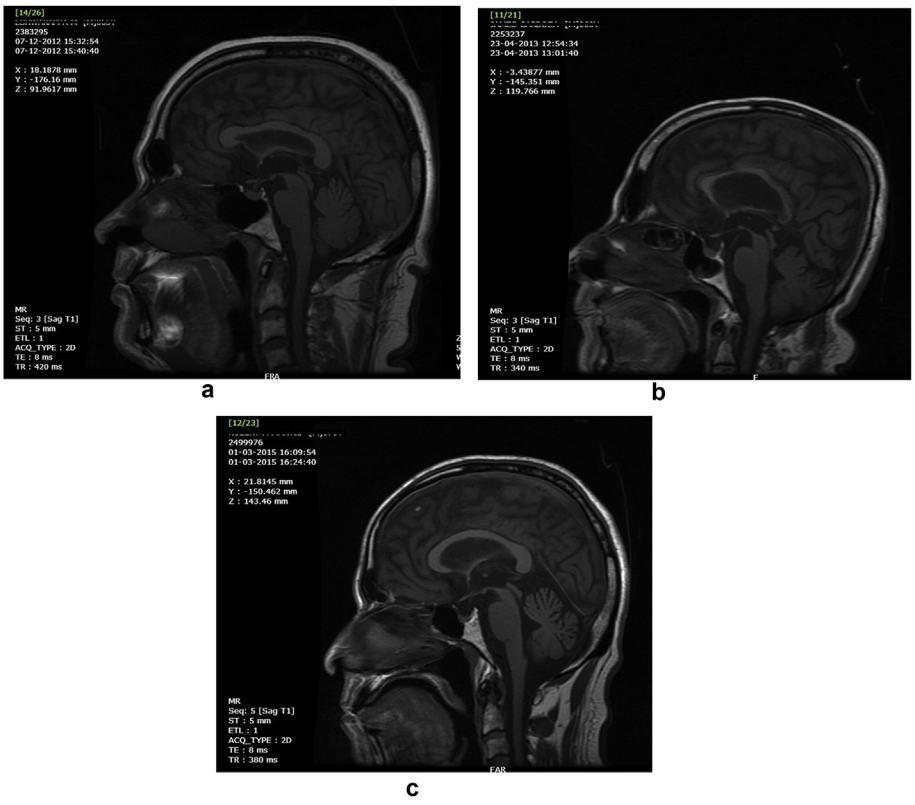

Figure 4: The superior profile of midbrain in midsagittal MR images classified as convex (4a), concave (4b), and flat (4c).

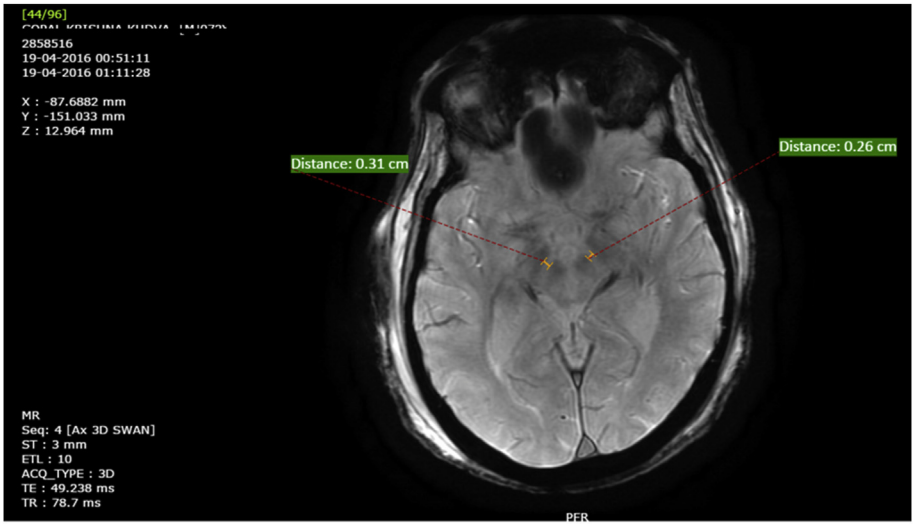

Figure 5: Thickness of pars compacta of substantia nigra measured as a hyperintense band anterior to red nucleus.

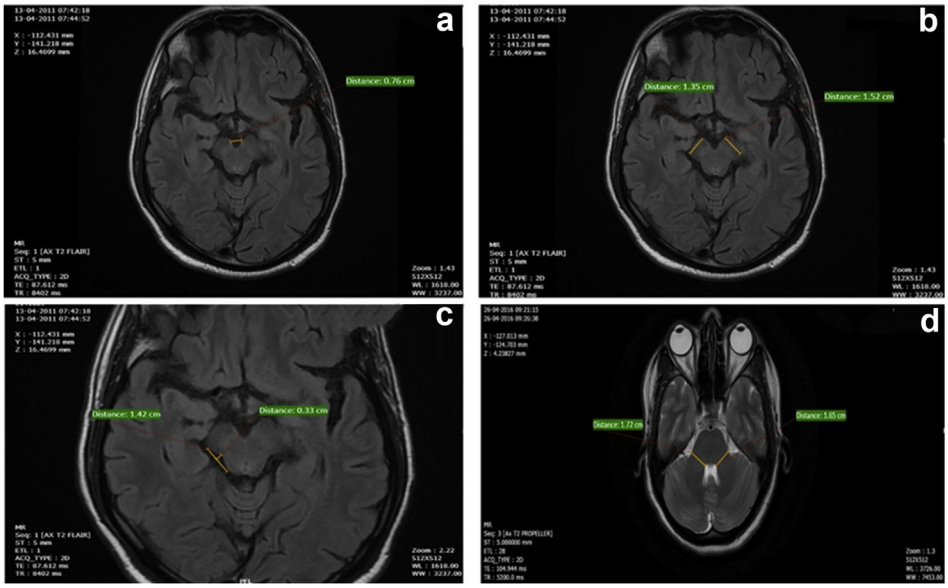

Figure 6: Interpeduncular distance (6a), width of cerebral crus (6b), concavity of lateral border of tegmentum (6c), and width of middle cerebellar peduncle (6d) were measured on axial sections.

Table 1: Study groups – demographic details.

Variable	Control (n = 50)	PD (n = 35)	PSP (n = 12)
Males	37	28	10
Females	13	7	2
Average age at MR examination (male)	54 ± 12.1	64.37 ± 10.50	65.4 ± 4.3
Average age at MR examination (female)	45 ± 6.7	58 ± 12	68.5 ± 14

Table 2: Comparison of measurements in different brain structures of PD and PSP patients with aged, healthy (control) individuals.

Parameters	Control (n = 50)	PD (n = 35)	PSP (n = 12)
AP diameter of midbrain	1 ± 0.15	1.11 ± 0.10	0.98 ± 0.20
AP diameter of pons	2.18 ± 0.19	2.25 ± 0.15	2.21 ± 0.11
Area of midbrain	1.45 ± 0.30	1.23 ± 0.30	1.06 ± 0.34
Area of pons	5.11 ± 0.46	5.14 ± 0.57	5.04 ± 0.55
Midbrain area/pons area	0.28 ± 0.11	0.24 ± 0.05	0.21 ± 0.06
Right cerebral crus width	1.38 ± 0.12	1.38 ± 0.21	1.24 ± 0.17
Left cerebral crus width	1.39 ± 0.14	1.35 ± 0.19	1.19 ± 0.13
Interpeduncular distance	0.84 ± 0.06	0.84 ± 0.11	0.86 ± 0.13
Concavity of right cerebral crus	0.24 ± 0.08	0.29 ± 0.05	0.24 ± 0.08
Concavity of left cerebral crus	0.22 ± 0.06	0.21 ± 0.15	0.23 ± 0.07
Thickness of pars compacta (R)	0.40 ± 0.05	0.34 ± 0.07	0.36 ± 0.05
Thickness of pars compacta (L)	0.42 ± 0.07	0.35 ± 0.08	0.34 ± 0.08
Right MCP width	1.38 ± 0.17	1.59 ± 0.15	1.46 ± 0.14
Left MCP width	1.39 ± 0.14	1.61 ± 0.15	1.47 ± 0.12

Table 3: Other parameters observed in patients of PD and PSP with aged healthy (control) individuals.

Other parameters	Control (n = 50)	PD (n = 35)	PSP (n = 12)
Cerebellar atrophy	1	3	2
Hyperintensity	0	5	0

We did not find cerebellar atrophy in control individuals. In the other groups, cerebellar atrophy was noted in 8.57% and 16.66% of PD and PSP patients, respectively.

Discussion

Although previous authors found a decreased average AP diameter in both brainstem segments, in the present study, no such changes were observed except in the midbrain area. This discrepancy could be due to the measurement methods especially considering that we measured on axial sections of the midbrain perpendicular to its main axis (Table 2). Significant reduction in the thickness of SN was observed in PD patients compared to control individuals. In general, the reduction in AP diameter of the midbrain is mainly due to the atrophy of either SN or red nuclei/both.[14–16] In the present study, characteristic alterations in the midbrain superior profile in midsagittal sections of MR images were observed. In more than 40% of PD patients, the superior profile of midbrain was either flat or concave. This could be due to neuronal loss in the mesencephalic nuclei in this area with substantial atrophy of medial fasciculus because these structures are located in the cranial as well as the dorsal portions of the midbrain.[13,17]

MRI findings in PD patients

MR imaging showed different signal intensities of SN with different MRI contrast. In conventional sequences, the SN appears as an area of high signal intensity. Few studies correlated the reduction in the width of SNc to the Unified Parkinson's Disease Rating Scale. In this regard, the measurement of SNc width may not be a reliable marker to grade motor deficits.[18] Hutchison and Raff (2000) described a new method which could be used for imaging and quantifying the changes in the morphology of the SN in PD, i.e. by comparing radiologic findings with clinical evaluation.[19]

Imaging of SNc showed loss of signal in a lateral to medial gradient in cases of PD, corresponding to an unknown pattern of neuronal degeneration. Visual inspection of the images confirmed that the SNc degenerates in both directions, i.e. from lateral-to-medial as well in anterior-to-posterior directions. For a patient with advanced-stage PD, there was a considerable signal loss and thinning of the SNc in the medial segments of the upper section whereas the lower section showed severe thinning.[8]

Morikawa and his co-workers (1992), analysed the width of SN in patients with PD and found that the mean calculated values of the width of SN were 2.95 ± 0.51 mm in control individuals and 2.68 ± 0.99 mm in PD patients on long TE images ($p < 0.01$). They measured the width of SNc, volume of putamen, and intensity of basal ganglia. These areas are rich in iron. They also found increased iron levels in dentate nuclei and red nuclei.[20] Several authors showed that oxygen radicals are generated due to an increase in iron content. When the concentration of iron in the brain increases, it produces local heterogenecity. These heterogenecities appear as areas of signal loss in T2 images. Thus, areas of iron deposition can be mapped on T2-weighted images as hypointense or dark areas.[21]

Reimao (2017) showed that iron accumulation increases significantly in pars compacta of SN in patients with PD. Further, the mean age of their patients' group was 66.7 ± 8.5 years and that of control group was 57.19 ± 9 years. Thus, it can be concluded that in advanced diseases of PD, atrophy of SN is easily seen in the axial sections of midbrain as decreased width of the relatively hyperintense band in T2-weighted images. Decreased width of SNc is attributed to both loss of neurons as well as increased iron deposition in SNr.[22] Patients could undergo serial MRI examination technique so that the presymptomatic stage of PD could be detected. Reduced thickness of SN can also be observed in MRI of patients with Parkinson's plus syndromes.

MRI findings in Progressive Supranuclear Palsy (PSP)

Atrophy of the midbrain is well appreciated in the midsagittal image sections in patients with PSP. Extension of the atrophy also extends to the diencephalon region. This causes the third ventricle to get enlarged. In radiological images, atrophy can be observed in the form of decreased anteroposterior diameter of midbrain, decreased area of midbrain, decreased ratio of midbrain area versus pons area.[17,23] Reduction of anteroposterior midline midbrain diameter causes 'mickey mouse' appearance on axial sections at the level of superior colliculi. This appears as increase in the concavity of the lateral margin of tegmentum. It is also described as 'morning glory sign,' as the lateral border of tegmentum resembles the lateral view of freshly-blossomed morning glory flower.[24] Atrophy of the midbrain causes the superior outline to become gradually flat, and in severe cases, it also becomes concave. It is caused by significant loss of neuronal mass and the fibre tracts which in turn results in total atrophy of the midbrain parenchyma. This is described as the 'humming bird sign' or 'penguin sign.' Histological studies showed severe loss of nuclear masses in the periaqueductal gray matter of the midbrain.[24]

Quattrone (2008) studied MR images of patients with PD and PSP. They assessed the diagnostic accuracy of various MR imaging morphometric details of midbrain, pons, MCP, and SCP to differentiate the aforementioned PDs. Significant reduction of the midbrain area and SCP width was noted in patients with PSP when compared with PD patients and control individuals.[17]

Andrea Righni (2004) studied the superior profile of the midbrain, atrophy of the midbrain, and the hyperintensities in tegmentum in T1-weighted image. They found abnormal superior profile of the midbrain, 68% sensitive and 77.7% specific, and tegmental hyperintensity was 100% specific. Thus, they described abnormal superior profile of the midbrain to be the most distinctive feature that differentiates PSP from PD.[13]

The investigations related to variations in the brainstem regions in relation to age and sex are still controversial. Antar and his colleagues noted that changes in the volumetric analysis of brainstem in MR images depends on regional factors, genetic factors, and the slice thickness. They also mentioned that there were no significant changes observed in brainstem morphometry based on age and sex.[25] The neuroimaging and postmortem studies on brain sexual

dimorphism revealed that the male brain is approximately 10% larger across all ages. However, the morphometric differences in both sexes in brain could be due to the subcortical nuclear masses like corpus callosum, amygdala, caudate nucleus, hippocampus, and cerebellum.[26,27] Murshed and his coworkers found no significant differences in brainstem measurements in either sex in a individuals aged 13–50 years. Between 51 and 77 years, the whole brainstem area was larger in males. They also mentioned that there were no significant differences of whole brainstem dimensions across all age groups.[27]

Conclusion

Accurate morphometric evaluation of the brainstem parameters by MR imaging helps us to compare the anatomical details in healthy, aging individuals and their variations in those with neurodegenerative diseases. As each neurodegenerative disease affects some specific brainstem structure, such data can be used for accurate diagnosis when combined with clinical data.

Source of funding

This project did not receive any specific grant from funding agencies in the public, commercial, or non-profit organisations.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This study was approved by institutional ethical committee wide approval letter IEC 512/2014, Dated 10th September 2014.

Authors' contributions

RKV designed, analysed and the interpreted data, conceptualisation, supervision of the image analysis and validation. AV conducted research, data collection. ASD provided the methodology, reviewed, and edited. MH provided logistical support, reviewed, and edited. LCP designed the study, project administration, supervision, and wrote final draft of the article. All authors critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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How to cite this article: Rajagopal KV, D'Souza AS, Verma A, Mamatha H, Prasanna LC. Comparative morphometric evaluation of the brainstem in neurodegenerative diseases with healthy individuals using magnetic resonance imaging. J Taibah Univ Med Sc 2022;17(1):87–95.