The midbrain to pons ratio
A simple and specific MRI sign of progressive supranuclear palsy

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; 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.16 In the clinically diagnosed group, participants fulfilled operational criteria17–19 and were assessed with clinimetric scales including Hoehn and Yahr,16 the Unified Parkinson’s Disease Rating Scale,17 Folstein Mini-Mental State Examination,16 the Frontal

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Assessment Battery,\textsuperscript{17} Golbe Progressive Supranuclear Palsy Rating Scale,\textsuperscript{18} or the Unified Multiple System Atrophy Rating Scale.\textsuperscript{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) 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

### Table 1 Demographic and clinimetric features of the pathologically confirmed and clinically diagnosed groups\textsuperscript{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)\textsuperscript{a} | 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) | 68.8 (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)\textsuperscript{a} | 2.2 (0.8) | 4.1 (0.7)\textsuperscript{a} | 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)\textsuperscript{a} | 10.2 (4.7) | 26.7 (8.1)\textsuperscript{a} | PSP and MSA > PD (\(p < 0.001\)) |
| UPDRS-III | — | 38.6 (12.0)\textsuperscript{a} | 23.9 (9.3) | 52.0 (9.4)\textsuperscript{a} | 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)\textsuperscript{a} | 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.

\textsuperscript{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.

\textsuperscript{b}Statistically significant differences (ANOVA).
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

| Measurement                  | Control | PSP       | PD       | MSA       | ANOVA                                                                 |
|------------------------------|---------|-----------|----------|-----------|------------------------------------------------------------------------|
| Pathologically confirmed     |         |           |          |           |                                                                        |
| Midbrain                     | 11.5 (0.4) | 8.1 (1.2) | 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) | 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) | 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) | MSA < PSP (p < 0.001); MSA < PD and control (p < 0.05)                 |
| Midbrain to pons ratio       | 0.62 (0.05) | 0.44 (0.08) | 0.63 (0.05) | 0.77 (0.18) | PSP < control, PD, MSA (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.

* Data are mean (SD) and measurements are in millimeters.

** 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.

Abbreviations: 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 confirmed 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. Midsagittal images are more reliably reproducible than axial images and linear measurements, and manual segmentation for measurement of area 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%. Furthermore, our results compare favorably with previous reports of midsagittal linear measurements, area measurements, and more detailed analysis of the area of the midbrain tegmentum.

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.

A previous study has reported a correlation of disease severity with midsagittal midbrain area and a midbrain to pons area ratio but other studies using linear measurements do not report this. 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.

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. Masey: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis.
Hans R. Jager: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, Dominik 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 Kalf: analysis or interpretation of data, statistical analysis. Janice L. Holton: drafting/revising the manuscript, acquisition of data. Tamás Revesz: drafting/revising the manuscript, study concept or design, acquisition of data. David J. Burns: drafting/revising the manuscript, acquisition of data. 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, study supervision.

ACKNOWLEDGMENT
The authors are indebted to the donors to the Queen Square Brain Bank for Neurological Disorders without whom this work would not have been possible. The authors are very grateful to Adrienne Wallis who retrieved many of the MRIs used in this study.

STUDY FUNDING
A.M.M. has been supported by a grant from the PSP (Europe) Association. N.F. has been supported by the Medical Research Council, Alzheimer Research UK, and the National Institute for Health Research. This work was undertaken at UCLH/UCL who received a proportion of funding from the UK Department of Health’s National Institute for Health Research Biomedical Research Centres funding scheme (UCLH/ UCL Comprehensive Biomedical Research Trust).

DISCLOSURE
L. A. Masey has been supported by a grant from the PSP (Europe) Association. H. Jager has been supported by grants from the Stroke Association/ Brittal Heart Foundation Joint Program Grant in Stroke and receives royalties from Churchill Livingstone (chapter in Grainger & Allison’s Textbook of Diagnostic Radiology). D. Paviour, C. Kallis, and L. A. Massey report no disclosures. S. O’Sullivan has received honoraria from UCB Pharmaceuticals and Teva Pharmaceuticals. H. Ling is supported by the PSP Association research grant (6aTV) and is employed by the Reta Lila Weston Trust for Medical Research, University College London. D. Williams has consultancies with Ipsen, and has received honoraria from Ipsen, Allergen, Hospira, and Novartis. He is supported from NHMRC, Cure PSP, and the Brain Foundation. T. Revesz has consultancies with and has received honoraria from Merck Serono and has been supported by grants from Parkinson’s UK, the Multiple System Atrophy Trust, and Alzheimer’s Research UK. She has been supported by the Reta Lila Weston Institute for Neurological Studies, the Multiple System Atrophy Trust, Alzheimer’s Research UK and Parkinson’s UK. T. Revesz has consultancies with and has received honoraria from Merck Serono and Novartis and was supported by a grant from Orion. He has been supported by grants from Parkinson’s UK, Alzheimer’s Research UK, and the Multiple System Atrophy Trust. D. Burn has had consultancies with the Michael J. Fox Foundation and GSK. He has received honoraria from Teva-Lundbeck and UCB. He is supported by grants from Parkinson’s UK, NIHR, Wellcome Trust, and the Michael J. Fox Foundation. T. Yousry has received honoraria from UCB, Brimble-Mye, Syilups, and Biogen Idec. He is supported by grants from NHMRC MRC, MS Society, PSP, Stroke, BHF, Wellcome Trust, GSK, Biogen Idec, and Novartis. A. Lees has a consultancy with Stada. He has received honoraria from Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergen, Orion, BIAL, Nocira, Merck, Abbott, and Roche. He is supported by grants from the PSP Association, Weston Trust, The Reta Lila Howard Foundation. N. Fox has consultancies with

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REFERENCES

Received September 20, 2012. Accepted in final form February 14, 2013.

This work was also supported by the NIHR Biomedical Research Centre funding scheme and Biomedical Research Unit–Dementia. Go to Neurology.org for full disclosures.

1. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002;125:861–870.

2. Massey LA, Micallef C, Paviour DC, et al. Conventional magnetic resonance imaging in confirmed progressive supranuclear palsy and multiple system atrophy. Mov Disord 2012;27:1754–1762.

3. Asano R, Aliguchi I, Muranaga S, Hashimoto N. Magnetic resonance imaging distinguishes progressive supranuclear palsy from multiple system atrophy. J Neurol Transm 2000;107:1427–1436.

4. Kato N, Arii K, Harimoto T. Study of the rostral midbrain atrophy in progressive supranuclear palsy. J Neurol Sci 2003;210:57–60.

5. Oba H, Yagishita A, Terada H, et al. New and reliable MRI diagnosis for progressive supranuclear palsy. Neurology 2005;64:2050–2055.

6. Quatrone A, Nicoletti G, Messina D, et al. MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy. Radiology 2008;246:214–221.

7. Righini A, Antonini A, De Notari R, et al. MR imaging of the superior profile of the midbrain: differential diagnosis between progressive supranuclear palsy and Parkinson disease. AJNR Am J Neuroradiol 2004;25:927–932.

8. Schrag A, Good CD, Miskiel K, et al. Differentiation of atypical parkinsonian syndromes with routine MRI. Neurology 2000;54:697–702.

9. Warmuth-Metz M, Naumann M, Corin I, Solyomos L. Measurement of the midbrain diameter on routine magnetic resonance imaging: a simple and accurate method of differentiating between Parkinson disease and progressive supranuclear palsy. Arch Neurol 2001;58:1076–1079.

10. Ince PG, Clarke B, Holton JL, Revesz T, Wharton S. Disorders of movement and system degenerations. In: Love S, Louis DN, Ellison DW, editors. Greenfield’s Neuropathology, 8th ed, Vol 1. Boca Raton, FL: CRC Press; 2008:889–1030.

11. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47:1–9.

12. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999;163:94–98.

13. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson’s disease. J Neurol Neurosurg Psychiatry 1988;51:745–752.

14. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.

15. Fahn S, Elton R; members of the UPDRS Development Committee. Recent Developments in Parkinson’s Disease, Vol 2. Florham Park, NJ: Macmillan Health Care Information; 1987.

16. Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State”: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

17. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology 2000;55:1621–1626.

18. Golbe LI, Olman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain 2007;130:1856–1864.

19. Wenning GK, Tison F, Seppi K, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 2004;19:1391–1402.

20. Groschel K, Kastrup A, Litvan I, Schulz JB. Penguins and hummingbirds: midbrain atrophy in progressive supranuclear palsy. Neurology 2008;66:949–950.

21. Slowinski J, Imamura A, Uttrr RJ, et al. MR imaging of brainstem atrophy in progressive supranuclear palsy. J Neurol 2008;255:37–44.

22. Groschel K, Hauser TK, Luft A, et al. Magnetic resonance imaging-based volumetry differentiates progressive supranuclear palsy from corticobasal degeneration. Neuroimage 2004;21:714–724.