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Original Article

Radiology Section

Effect of Ageing on Midbrain to Pons Area Ratio using MRI: A Cross-sectional Study

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ABSTRACT

Introduction: There is brainstem atrophy with normal ageing. It is pertinent to determine, if this atrophy with ageing, is associated with significant alteration in the midbrain to pons ratio.

Aim: To determine size and ratio of midbrain and pons area among adults and elderly.

Materials and Methods: This cross-sectional, analytical study was done in a tertiary care hospital, S Nijalingappa Medical College, Bagalkot, Karnataka, India from January 2022 to March 2022, including 200 apparently healthy adult and elderly participants. They were divided into two groups, 100 men (M1 ≤50 years and M2 >50 years) and 100 women (F1 ≤50 years and F2 >50 years). Each underwent multiplanar T1 Magnetic Resonance Imaging (MRI) of the brain. An experienced Radiologist identified midsagittal image, and measured midbrain and pons areas on that image. Mean and standard deviations of midbrain and pons area and midbrain to pons area ratio was estimated for each of the groups. Independent Sample t-test was used to determine significance of differences between groups.

Results: A total of 200 participants were included in the study with mean age of 51 years and 3 months. The midbrain to pons area ratio among M2 and F2 groups ranged from 0.20 to 0.39, and in M1 and F1 groups it ranged from 0.23 to 0.47. Midbrain areas and midbrain to pons area ratio were significantly more among participants aged ≤50 years among both males (p-value=0.014 and 0.024) and females (p-value=0.011 and 0.032) in comparison with participants aged more than 50 years.

Conclusion: Midbrain to pons area ratio decreases significantly in older age, and hence, age needs to be accounted for, while interpreting the ratio.

Keywords: Brainstem atrophy, Magnetic resonance imaging, Morphometry of brainstem, Parkinson's, Progressive supranuclear palsy

INTRODUCTION

Brainstem harbours many important centres related to corticospinal reflexes, cranial nerve nuclei and various tracts. It is well known, that there is gradual atrophy of brainstem with age [1]. The pattern of brainstem atrophy can provide vital clues to the psychomotor signs and symptoms of ageing and thus, adding to the pathophysiology of ageing [2]. Midbrain-pons ratio has been used as an imaging marker for diagnosing Progressive Supranuclear Palsy (PSP) and other Parkinson's spectrum of diseases [3]. Studies have found that in PSP, the midbrain-pons ratios were equal to or less than 0.23-0.21 [4,5]. Alterations in midbrain-pons ratio indicate asymmetric atrophy of brainstem, the lesser the ratio, more severe the midbrain atrophy relative to pons. There are instances where the cut-off values defined, overlap with that of individuals without clinical manifestations of Parkinson's and plus syndromes, especially in elderly. Further, there is scant literature comparing midbrain to pons area ratio between elderly and young and middle aged adults. The pattern of alteration of the ratio, if any, can help in understanding the clinical manifestations of ageing better.

In this context, the present study was done to assess whether there was significant differences in sizes and ratios of midbrain and pons areas among adults and elderly.

MATERIALS AND METHODS

This cross-sectional, analytical study was done in a tertiary care hospital of S Nijalingappa Medical College, Bagalkot, Karnataka, India, from January 2022 to March 2022, including 200 apparently healthy adult and elderly participants. Ethical clearance was taken from Institutional Ethical Committee. Informed consent was taken from each participant at the time of enrolment into the study.

Sample size calculation: Sample size was determined by using the formula for comparing means.

$$N=2(Z_{\alpha/2}-Z_{\beta})^2\ \sigma^2/d^2\ [6],$$

where N is sample size, $Z_{\alpha/2}$ and Z_{β} are constants and for confidence level 95% and power of 80% they are 1.96 and 0.84 respectively, σ is population standard deviation (0.15- based on pilot study) and d is difference in mean values expected. The value obtained was approximately 160 after catering for all the study variables. Hence, a final sample size of 200 was considered for final analysis.

Of the 200 participants, 100 were males and 100 were females. They were further divided into two groups, each consisting of participants below 50 years and above 50 years of age. Overall four groups consisting of 50 participants each, were part of the study and were designated as:

- M1 (Male between 18 to 50 years),
- M2 (Males>50 years),
- F1 (Females between 18 to 50 years) and
- F2 (Females > 50 years).

Inclusion criteria: Patients presenting to Radiology Department for indications like headache, trauma, pain abdomen, gynaecological disorders etc. which were unlikely to affect the brainstem, were considered for inclusion. Further, only those fulfilling criteria of any of the four groups were included in the study, subject to maximum of 50 participants per group.

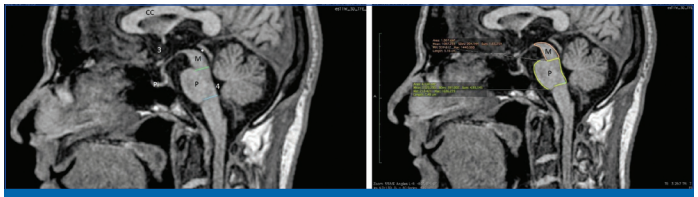
Exclusion criteria: Patients with signs of dementia (Diagnostic and Statistical manual of Mental disorders- DSM 5 criteria) [7], Parkinson's and plus syndromes including PSP and Multiple System Atrophy (MSA) [8,9] assessed by an experienced Psychiatrist, were excluded from the study. Participants found to have organic intracranial abnormalities on imaging were also excluded.

Procedure

Patients who found to have significant cerebral and brainstem gliosis, encephalomalacia and severe cerebral and brainstem atrophy as reported by loss of contour, enlarged ventricles and sulci on MRI of brain done with 1.5 Tesla Philips Multiva MRI scanner were not considered for the study. Also an axial plane Fluid Attenuation Inversion Recovery (FLAIR) sequence was done to screen for abnormalities.

A thin slice multiplanar Fast Field Echo T1 (FFE T1) weighted sequence was run in sagittal plane, which was planned parallel to the Corpus Callosum and Falx Cerebri on axial FLAIR images. The parameters used for T1 FFE were TR (Repetition Time)- 7.1 milliseconds, TE (Time to Echo)- 3.2 milliseconds, Slice thickness- 1 mm with 0 slice gap, number of signal averages- 1, Acquisition matrix- 256×232.

All the T1 FFE datasets were anonymised and made available on Osirix application for analysis. A Radiologist with 8 years of experience in neuroimaging viewed the images and identified midsagittal image in which corpus callosum, third and fourth ventricles, aqueduct, tectum and pituitary gland were visualised. On this image, a horizontal line was drawn from superior pontine notch, anteriorly to quadrigeminal plate, posteriorly was regarded as midbrain–pons junction [Table/Fig-1]. Midbrain was traced [Table/Fig-2] above this line, using closed polygon measurement tool. Another line at the level of inferior pontine notch and parallel to the first line was considered as ponto-medullary junction and pons was traced in between the two lines [10,11]. The midbrain to pons area ratio values obtained were tabulated and ratio of the areas were calculated.



[Table/Fig-1]: T1 weighted mid-sagittal image of the brain depicting midbrain-pons junction (Green line) and ponto-medullary junction (Blue Line).
[Table/Fig-2]: Racing of midbrain (Orange line) and pons (Yellow line) image in a T1 weighted mid-sagittal image.
M: Midbrain; P: Pons; (Images from left to right); M: Midbrain; P: Pons; CC: Corpus callosum; 3-III ventricle; 4-IV ventricle; *-Cerebral aqueduct of sylvius; Pi: Pituitary gland

STATISTICAL ANALYSIS

The data was entered and further analysed using the Statistical Package for Social Sciences software (SPSS) version 23.0. Mean and standard deviations of the area measurements of midbrain and pons and midbrain-pons area ratio were estimated for each of the groups, males and females. Further Independent sample t-test was used to determine whether the differences of values between groups and males and females were significant at 95% confidence limits. A p-value <0.05 is considered to be statistically significant.

RESULTS

A total of 200 participants were included in the study with mean age of 51 years and 3 months (SD-10 years 1 month). The mean midbrain to pons ratio among M2 and F2 groups was 0.27 in each group with values varying from 0.20 to 0.39. Ratio of 0.20 was seen among participants aged above 80 years. Similarly, in M1 and F1 groups the mean ratios were 0.37 and 0.35 respectively, (range=0.23 to 0.47), the highest corresponding to a person aged 45 years [Table/Fig-3].

As can be ascertained from [Table/Fig-3,4] midbrain areas and midbrain to pons area ratios were significantly more among participants aged ≤50 years among both males (p-value=0.014 and 0.024) and females (p-value= 0.011 and 0.032) in comparison with participants aged more than 50 years. The areas of pons showed no significant difference among any of the groups. There was no significant difference between males and females in general in any of the measured parameters.

Group	Age range (mean)	Gender	Number of participants	Area of midbrain (mm^2) Mean (SD)	Area of pons (mm^2) Mean (SD)	Midbrain to pons area ratio Mean (SD)
M1	18-50 years (33 years 1 month)	Males	50	162.51 (23.11)	433.28 (48.86)	0.37 (0.04)
M2	>50 years (69 years 8 months)	Males	50	122.54 (16.86)	444.32 (45.85)	0.27 (0.04)
F1	18-50 years (35 years)	Females	50	155.52 (22.97)	447.94 (50.52)	0.35 (0.05)
F2	>50 years (67 years 3 months)	Females	50	117.06 (19.06)	434.88 (52.43)	0.27 (0.04)
All males (M1+M2)	Above 18 years (51 years 4 months)	Males	100	142.53 (19.99)	438.8 (47.36)	0.32 (0.04)
All females (F1+F2)	Above 18 years (51 years 1 month)	Females	100	136.29 (21.02)	441.41 (51.48)	0.31 (0.04)
All groups (M1+M2+ F1+F2)	Above 18 years (51 years 3 months)	Both males and females	200	139.41 (20.51)	440.1 (49.42)	0.32 (0.04)

[Table/Fig-3]: Mean values and standard deviations of study variables.

Comparison groups	Midbrain areas p-value	Pons areas p-value	Midbrain to pons area ratio p-value
M1 and M2	0.014*	0.342	0.024*
F1 and F2	0.011*	0.121	0.032*
M1 and F1	0.174	0.087	0.484
M2 and F2	0.245	0.169	0.512
Males and females	0.198	0.476	0.543

[Table/Fig-4]: Comparison of means for significance of difference.
Independent t test was used. *Significant p-values; M1: Males between 18 to 50 years of age; M2: Males above 50 years of age; F1: Females between 18 to 50 years of age; F2: Females above 50 years of age; p-value <0.05 considered significant

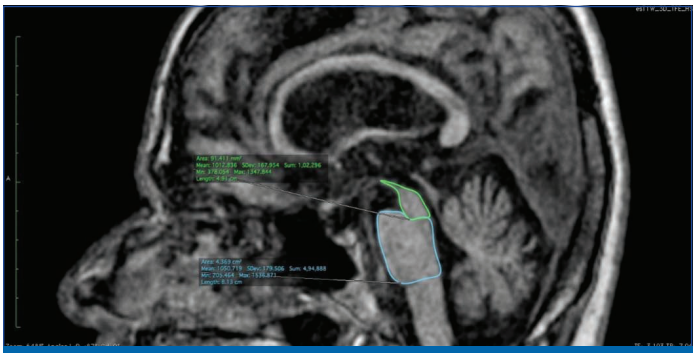
DISCUSSION

The midbrain to pons area ratio were found to decrease with advancing age. In terms of sample size, the present study enrolled 200 participants which is higher than similar studies [4,5,12].

Midbrain and Pons areas and ratio: Rajagopal KV et al., found mean midbrain and pons areas in mid-sagittal image to be 1.45 and 5.11 sq cm respectively among apparently normal controls which are similar to the values obtained by Morelli M et al., (1.42 and 5.28 sq cm respectively among control group) [4,12]. In the present study, though the midbrain area (1.39 sq cm) obtained is similar, pons area values (4.4 sq cm) obtained were lower than the quoted studies. The plausible reasons could be heterogeneity of age groups of participants and the larger sample size in the present study. Midbrain to pons area ratios obtained by Rajagopal KV et al., (0.28) and Morelli M et al., (0.27) among control groups are in concurrence with that of present study (0.32) [4,12].

Midbrain to pons area ratio with ageing and PSP: A significant and interesting observation in the present study, was that the reduced value of midbrain to pons area ratio among elderly, was due to significantly smaller size of midbrain, as pons showed similar sizes among all the groups. This suggests, that with ageing there is midbrain atrophy with near normal pons even in the absence of Parkinson's, PSP or MSA, though the extent of midbrain atrophy may be severe in the later conditions as suggested by low values of midbrain to pons ratios. Cui SS et al., found midbrain to pons area ratio of 0.21 in PSP [5]. Similarly Morelli M et al., found the

values in the range of 0.13-0.23 whereas Oba H et al., found ratios of less than 0.16 in PSP [4,10]. Values close to 0.20 were seen in few apparently normal individuals, aged above 80 years of age in the present study [Table/Fig-5]. The myth of symmetric brainstem atrophy with ageing in otherwise normal individuals is thus negated. This also, enhances the importance of determining midbrain to pons ratio accurately in suspected PSP, Parkinson's and other associated diseases. Thus, age is an important factor, to be considered everytime the ratio is interpreted.



[Table/Fig-5]: T1 weighted mid-sagittal image of a 80-year-old male with midbrain-pons area ratio of 0.21.

Limitation(s)

Only effect of ageing on midbrain and pons ratio was determined and not compared with changes observed in PSP and other Parkinsonian syndromes. Midbrain to pons areas measured in a single midsagittal plane, may not be true representation of their actual sizes in contrast to volume measurements.

CONCLUSION(S)

Midbrain to pons area ratio decreases significantly in older age and hence, age needs to be accounted for, while interpreting the ratio. The decrease in ratio was a result of significant midbrain thinning and near normal pons.

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