

Pontine Diameter in MRI- A Tool for Early Diagnosis of Multiple System Atrophy (MSA)

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ABSTRACT

BACKGROUND

As clinical features of degenerative Parkinsonism can overlap, early differentiation of MSA is difficult. So, we studied pontine diameter in patients of Multiple System Atrophy in comparison with other causes of Degenerative Parkinsonism [(Progressive Supranuclear Palsy (PSP), Parkinson's disease, Corticobasal syndrome (CBS))] as a tool for early diagnosis of MSA. We wanted to investigate the usefulness of pontine diameter in midsagittal sections of MRI for differentiation of MSA from neurodegenerative parkinsonism.

METHODS

Patients who presented to the neurology department with clinical features of degenerative Parkinsonism were included; 120 patients who met the inclusion criteria underwent MRI imaging in a 1.5 tesla machine and midsagittal T1 images were read to obtain pontine diameter. Comparison was made between pontine diameter of MSA (n=30) with Progressive Supranuclear Palsy (n=30), Parkinson's disease (n=30) and Corticobasal syndrome (n=4).

RESULTS

Mean age of onset in MSA is 58.63 with a SD of 3.891. Mean age of patients in progressive supranuclear palsy is 59.47 with a standard deviation of 3.86. Mean disease duration in PSP was 2.97 with an SD of 1.035; whereas, the disease duration was higher in MSA and PD with a mean of 3.56 and 3.96 respectively. In multiple system atrophy, the mean pontine diameter was 14.96 with an SD of 0.88. Mean pontine diameter is lower in MSA when compared to other groups and is statistically significant ($p < 0.001$). This shows that pons is significantly atrophied in MSA when compared to other parkinsonian syndromes.

CONCLUSIONS

Pontine diameter is significantly lower in MSA when compared to PSP, PD, CBS and Control Group. So pontine diameter in MRI can be useful tool for differentiating MSA from other causes of degenerative parkinsonism.

KEYWORDS

Magnetic Resonance Imaging, Degenerative Parkinsonism, Pontine Diameter

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BACKGROUND

Multiple system atrophy (MSA) is a neurodegenerative Parkinson plus syndrome with clinical features of Parkinsonism, cerebellar, pyramidal and autonomic dysfunction.¹ Prevalence of MSA ranges from 1.86 to 4.9 cases/1 lakh.² Early differentiation from other Parkinson plus syndromes by clinically can be challenging. Differentiation of various degenerative Parkinsonism is important for number of reasons, including differences in natural history, Patient counselling and treatment response. Recent advances have revealed novel targets for potentially disease modifying therapy in MSA. Shulz, Martin Skalej, Dirk Wedekind et al, Magnetic resonance imaging-based volumetry differentiates idiopathic parkinson s disease from multiple system atrophy and progressive supranuclear palsy. For starting; disease modifying therapy early differentiation between MSA and other neurodegenerative Parkinsonism is important, Variants of MSA includes MSA-C (cerebellar), MSA-P (parkinsonism) and MSA-A (autonomic). Patients with predominant cerebellar dysfunction and predominant Parkinsonism are designated as MSA-C and MSA-P respectively.³

Even though hot-cross bun sign and hyperintense putaminal sign considered as a feature of MSA,⁴ it can be found in other forms of parkinsonism and these features are seen in only late stages of MSA.⁵ So we conducted a study to assess the usefulness of pontine diameter in MRI in patients of MSA and compared it with other conditions causing neurodegenerative Parkinsonism.

METHODS

This descriptive study was conducted in the Department of Neurology of Government Medical College Kottayam, a tertiary care institution in Kerala, India. Recent advances have revealed novel targets for potentially disease modifying therapy in MSA. The study was approved by the Scientific Review Committee and Institutional Ethics Committee.

Sample size was calculated by the formula

$$N = \frac{-2[Z_{\alpha/2} - Z_{1-\beta}]^2 \sigma^2}{D^2}$$

$Z_{\alpha/2} = 1.96$
 $Z_{1-\beta} = 0.842$
 $\sigma^2 =$ the standard deviation
 $D =$ margin of error

$$N = \frac{2(1.96+0.842)^2 \cdot 0.75}{0.6 \times 0.6}$$

$$N = \frac{11.76}{0.36}; N = 31.$$

Total size required for all groups = $4 \times 31 = 124$

Study Tools

1. Case record
2. Investigation reports.

Inclusion Criteria

Patients with clinical features of multiple system atrophy, Progressive supranuclear palsy, Idiopathic Parkinson's disease, Corticobasal degeneration were included as cases. Differentiation of various degenerative Parkinsonism is important for number of reasons, including differences in natural history, Patient counselling and treatment response. Recent advances have revealed novel targets for potentially disease modifying therapy in MSA. Control population included those who had taken MRI for other reasons attending neurology outpatient department and those who are admitted in neurology ward are enrolled in the study.

MSA

Probable MSA²- A sporadic, progressive, adult (>30 yrs.)-onset disease characterized by autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mmHg diastolic blood pressure and Poor levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction).

Possible MSA- A sporadic, progressive, adult (>30yr)-onset disease characterized by autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mm Hg diastolic blood pressure and Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) and A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction).

PSP

- Mandatory Inclusion Criteria
- Possible PSP
 - Gradually progressive disorder
 - Onset at age 40 or later
- Either vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with tendency to fall in the first year of disease onset.
- No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria.
- Probable PSP.
 - Gradually progressive disorder.
 - Onset at age 40 or later.
- Vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with tendency to fall in the first year of disease onset.
- No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria.

- Definite PSP
- Either possible or probable PSP with a clinicopathological correlation.

Idiopathic Parkinsonism

- Bradykinesia
- Rest tremor
- Rigidity
- Postural instability

Cortico-Basal Syndrome (CBS)

Probable CBS- Asymmetric presentation of two of 1) limb rigidity or akinesia 2) limb dystonia 3) limb myoclonus plus two of 4) orobuccal or limb apraxia 5) alien limb phenomenon 6) cortical sensory deficit.

Possible CBS- May be symmetric presentation of two of 1) Limb rigidity or akinesia 2) Limb dystonia 3) Limb myoclonus plus one of 4) Orobuccal or limb apraxia 5) alien limb phenomenon 6) Cortical sensory deficit.

Exclusion Criteria

1. Patients not giving informed written consent.
2. Patients on psychiatric medications.
3. Claustrophobic patients.
4. Patients with cardiac pacemaker or cochlear implants.

Study Procedure

All scans were performed on a 1.5 T MRI machine using a standard receive and transmit head coil. Mid sagittal T1 weighted images were used to assess the pontine diameter. The maximal measurement perpendicular to the major axis was taken. Technique to assess the diameter is given below with the help of a diagram. Images were reviewed on a BARCO 5 mega pixel image viewer by Dr. Gourisankar MD FRCR (Senior Consultant Neuro-Radiologist), with >15 years of experience, who was blinded to the clinical diagnosis.



Figure 1. A) Midsagittal T1 Image On Conventional MRI. (B) Elliptical Regions Of Interest Were Placed Over The Pons In The Midsagittal Slice

Two lines were drawn to define the major axes of the ellipses, corresponding to oblique superior-inferior axes (thin white lines). The maximal measurement perpendicular to the major axis was taken (thick white lines). In all cases, the posterior border of the pons was clearly identifiable and did not include the pontine tegmentum.

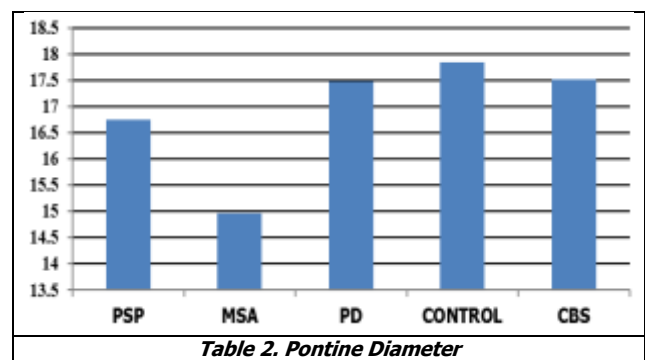
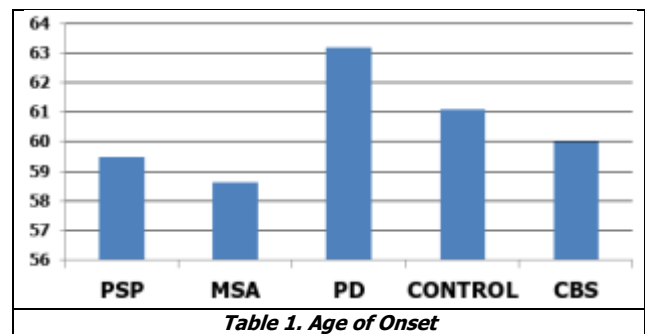
Statistical Analysis

Data was entered in to microsoft excel data sheet and was analyzed using SPSS software.V 20. Quantitative analysis of 5 groups were done using ANOVA with post hoc Tukey correction.

RESULTS

Total of 124 patient cohorts were enrolled in to the study. MSA, PSP,PD and Control group contained 30 patients each whereas only 4 patients with CBS were analysed. Mean age of onset in MSA is 58.63 with a SD of 3.891. Mean age of patients in progressive supranuclear palsy was 59.47 with a standard deviation of 3.86. Mean age of onset in parkinson disease is 63.17 with a SD of 3.270. Incidence of parkinson disease rises 5-10 folds during the sixth decade of life. Mean age of control population is 61.10 with a SD of .397. Mean age of onset in corticobasal syndrome is 60.00 with a SD of 2.160. Mean disease duration was higher in MSA and PD with a mean of 3.56 and 3.96 respectively. Mean disease duration in PSP was 2.97 with a SD of 1.035.

Mean pontine diameter in MSA was 14.96 with a SD of 0.88. Mean pontine diameter in PSP was 16.75 with a SD of 1.314. Mean pontine diameter in PD was 17.48 with a SD of 1.14. Mean pontine diameter in control group was 17.84 with a SD of 0.52. Mean pontine diameter in CBS was 17.52 with a SD of 0.655 . Post hoc tukey analysis showed statistically significant difference in pontine diameter was obtained between MSA and other groups (p<0.05).



Pontine Diameter	Between Groups	149.389	4	37.347	29.704	.000
	Within Groups	149.621	119	1.257		
	Total	299.011	123			

Table 3. ANOVA

Measurement	PSP	MSA	PD	Control	CBS	Anova
Pontine Diameter	16.75 (1.314)	14.96 (0.88)	17.48 (1.15)	17.84 (1.12)	17.52 (0.665)	MSA < PSP, PD, CBS, Control (p<0.001)

Table 4. Post HOC Tukey Analysis

DISCUSSION

MSA is a synucleinopathy like parkinson's disease and dementia with Lewy bodies. The mean age group for MSA is 55.4+8.3 years. Although definitive diagnosis of MSA can only be made by neuropathological criteria, clinical and MRI features can be useful for diagnosis. MRI is a useful diagnostic tool in evaluation of degenerative parkinsonism. Horimoto et al described hotcross bun sign and lenticular nucleus sign in MSA-C and MSA-P respectively.⁶ The cruciform T2 hyperintensity in hot cross bun sign is formed due to selective loss of transverse pontocerebellar fibers and pontine raphe neurons with preservation of pontine tegmentum and corticospinal tracts. Histological section at the level of cruciform signal showed gliosis of middle part of the reticular formation, pontocerebellar fibre between the medial lemniscus, and pyramidal tract and the crossing part of the pontocerebellar fibers at the basis pontis. However these signs are not seen in early disease, so differentiation between various parkinson plus syndromes is difficult. Hotcross bun sign can be seen in other diseases also. Mean age of onset in MSA is usually in the 6 th decade. Mean age of onset in our study was 58.6 years. Age of our patients fit with the the mean age group previously reported. In multiple system atrophy, the mean pontine diameter was 14.96 with a SD of 0.88. Mean pontine diameter is lower in MSA when compared to other groups and is statistically significant (p<0.001). This shows that pons is significantly atrophied in MSA when compared to other parkinsonian syndromes. In the study done by Massey et al, the mean pontine diameter in pathologically proven cases and clinically diagnosed cases were 14.8 and 15.5 mm respectively.⁷ Asato et al study demonstrated caudal pontine diameter of MSA-P and MSA-C patients were 16.3+3.23 and 15.8+2.88 respectively.⁸ Study by Nicoletti et al found that the average MCP width was significantly lower among patients with MSA compared with other groups.⁹ Shultz et al demonstrated significant decrease in mean brainstem and striatal volume in MSA patients.¹⁰ Study by Nicoletti et al demonstrated significantly lower MCP width in MSA patients compared with PD and controls.⁹ Watanabe et al showed atrophy of cerebellar and pontine base with the interval following the appearance of cerebellar symptoms in MSC-C.¹¹ Study by Stephanie Mangesius showed a pontine diameter in MSA of 15.83 against 16.81 and 17.50 in parkinson's disease and PSP respectively.¹² They also showed decreased mean pontine area of 451.62 in MSA compared with 544.50 and 523.08 in Parkinson's disease and PSP respectively. annual whole and regional brain atrophy rates were greatest in pons and cerebellum, reaching values of up to 4.5% and 3.2% atrophy per year.¹³ In a study by A Schrag et al macroscopic pathological examination disclosed considerable atrophy of

the basis pontis and cerebellum. Pontine neurons and myelinated transverse pontocerebellar fibers were severely depleted, resulting in pallor and considerable atrophy of the basis pontis and middle cerebellar peduncles. The fibres of the corticospinal tract, which run craniocaudally in the dorsal pons, pontine tegmentum and the superior cerebellar peduncles ventrally, were all preserved.

Limitations

We used 1.5 tesla machine instead of 3 tesla. Other parameters like pontine area and pontine midbrain ratio were not studied.

CONCLUSIONS

Pontine diameter in midsagittal section in MRI in patients of MSA was significantly lower as compared to other neurodegenerative parkinsonism plus syndromes. (p<0.001). Pontine diameter in MRI can be a useful tool for differentiating MSA from other causes of degenerative parkinsonism.

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