The midbrain to pons ratio

A simple and specific MRI sign of progressive supranuclear palsy

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ABSTRACT

Objectives: MRI-based measurements used to diagnose progressive supranuclear palsy (PSP) typically lack pathologic verification and are not easy to use routinely. We aimed to develop in histologically proven disease a simple measure of the midbrain and pons on sagittal MRI to identify PSP.

Methods: Measurements of the midbrain and pontine base on midsagittal T1-weighted MRI were performed in confirmed PSP (n = 12), Parkinson disease (n = 2), and multiple system atrophy (MSA) (n = 7), and in controls (n = 8). Using receiver operating characteristic curve analysis, cutoff values were applied to a clinically diagnosed cohort of 62 subjects that included PSP (n = 21), Parkinson disease (n = 10), MSA (n = 10), and controls (n = 21).

Results: The mean midbrain measurement of 8.1 mm was reduced in PSP ($p < 0.001$) with reduction in the midbrain to pons ratio (PSP smaller than MSA; $p < 0.001$). In controls, the mean midbrain ratio was approximately two-thirds of the pontine base, in PSP it was <52%, and in MSA the ratio was greater than two-thirds. A midbrain measurement of <9.35 mm and ratio of 0.52 had 100% specificity for PSP. In the clinically defined group, 19 of 21 PSP cases (90.5%) had a midbrain measurement of <9.35 mm.

Conclusions: We have developed a simple and reliable measurement in pathologically confirmed disease based on the topography of atrophy in PSP with high sensitivity and specificity that may be a useful tool in the clinic. *Neurology*® 2013;80:1856–1861

GLOSSARY

MSA = multiple system atrophy; **PD** = Parkinson disease; **PSP** = progressive supranuclear palsy.

Neurodegenerative diseases presenting with parkinsonism including idiopathic Parkinson disease (PD), progressive supranuclear palsy (PSP), and multiple system atrophy (MSA) can be difficult to differentiate clinically particularly early in the disease course.[1] Characteristic midbrain atrophy in PSP and pontine atrophy in MSA can be assessed on MRI[2]; however, many magnetic resonance–based measurements proposed as diagnostic for PSP or MSA lack pathologic verification and are often not easy to apply routinely.[3–9]

Our hypothesis was that simple measurements of the midbrain and pons (or their ratio) on midsagittal MRI would identify confirmed PSP and MSA.

METHODS

Standard protocol approvals, registrations, and patient consents. A pathologically confirmed cohort of PSP, PD, and MSA subjects (table 1) was selected from the Queen Square Brain Bank at UCL Institute of Neurology; brains were donated following ethically approved protocols under license from the Human Tissue Authority. A cohort of PSP, PD, MSA, and healthy subjects was prospectively recruited at the National Hospital for Neurology and Neurosurgery, as part of an ethically approved study with written informed consent.

Participants and protocols. In the pathologically confirmed group, the diagnosis was determined using standard neuropathologic criteria.[10] In the clinically diagnosed group, participants fulfilled operational criteria[11–13] and were assessed with clinimetric scales including Hoehn and Yahr,[14] the Unified Parkinson's Disease Rating Scale,[15] Folstein Mini-Mental State Examination,[16] the Frontal

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Table 1 Demographic and clinimetric features of the pathologically confirmed and clinically diagnosed groups[a]

Measurement	Control	PSP	PD	MSA	ANOVA
Pathologically confirmed group					
No.	8	12	2	7	—
Age at scan, y	66.8 (8.5)	69.5 (5.0)	70.5 (6.2)	58.4 (5.2)[b]	MSA < PSP ($p < 0.001$); MSA < PD ($p < 0.05$)
Disease duration at scan, y	—	3.9 (2.4)	10.7 (9.4)	5.6 (2.9)	NS
Clinically diagnosed group					
No.	21	21	10	10	—
Age at scan, y	65.9 (5.6)	69.4 (6.5)	66.6 (6.0)	63.4 (8.2)	NS
Disease duration, y	—	4.6 (3.1)	7.3 (4.1)	4.9 (2.1)	NS
H&Y	—	3.8 (0.8)[b]	2.2 (0.8)	4.1 (0.7)[b]	PSP and MSA > PD ($p < 0.001$)
UPDRS-I	—	3.5 (1.9)	2.6 (1.6)	3.4 (1.7)	NS
UPDRS-II	—	20.5 (7.5)[b]	10.2 (4.7)	26.7 (6.1)[b]	PSP and MSA > PD ($p < 0.001$)
UPDRS-III	—	38.6 (12.0)[b]	23.9 (9.3)	52.0 (9.4)[b]	PSP > PD ($p = 0.003$); MSA > PD ($p < 0.001$); MSA > PSP ($p = 0.008$)
MMSE	—	27.5 (2.3)	28.9 (1.2)	28.8 (1.0)	NS
FAB	—	12.5 (4.3)[b]	17.0 (0.9)	16.0 (1.7)	PSP < PD ($p = 0.003$); PSP < MSA ($p = 0.025$)
PSPRS	—	38.5 (11.7)	—	—	—
UMSARS	—	—	—	54.9 (12.4)	—

Abbreviations: ANOVA = analysis of variance; FAB = Frontal Assessment Battery; H&Y = Hoehn and Yahr; MMSE = Mini-Mental State Examination; MSA = multiple system atrophy; NS = not significant; PD = Parkinson disease; PSP = progressive supranuclear palsy; PSPRS = Progressive Supranuclear Palsy Rating Scale; UMSARS = Unified Multiple System Atrophy Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Data are mean (SD). In the clinical cohort, 17 of 21 were probable and 4 of 21 possible PSP and 7 of 10 MSA were probable, 3 of 10 possible by research criteria. Eight of 10 MSA cases were of the parkinsonian predominant phenotype in the clinically diagnosed group.

[b] Statistically significant differences (ANOVA).

Assessment Battery,[17] Golbe Progressive Supranuclear Palsy Rating Scale,[18] or the Unified Multiple System Atrophy Rating Scale.[19] Healthy controls had no history of neurologic illness at the time of imaging (figure 1).

In the pathologically confirmed group, cases were selected in which conventional 1.5-tesla, midsagittal, T1-weighted images were electronically available. In the clinically diagnosed group, all had 3-tesla MRI with volumetric T1-weighted images.

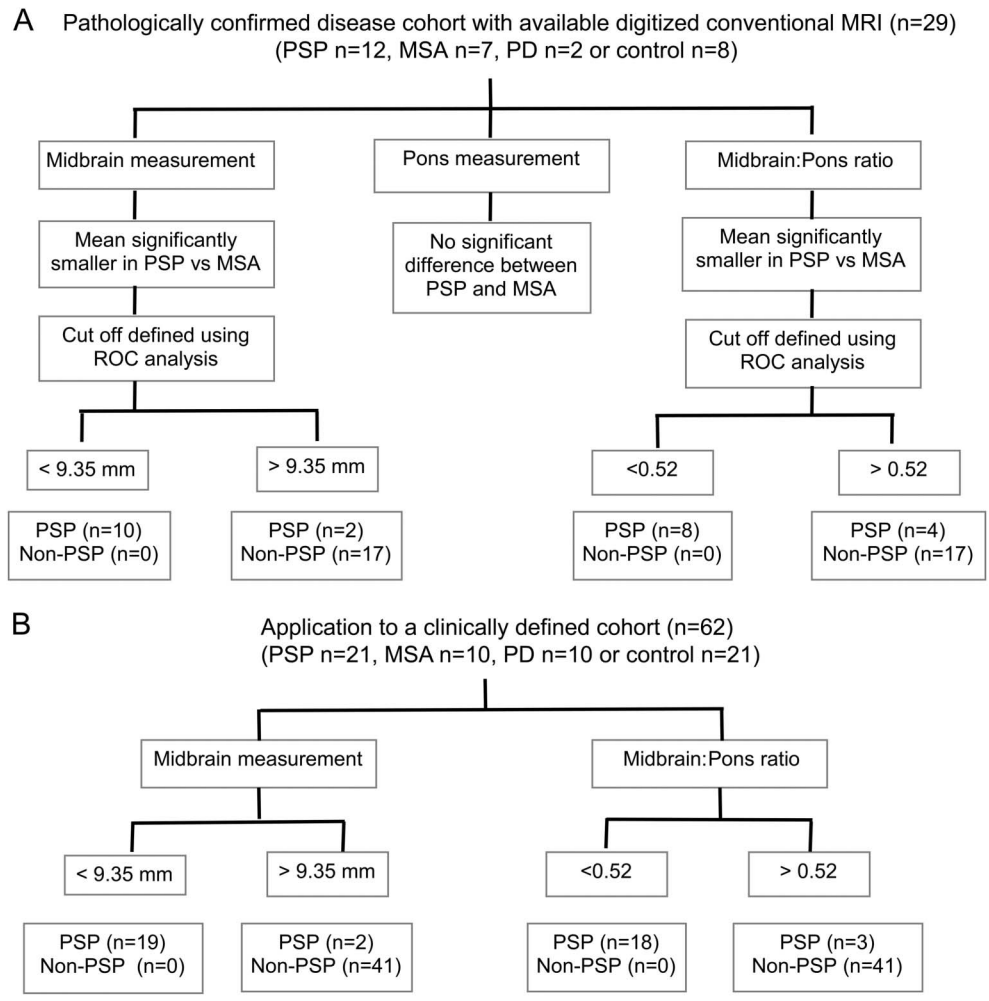
Midbrain and pons measurements and the midbrain to pons ratio. The measurements were taken as described in figure 2. The midbrain to pons ratio was derived by dividing the midbrain by the pons measurements. In the pathologically confirmed group (n = 29), measurements were made blinded to clinical and pathologic information (C.M., neuroradiologist); a randomly chosen subset (n = 8) was measured by another rater (N.F., neurologist) for interrater assessment. In the clinically diagnosed group (n = 62), a third rater (L.M., neurology trainee) performed all measurements.

Statistical analysis. Group characteristics were compared using multivariate analysis with post hoc Bonferroni correction. An intraclass correlation coefficient was used to assess interrater agreement and receiver operating characteristic curve analysis to define cutoff values (maximal sum of sensitivity and specificity) in the pathologically confirmed group that were subsequently applied to the clinical group. Pearson correlation coefficient was used to assess correlation of the midbrain measurement and ratio with age at onset, age at scan, and disease duration in the pathologically confirmed group, and in the clinically diagnosed group clinical scores. SPSS 20.0 (IBM SPSS Statistics, Armonk, NY) for Mac was used for statistical analysis.

RESULTS The demographic features of both cohorts are described in table 1. In pathologically confirmed PSP, the mean midbrain measurement and the midbrain to pons ratio were significantly smaller than in controls and MSA; in the MSA group, there was a trend for the pons measurement to be smaller than in controls. Additionally, in the clinically diagnosed group, the pons was significantly smaller and the midbrain to pons ratio was significantly increased in MSA relative to PSP, to PD, and to controls (table 2, figure 3). Single-measure, intraclass correlation coefficients were 0.97 for the midbrain measurement and 0.94 for the pontine measurement ($p < 0.001$ for both).

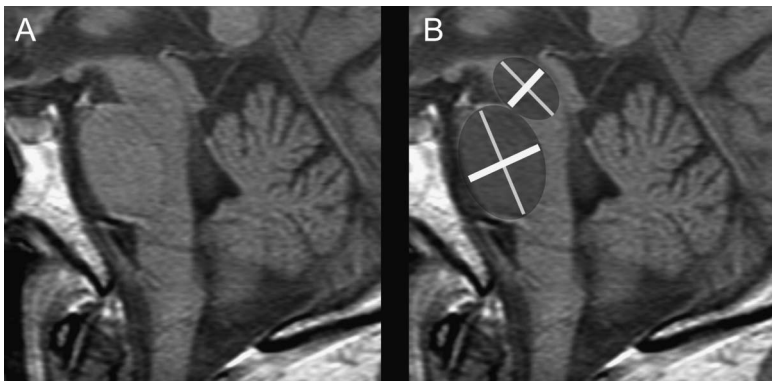
Defined by the maximum sum of sensitivity and specificity from the receiver operating characteristic curve in pathologically confirmed cases, a midbrain

Figure 1 Flow diagram in the pathologically confirmed group (A) and application of cutoff values to the clinically defined group (B)



MSA = multiple system atrophy; PD = Parkinson disease; PSP = progressive supranuclear palsy; ROC = receiver operating characteristic.

Figure 2 Measuring the anterior-posterior distance of the pons and midbrain



(A) Midsagittal T1 image on conventional MRI. (B) Elliptical regions of interest were placed over the pons and the midbrain 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; the midbrain measurement did not include the collicular plate and was chosen to maximize the chance of detecting atrophy of this region in progressive supranuclear palsy as exhibited by the concave appearance in the midsagittal plane.[7]

measurement of <9.35 mm had 83% sensitivity, 100% specificity, and positive predictive value for PSP (area under the curve 0.94; $p = 0.002$), and a ratio of <0.52 had 67% sensitivity, 100% specificity, and positive predictive value for PSP (area under the curve 0.95; $p = 0.001$) when compared with MSA (figure 3).

In the clinically diagnosed PSP group, a threshold of 9.35 mm for midbrain diameter had 100% specificity and positive predictive value for PSP and only 2 cases are not classified as PSP (2/21 = 9.5%). Outliers included 1 probable PSP with a disease duration of 3.7 years and 1 possible PSP with a disease duration of 4.7 years. For a diagnosis of PSP using a threshold of 0.52 for the midbrain to pons ratio, there was a specificity and positive predictive value of 100% and sensitivity of 85.7%.

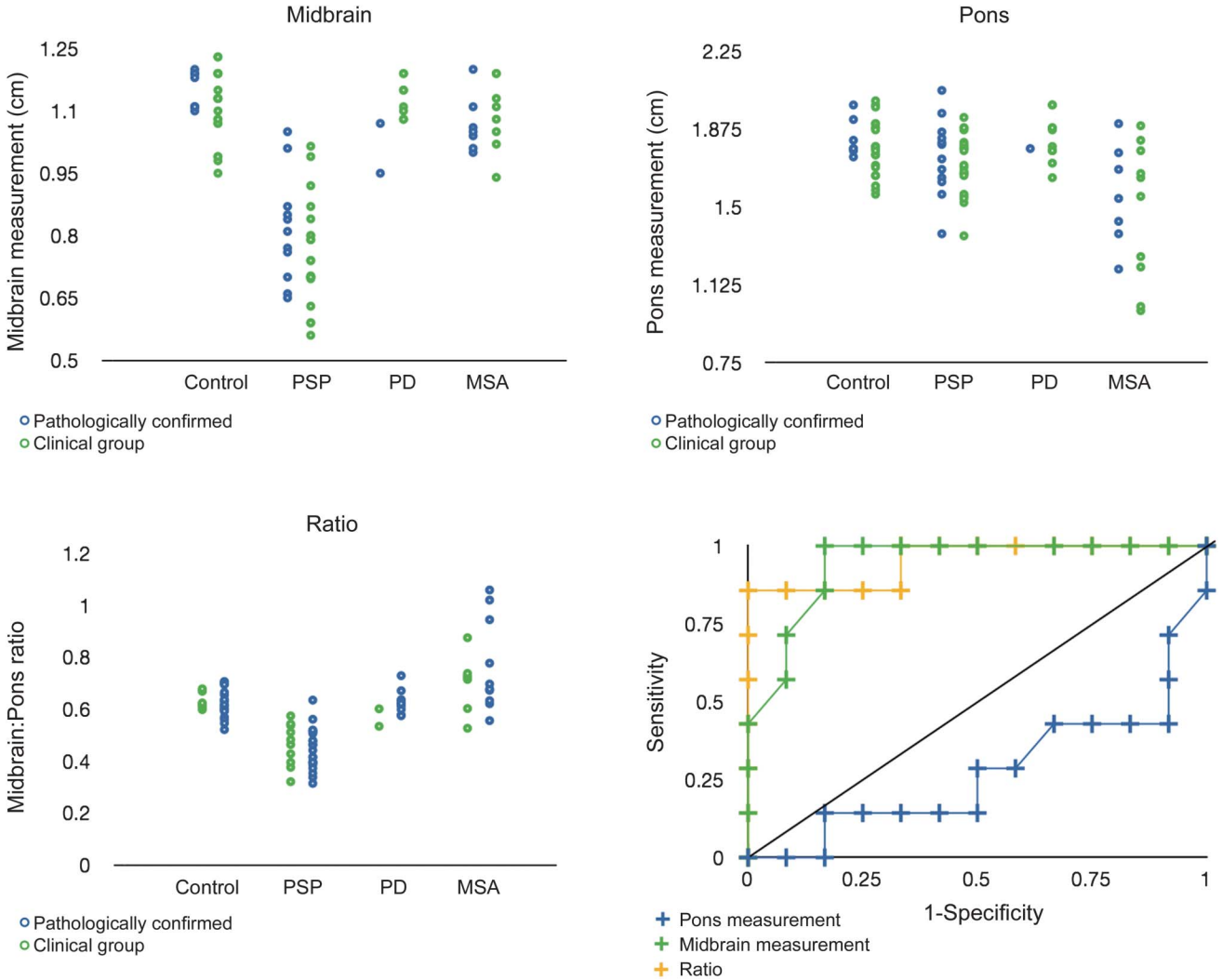
No correlation was found between age, disease duration, or clinimetric scores with the midbrain or pons measurements or ratio.

Table 2 Measurements in the pathologically confirmed and clinically diagnosed groups[a]

Measurement	Control	PSP	PD	MSA	ANOVA
Pathologically confirmed group					
Midbrain	11.5 (0.4)	8.1 (1.2)[b]	10.1 (0.8)	10.7 (0.7)	PSP < control and MSA ($p < 0.001$)
Pons	18.2 (0.9)	17.4 (1.8)	17.8 (0.0)	15.5 (2.4)	MSA < control ($p = 0.061$)
Midbrain to pons ratio	0.63 (0.03)	0.47 (0.08)[b]	0.57 (0.05)	0.70 (0.11)	PSP < control and MSA ($p < 0.001$)
Clinically diagnosed group					
Midbrain	11.1 (0.8)	7.55 (1.12)[b]	11.4 (0.7)	10.8 (0.8)	PSP < control, PD, MSA ($p < 0.001$)
Pons	17.8 (1.4)	17.1 (1.4)	18.3 (1.1)	14.8 (3.3)[b]	MSA < PSP ($p < 0.001$); MSA < PD and control ($p < 0.05$)
Midbrain to pons ratio	0.62 (0.05)	0.44 (0.08)[b]	0.63 (0.05)	0.77 (0.18)[b]	PSP < control, PD, MSA ($p < 0.001$); MSA > PSP ($p < 0.001$); MSA > PD and control ($p < 0.05$)

Abbreviations: ANOVA = analysis of variance; MSA = multiple system atrophy; PD = Parkinson disease; PSP = progressive supranuclear palsy.
[a] Data are mean (SD) and measurements are in millimeters.
[b] Statistically significant differences (ANOVA).

Figure 3 Scatterplots of the midbrain and pons measurements showing both pathologically confirmed and clinically diagnosed groups, and receiver operating characteristic curve analysis in the pathologically confirmed group comparing PSP and MSA



MSA = multiple system atrophy; PD = Parkinson disease; PSP = progressive supranuclear palsy.

DISCUSSION We found that in normal controls the midbrain tegmentum was approximately two-thirds of the pontine base, whereas in PSP it was half or less of the pontine base and in MSA it was greater than two-thirds (table 2, figure 3). All non-PSP subjects had a midbrain to pons ratio >52%; 67% (pathologically confimed PSP) and 86% (clinically diagnosed PSP) had a ratio of <52%. There was excellent interrater reliability in the measures.

The strengths of our study lie in the pathologic validation of the diagnosis and the rationalized approach to developing simple measurement based on knowledge of the pathologic topography measured on readily available, conventional, midsagittal MRI. Although there was a relatively small sample size of the pathologically confirmed group, our findings appeared to be confirmed in a larger, albeit clinically diagnosed, cohort.

The midbrain measurement and midbrain to pons ratio are approximately equivalent in terms of area under the curve in predicting the diagnosis: the midbrain measurement has higher sensitivity but the ratio controls for head size, which is a confounding factor of simpler measurements. Furthermore, a ratio is easier to estimate using visual inspection. Previous work has shown the hummingbird sign to be a useful indicator of midbrain atrophy in PSP.[2,4] Midsagittal images are more reliably reproducible than axial images and linear measurements,[3] and manual segmentation for measurement of area[4,5] has been studied in clinically diagnosed cases. Our midsagittal midbrain measurement performed better than qualitative visual assessment where a hummingbird sign may be seen in only 67%.[2] Furthermore, our results compare favorably with previous reports of midsagittal linear measurements,[9] area measurements,[5,20] and more detailed analysis of the area of the midbrain tegmentum.[4,21]

Our results support the hypothesis that because of differential patterns of atrophy, a simple ratio measurement of midbrain to pons helps in differentiating PSP and MSA (figure 3). This is part of the rationale used in the Magnetic Resonance Parkinson Index.[6]

A previous study has reported a correlation of disease severity with midsagittal midbrain area and a midbrain to pons area ratio[5] but other studies using linear measurements do not report this.[4,6–8] It may be too much to expect correlation of linear measurements with disease severity—others reported that midsagittal midbrain area measurements do not correlate with disease severity, although a 3-dimensional technique may be helpful.[20,22]

Although promising, this method will need to be corroborated in larger cohorts and also assessed in early disease where diagnostic uncertainty is greatest. Ideally, these studies would also include pathologic confirmation.

AUTHOR CONTRIBUTIONS

Luke A. Massey: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis. Hans R. Jäger: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dominic C. Paviour: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Sean S. O'Sullivan: drafting/revising the manuscript, study concept or design, acquisition of data, study supervision. Helen Ling: analysis or interpretation of data, acquisition of data. David R. Williams: drafting/revising the manuscript, study concept or design, study supervision. Constantinos Kallis: analysis or interpretation of data, statistical analysis. Janice L. Holton: drafting/revising the manuscript, acquisition of data. Tamas Revesz: drafting/revising the manuscript, study concept or design, acquisition of data. David J. Burn: drafting/revising the manuscript, acquisition of data. Tarek A. Yousry: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision, obtaining funding. Andrew J. Lees: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Nick C. Fox: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Caroline Micallef: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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