Clinical Parkinsonism & Related Disorders 3 (2020) 100033

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.elsevier.com/locate/prdoa

Methods and utility of quantitative brainstem measurements in progressive supranuclear palsy versus Parkinson's disease in a routine clinical setting

Jessica Cooperrider [a,*], Brent Bluett [b,c], Stephen E. Jones [b]

[a] Cleveland Clinic Lerner College of Medicine, 9980 Carnegie Ave, Cleveland, OH 44195, United States of America
[b] Cleveland Clinic Imaging Institute, 9500 Euclid Ave, Cleveland, OH 44195, United States of America
[c] Stanford University Department of Neurology and Neurological Sciences, 300 Pasteur Dr, Palo Alto, CA 94304, United States of America

ARTICLE INFO

Article history:
Received 20 August 2019
Received in revised form 26 November 2019
Accepted 17 December 2019
Available online 14 January 2020

Keywords:
Progressive supranuclear palsy
Midbrain atrophy
MRPI
Midbrain to pons area ratio

ABSTRACT

Background and Purpose: The clinical diagnosis of progressive supranuclear palsy can be challenging, as the clinical presentation overlaps with that of Parkinson's disease and multiple system atrophy. We sought to examine the practical utility of radiologic markers of progressive supranuclear palsy by investigating whether these markers could distinguish between patients with progressive supranuclear palsy-Richardson syndrome (PSP-RS) and those with Parkinson's disease based on imaging obtained in a typical clinical setting, not in a prospective research environment.
Materials and methods: This retrospective study included 13 patients with PSP-RS and 13 patients with Parkinson's disease who were followed for either condition at our institution at the time of the study and who had MRI records available. Patients were selected without regard to type of imaging obtained. All diagnoses were confirmed by a trained movement disorders specialist using validated diagnostic criteria. Groups were matched for age and disease duration at the time of scanning. MRI records were retrospectively obtained, and image analysis was performed by investigators blinded to disease classification. Midbrain area, midbrain to pons area ratio, midbrain anterior-posterior diameter, and MR parkinsonism index were calculated for each patient.
Results: All established measures of identifying progressive supranuclear palsy (midbrain area, midbrain to pons area ratio, midbrain anterior-posterior diameter, and MR parkinsonism index) were significantly different between patients with PSP-RS and those with Parkinson's disease.
Conclusion: Previously established radiographic markers distinguishing between PSP-RS and Parkinson's disease have practical utility in the clinical setting and not just in well-designed prospective analyses.

1. Introduction

Early recognition and diagnosis of progressive supranuclear palsy (PSP) can be difficult. In the early stages of this disease, patients often present to the clinic with nonspecific cognitive complaints that may be confused with Alzheimer's disease or other dementias. Additionally, as preliminary motor symptoms arise, distinguishing between PSP and other parkinsonian disorders can be a challenge.

Typically, it takes 4 years before a movement disorders specialist can distinguish Parkinson's disease (PD) from other atypical parkinsonian disorders, such as PSP [1]. To aid an earlier diagnosis, carbidopa-levodopa is often given to the patient on a trial basis, but this treatment is effective in only 25% to 33% of patients with PSP [2]. The International Parkinson's and Movement Disorder Society recently revised the diagnostic criteria of PD to improve early identification, taking into account prodromal symptoms, such as constipation and REM behavioral disorder, and "red flags," such as vertical gaze palsy and early falls, that can indicate atypical parkinsonian disorders such as PSP [3]. Early and accurate classification of PD, PSP, and other parkinsonian disorders is helpful to achieve appropriate patient care and for enrolling the correct patient population in clinical trials assessing therapeutic interventions.

In order to aid diagnosis of neurodegenerative disease, many biomarkers have been proposed, with several showing promise [4–11]. For example, levels of serum markers such as cystatin C, low-density lipoprotein cholesterol (LDL-C), trefoil factor 3, cholinesterase and homocysteine have been associated with various types of parkinsonism, with cystatin C and LDL-C associated with PSP specifically [6,11]. Additionally, various markers seen on imaging, such as cortical thickness, medial temporal lobe atrophy and white matter hyperintensity, have been linked to some of the cognitive changes associated with neurodegenerative diseases [8,9].

In patients with parkinsonian disorders, imaging has shown promise as a method to augment accurate diagnosis. Midbrain atrophy is often present

* Corresponding author at: Cleveland Clinic Lerner College of Medicine, 9980 Carnegie Ave, Cleveland, OH 44195.
E-mail address: cooperj5@ccf.org. (J. Cooperrider).

http://dx.doi.org/10.1016/j.prdoa.2020.100033

in patients with PSP, and a number of measurements have been proposed to quantify this change, including the midbrain area, midbrain to pons area ratio, midbrain anterior-posterior distance, and MR parkinsonism index (MRPI) [12–16]. Midbrain atrophy has been shown to progress differently in patients with PSP-Richardson (PSP-RS), PSP-Parkinsonism (PSP-P), and PD, with PSP-RS showing the largest change in pons/midbrain area ratio over time, PSP-Parkinsonism showing smaller change in pons/midbrain ratio, and PD patients showing no change [17]. Indeed, midbrain atrophic changes seem to be most prominent in PSP-RS and are less apparent in other subtypes of PSP [18]. The MRPI is a measurement that incorporates both midbrain atrophy and superior cerebellar peduncle (SCP) atrophy, both of which are sometimes present in patients with PSP [14]. One study has suggested that MRI findings may precede the development of characteristic PSP features, concluding that MRPI could help to predict the evolution of clinically undifferentiated parkinsonism to PSP [19]. Studies of these measurements have demonstrated clear associations between structural brain abnormalities and PSP, but these investigations have typically been carried out in well-controlled research settings. Furthermore, a detailed protocol for measuring and quantifying the structural abnormalities of interest was sometimes absent from these reports.

Here, we sought to investigate whether a detailed procedure to measure commonly evaluated radiographic markers of PSP (e.g., midbrain and pontine areas, midbrain anterior-posterior distance, MRPI) had practical clinical utility in distinguishing between patients with PD and those with PSP-RS outside of a well-controlled research environment. To this end, we replicated and expanded on previously published methods in an analysis of patients with known PSP-RS or PD who were scanned within the routine clinical service of a large multisite tertiary hospital system using a variety of MRI scanners, field strengths, and protocols. We proposed that this systematic procedure for analyzing representative patient imaging data may hold practical clinical utility in distinguishing between patients with PD and those with PSP-RS.

2. Materials and methods

2.1. Subject Selection

This retrospective study was approved by the institutional review board with a waiver of informed consent, and all personal health information requirements were strictly followed. The study population included 13 subjects with PSP-Richardson and 13 subjects with PD who were being followed for either condition at our institution at the time of the study and who had undergone at least 1 clinical MRI examination. Subjects were selected without regard to the type of MRI scanner (including variables such as vendor, field strength, or head coil) or MRI protocol (which may have included routine protocols without 3D volumetric sequence or dedicated dementia protocols that featured such sequences) used for scanning. Diagnoses of either PSP or PD were assigned by a trained movement disorders specialist using validated diagnostic criteria. Only subjects with PSP-Richardson subtype were included in this study; other subtypes such as PSP-Parkinsonism were excluded because of clinical ambiguity and overlap of symptoms with PD. MRI records were retrospectively collected, with groups matched for age and disease duration at the time of the scan.

In a separate analysis, we also sought to estimate the predictive value of a radiologist incidentally observing a small midbrain and subsequently considering a clinical diagnosis of PSP. To evaluate this question, we searched all MRI reports from the radiology database over a 2-year period for the term “PSP” in the body or impression of the report. Reports were excluded if PSP was provided in the clinical history; this ensured that the radiologist's suggestion of PSP was unprompted and noted as an incidental finding. The candidate reports were then reviewed and included only if the neuroradiologist's description of PSP included a qualitative assessment that a small midbrain suggested possible PSP (no reports were found that included quantitative measurements). The electronic medical records for these patients were then reviewed for the presence or absence of a clinical diagnosis of PSP from a neurologist. Images from these patients were then assessed to determine the midbrain to pons area ratio, which presumably corresponded to what the radiologist's eye noted as qualitatively reduced.

2.2. Image Analysis

MRI examinations were performed on a variety of clinical scanners with various field strengths and from different manufacturers (Supplementary Table 1). In addition, this retrospective analysis included patients scanned with any MRI protocol, which may have included routine brain MRI examinations without contrast or dedicated dementia protocols (for example, those following the Alzheimer's Disease Neuroimaging Initiative design). Altogether, this assortment was considered to reflect what might be encountered in a typical clinical practice, which was one of the goals of this research. The MRI sequences reviewed for this study focused on T1- and T2-weighted images, with a preference for volumetric T1-weighted MPRAGE if available (typically 1.2 mm thick in the sagittal plane), followed by spin echo T1- and T2-weighted sequences in either the axial or coronal plane (often up to 5 mm thick). The preferred sequences chosen reflected the desired measurement, as detailed in the next section.

All analyses were performed by investigators blinded to disease classification. The DICOM viewer IMPAX 6 (Agfa, Mortsel, Belgium) was used for image visualization and measurements. A total of 5 measurements were obtained for each patient: (1) midbrain area; (2) pontine area; (3) the midbrain anterior-posterior diameter; (4) the width of the SCP; and (5) the width of the middle cerebellar peduncles (MCP). The MRPI was then calculated by multiplying the pons to midbrain area ratio by the ratio of the width of the MCP to the width of the SCP [14].

2.2.1. Midbrain to pons area ratio

The areas of the midbrain and pons were calculated using a midsagittal image (Fig. 1), as proposed by Oba et al. [12]. Within this midsagittal plane, a transverse boundary was defined by drawing a line from the superior pontine notch to the inferior border of the tectum, to which other lines are parallel. The inferior pontine edge was defined by a line parallel to the first line originating at the inferior pontine notch. The pontine area traced between these 2 parallel lines was considered the area of the pons. The midbrain area was defined as the midbrain tegmentum area superior to the line marking the superior edge of the pons. The example in Fig. 1 shows the midbrain area to be 1.26 cm^2 and the pontine area to be 4.88 cm^2; thus, the midbrain to pons area ratio was 0.26.

2.2.2. Midbrain anterior-posterior diameter

The definition of midbrain anterior-posterior diameter used in this study (Fig. 2) was similar to the definition provided by Kim et al. [15] and was referenced to the anterior commissure-posterior commissure line. A second line was drawn parallel and inferior to this line and passing through the center of the mammillary body. Using this second line, an oblique-axial plane was obtained parallel to that line and perpendicular to the midsagittal plane. Within this plane, a new line was drawn in the midline from the posterior notch of the interpeduncular fossa to the ventral aspect of the cerebral aqueduct. The midbrain anterior-posterior diameter was then taken as the length of this line segment. In the example shown in Fig. 2, the diameter was 13 mm.

2.2.3. Width of the SCP

To determine the width of the SCP (Fig. 3), a line was drawn parallel to the posterior margin of the pontomedullary surface in the midsagittal plane. An oblique coronal plane that was parallel to that line and perpendicular to the midsagittal plane was then obtained. Within this plane, all 4 of the tectal colliculi are often visible; inferior to them are both SCPs. The SCP width was then defined as the linear distance perpendicular to the superior-inferior axis, measured between the lateral and medial edges of the SCPs at the midpoint of their extension. SCP widths were measured

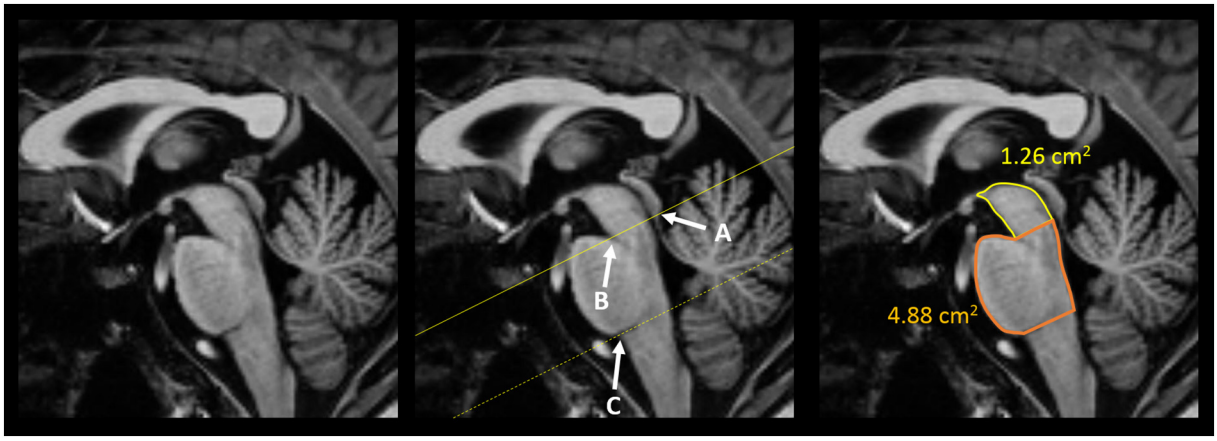

Fig. 1. Measurement of the midbrain to pons area ratio. *Left*: Midsagittal plane from a T1-weighted MPRAGE sequence. *Center*: Two overlaid oblique lines. The top line passes through the 2 points of the interpeduncular notch (B) and the inferior margin of the midbrain tectum (A). The bottom line is parallel to the first, passing to the pontomedullary junction (C). *Right*: Segmented areas of the midbrain tegmentum and pons, using the lines from the center figure as boundaries. In this example, the midbrain area is 1.26 cm^2 and the pontine area is 4.88 cm^2; thus, the midbrain to pons area ratio is 0.26. (Images obtained at 7 T using an MP2RAGE sequence.)

bilaterally and then averaged to obtain a single measure. The example in Fig. 3 shows 2 measurements of 4.0 and 4.5 mm, for an average of 4.25 mm.

2.2.4. Width of the MCP

The values for the size of the MCP (Fig. 3) were determined by first setting an axis in the notch between the SCP and the folia of the cerebellum on the coronal view. A line was then drawn from the superior to the inferior edge of the MCP on the corresponding sagittal section. Bilateral MCP lengths were then obtained and averaged. The example in Fig. 3 shows a final measurement of 13 mm.

2.3. Measurement techniques when a 3D sequence was not used

Nearly half of the included MRI studies did not feature a T1-weighted 3D volumetric acquisition. Whereas 3D sequences provide nearly isotropic voxels (for example, 1 × 1 × 1.2 mm in the Alzheimer's Disease Neuroimaging Initiative sequence), typical 2D sequences provide voxels with high aspect ratios. For example, 2D sequences usually have submillimeter dimensions in plane with 3 to 5 mm between planes, yielding a voxel aspect ratio that can be as high as 10:1. Nevertheless, it is still possible to obtain reasonable measurements from a 2D MRI protocol if a 3D reformatting tool is available to coregister different 2D sequences and effectively combine them. In this manner, the high spatial dimension of one 2D sequence can be translated to the high spatial dimension of a different sequence. Typically, a 2D sagittal T1-weighted sequence was obtained in most non-3D MRI protocols; this sequence features high in-plane resolution and approximately 4 to 5 mm between-plane spacing. This same sequence can be used to determine the midbrain to pons area ratio, as the sagittal contour of the midplane brainstem is nearly the same across several millimeters of adjacent planes.

To obtain the other 3 measurements, a 3D coregistration tool (eg, axial FLAIR) that can match two 2D sequences (in this case, the sagittal volume to a nonsagittal volume) is required. The high-resolution features in the

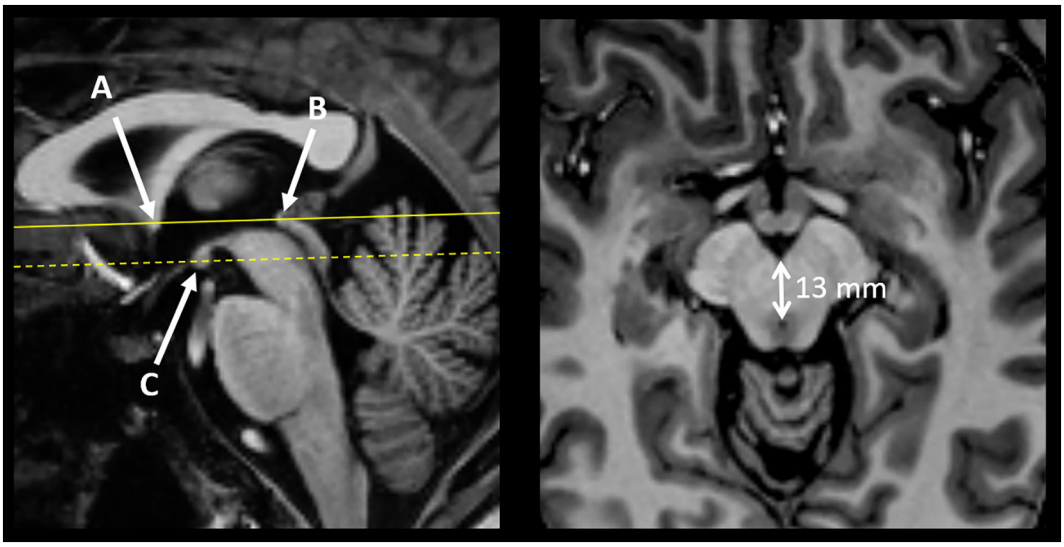

Fig. 2. Measurement of the midbrain anterior-posterior diameter. *Left*: Midsagittal plane from a T1-weighted MPRAGE sequence. The solid yellow line is the anterior commissure (A)-posterior commissure (B) line. The dashed line is parallel to the anterior commissure-posterior commissure line and passes through the center of the mammillary body (C). *Right*: Axial-oblique plane parallel to the dashed line in the left figure. The midbrain anterior-posterior diameter is measured from the interpeduncular fossa to the anterior margin of the cerebral aqueduct. In this example, the diameter is 13 mm. (Images obtained at 7 T using an MP2RAGE sequence.)

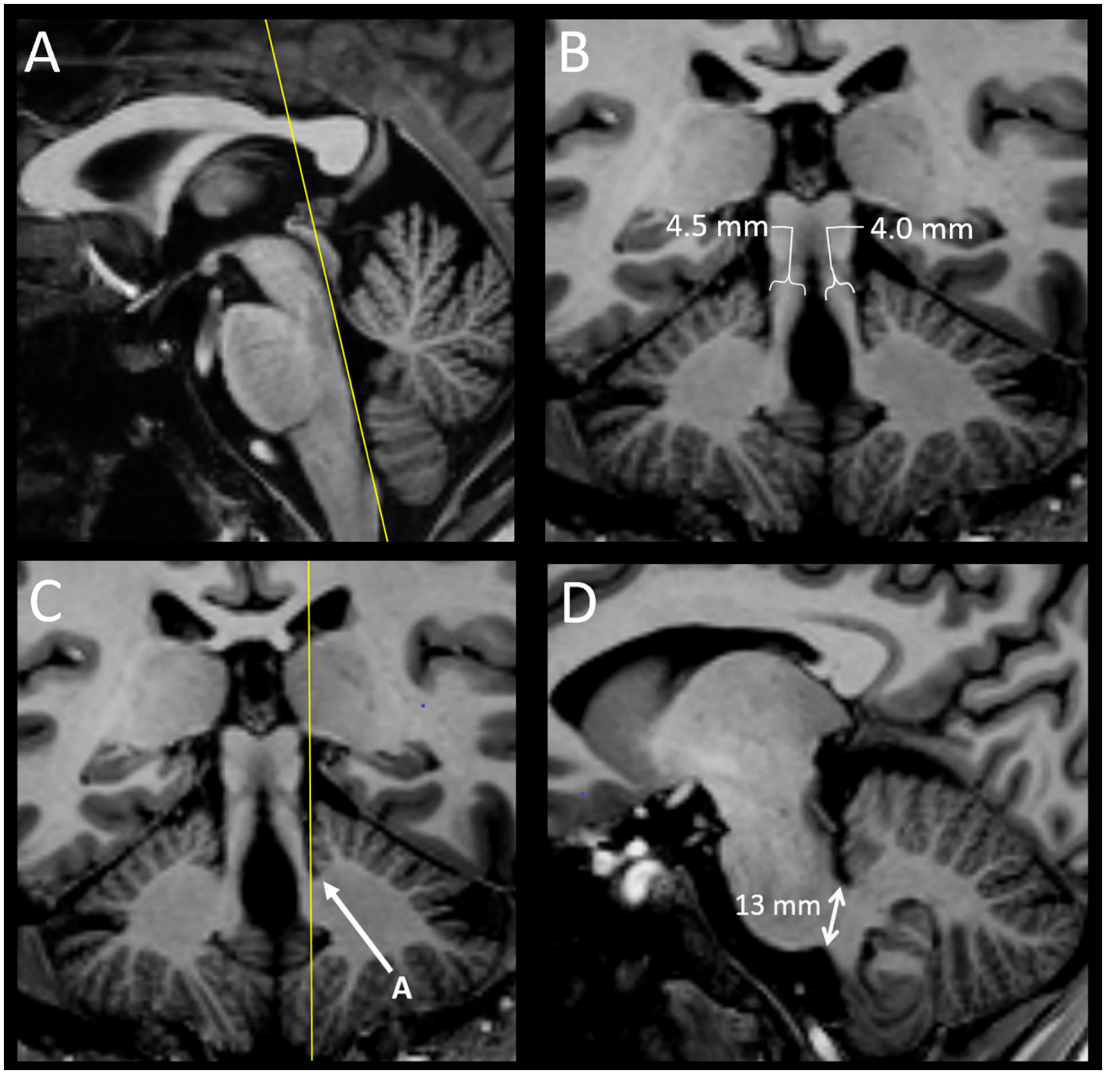

Fig. 3. Measurement of the width of the SCP (A,B) and MCP (C,D). *A*: Midsagittal plane from a T1-weighted MPRAGE sequence. The yellow line is parallel to the posterior margin of the midbrain-pontine-medullary contour. *B*: Coronal oblique plane that is parallel to the yellow line in the left image. The width of the SCP is shown by the white bracket, obtained at the 50% point between the pons and midbrain. In this example, the width is 4.5 mm on the right and 4.0 mm on the left. *C*: The yellow line is parallel to the midline and passes through the notch between the peduncle and the cerebellar folia (A). *D*: Sagittal plane parallel to the yellow line in the left image. The width of the MCP is shown by the double-headed arrow and measures 13 mm in this example. (Images obtained at 7 T using an MP2RAGE sequence.)

sagittal plane can then be used to cross-correlate to high-resolution features in a different plane obtained from another 2D sequence. Supplementary Fig. 1 shows an example of the procedure used to obtain midbrain anterior-posterior diameter when the 3D sequence was not available. SCP and MC*P* values were calculated similarly when a 3D sequence was not available (supplemental Figs. 2 and 3, respectively).

2.4. Statistical analysis

Most differences between groups were compared using the Mann-Whitney rank sum test. Fisher's exact test was used to compare the difference in proportion of patients with cognitive impairment between groups. A P value $< .05$ was considered statistically significant.

3. Results

A total of 26 patients were included in the study. There was no significant difference between the PD and PSP groups in age, disease duration at the time of MR examination, or age at disease onset ($P > .05$ for all comparisons; Supplementary Table 2). However, the PSP group had more patients with a complaint or diagnosis of cognitive impairment compared to the PD group (12 vs. 5, respectively, $P = .01$; Supplementary Table 2).

The midbrain area was significantly smaller in the PSP group than in the PD group, as was the anteroposterior midbrain diameter ($P < .001$ and $P = .001$, respectively; Table 1). The midbrain to pons area ratio was also

Table 1
Quantitative MR measurements in PSP and PD groups.

Measurement	PSP Group[a]	PD Group[a]	P[b]
Midbrain area (mm^2)	85.7 (20.3)	122.7 (20.6)	< **0.001**
Anteroposterior midbrain diameter (mm^2)	11.7 (1.6)	14.1 (1.7)	**0.001**
Midbrain to pons area ratio	0.16 (0.02)	0.21 (0.03)	< **0.001**
MCP (mm)	10.0 (1.9)	11.0 (1.8)	0.40
SCP (mm)	4.8 (1.1)	5.6 (0.9)	0.08
MRPI	13.5 (3.5)	9.6 (2.6)	**0.006**

Note.—PSP indicates progressive supranuclear palsy; PD, Parkinson's disease; MRPI, MR parkinsonism index; MCP, middle cerebellar peduncle; SCP, superior cerebellar peduncle.

[a] Data are mean (SD).

[b] P values determined by Mann-Whitney U test.

smaller in patients with PSP than in those with PD ($P < .001$; Table 1). Furthermore, patients with PSP had a significantly larger MRPI than patients with PD ($P = .006$; Table 1).

Because some of the patients included in this study (8 patients in the PSP group and 7 in the PD group) had only 2D sequences available, we analyzed the measurements obtained from these patients separately to verify that these results were not affecting the overall analysis. Significant differences between the PSP and PD groups were still seen across the same measures when only results from 2D images were compared (Supplementary Table 3).

Over a period of 2 years, a total of 20 neuroradiology reports were identified that incidentally suggested a clinical finding of PSP based on the qualitative observation of a small midbrain. Supplementary Table 4 lists the associated clinical diagnoses from review of the electronic medical records. Only 2 patients were noted to have possible PSP. The mean ± (SD) midbrain to pons area ratio for this group of 20 patients was 0.24 ± 0.10 versus 0.16 ± 0.02 for the group of 13 patients with diagnosed PSP presented earlier ($P = .01$).

4. Discussion

Clinical diagnosis of PSP, especially in the early stages, can be extremely difficult. Specificity for the original criteria from the National Institute of Neurological Disorders and Stroke and the Society for PSP ranges from 95% to 100%, but sensitivity is only 80% for probable PSP and approximately 93% for possible PSP [20]. As therapeutic trials for PSP and other tauopathies gain momentum, early identification of these conditions becomes even more important. MRI is an important tool that can aid the clinician in the early diagnosis of PSP and may also prove useful as a surrogate marker in clinical trials to identify effective therapeutic agents.

In this study, we examined the practical utility of radiologic markers of PSP by investigating whether these markers could distinguish between patients with PSP-RS and those with PD in a clinical setting. We performed this analysis by retrospectively analyzing patient records to mimic the challenges that radiologic analysis would pose in a typical clinical setting as opposed to a well-controlled research study. This setting included a variety of scanners and protocols, similar to what might be seen in a large academic enterprise. We found that there were significant differences between patients with PSP-RS and those with PD in all measures evaluated, including the midbrain area, midbrain to pons area ratio, midbrain anterior-posterior diameter, and MRPI. In general, our results were comparable to those of previously published studies. In our study, the values for midbrain area were comparable to or slightly larger than the values reported in previous studies [12,14,21], and the midbrain to pons area ratios we calculated were comparable to those calculated in other studies that used the method published by Oba et al. [12,15]. The results we obtained for measurements of midbrain diameter and MRPI were also similar to previously published results evaluating patients with PSP and PD [14,22], although the difference between the PSP and PD groups in MRPI was not as striking in our study as in some previous studies [14,21], perhaps due to variations in measurement of small structures such as the MCP and SCP or the smaller sample size in our study.

In this study, neuroradiologists incidentally noted PSP as a possible finding based on qualitative observation of a small midbrain in 20 cases, but only 10% of these patients were found to actually have a clinical history of PSP; the remaining 90% had a wide range of other conditions, many of which did not feature a neurological diagnosis. Thus, the finding of a small midbrain is generally nonspecific. A limitation of this finding is that many of these cases were not necessarily evaluated by a neurologist to assess for the presence or absence of PSP. For example, patients may have undergone MRI for indications such as headache or mental status change, and although the neuroradiologist noted the presence of a small midbrain, the evaluation focused more on acute findings rather than on neurodegenerative disease. Accordingly, these results suggest that prospective diagnosis of PSP based on imaging findings in the absence of a relevant history may be prone to a high false positive rate (that is, low specificity). These results do not aid in characterizing the sensitivity of these MR findings.

Overall, this study confirms the usefulness of quantitative measures of atrophic brain changes in differentiating between PSP-RS and PD in a clinical setting. The association of midbrain atrophy with PSP is well-established [15,16,18,23], and this study highlights that measurements of midbrain atrophy, along with the size of other structures such as SCP and MCP, can play a valuable diagnostic role. Compared to patients with PD and controls, patients with PSP have atrophy of cerebral peduncles and midbrain, and minimal involvement of the frontal lobe [24]. Interestingly, the midbrain atrophy rate can predict clinical decline of PSP [25]. Furthermore, quantification of midbrain size may be less useful in patients with variants of PSP, such as PSP-P, who typically have less midbrain atrophy [26]. These findings by other groups highlight the midbrain changes associated with PSP, and our study has corroborated the usefulness of midbrain changes in aiding diagnosis.

One limitation of this study overall is that diagnoses were based on clinical information, not on verified pathology. Furthermore, because this study was designed to test whether radiologic markers of PSP were useful in a typical clinical population, MRI acquisition was not standardized across patients. Although the duration of PSP and PD in this study was similar, given the typically much more rapid progression of PSP compared to PD, the degree of neurodegeneration in the PSP subjects is likely to be substantially more advanced than in the PD subjects. There is additional variation in the time of diagnosis compared to the onset of disease in PSP and PD that further confounds interpretation of this data.

5. Conclusion

Quantitative MRI measures that have been associated with PSP in well-controlled research populations can be reproduced in a real-word clinical setting featuring a variety of MRI scanners and protocols. This demonstrates the utility of MRI in distinguishing between PD and PSP-RS when there is clinical suspicion of parkinsonism but an exact diagnosis remains unknown. Previous studies have described a set of MRI measures that can be used to identify PSP, and this study details how these methods can be applied in a clinical setting.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2020.100033.

Declarations of Interest

None.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship

All authors played a role in the conception and design of the study. JC and SJ analyzed and interpreted data. All authors drafted the manuscript and gave final approval.

References

[1] D.R. Williams, I. Litvan, Parkinsonian syndromes, Contin. Minneap. Minn. 19 (2013) 1189–1212, https://doi.org/10.1212/01.CON.0000436152.24038.e0.

[2] B. Bluett, Atypical parkinsonism. In: Neuro-Geriatrics: A Clinical Manual. Tousi G, Cummings J., 2017.

[3] G.U. Höglinger, G. Respondek, M. Stamelou, C. Kurz, K.A. Josephs, A.E. Lang, B. Mollenhauer, U. Müller, C. Nilsson, J.L. Whitwell, T. Arzberger, E. Englund, E. Gelpi, A. Giese, D.J. Irwin, W.G. Meissner, A. Pantelyat, A. Rajput, J.C. van Swieten, C. Troakes, A. Antonini, K.P. Bhatia, Y. Bordelon, Y. Compta, J.-C. Corvol, C. Colosimo, D.W. Dickson, R. Dodel, L. Ferguson, M. Grossman, J. Kassubek, F. Krismer, J. Levin, S. Lorenzl, H.R. Morris, P. Nestor, W.H. Oertel, W. Poewe, G. Rabinovici, J.B. Rowe, G.D. Schellenberg, K. Seppi, T. van Eimeren, G.K. Wenning, A.L. Boxer, L.I. Golbe, I. Litvan, Movement Disorder Society-endorsed PSP Study Group, Clinical diagnosis of

progressive supranuclear palsy: The movement disorder society criteria, Mov. Disord. Off. J. Mov. Disord. Soc. 32 (2017) 853–864, https://doi.org/10.1002/mds.26987.

[4] F. Xie, X. Gao, W. Yang, Z. Chang, X. Yang, X. Wei, Z. Huang, H. Xie, Z. Yue, F. Zhou, Q. Wang, Advances in the research of risk factors and prodromal biomarkers of Parkinson's disease, ACS Chem. Neurosci. 10 (2019) 973–990, https://doi.org/10.1021/acschemneuro.8b00520.

[5] D. Lv, J. Li, H. Li, Y. Fu, W. Wang, Imaging and quantitative analysis of the interstitial space in the caudate nucleus in a rotenone-induced rat model of Parkinson's disease using tracer-based MRI, Aging Dis. 8 (2017) 1–6, https://doi.org/10.14336/AD.2016.0625.

[6] R. Weng, X. Wei, B. Yu, S. Zhu, X. Yang, F. Xie, M. Zhang, Y. Jiang, Z.-P. Feng, H.-S. Sun, Y. Xia, K. Jin, P. Chan, Q. Wang, X. Gao, Combined measurement of plasma cystatin C and low-density lipoprotein cholesterol: a valuable tool for evaluating progressive supranuclear palsy, Parkinsonism Relat. Disord. 52 (2018) 37–42, https://doi.org/10.1016/j.parkreldis.2018.03.014.

[7] J. Zou, Z. Chen, X. Wei, Z. Chen, Y. Fu, X. Yang, D. Chen, R. Wang, P. Jenner, J.-H. Lu, M. Li, Z. Zhang, B. Tang, K. Jin, Q. Wang, Cystatin C as a potential therapeutic mediator against Parkinson's disease via VEGF-induced angiogenesis and enhanced neuronal autophagy in neurovascular units, Cell Death Dis. 8 (2017), e2854. https://doi.org/10.1038/cddis.2017.240.

[8] C.P.-W. Cheng, S.-T. Cheng, C.W.-C. Tam, W.-C. Chan, W.C.-W. Chu, L.C.-W. Lam, Relationship between cortical thickness and neuropsychological performance in Normal older adults and those with mild cognitive impairment, Aging Dis. 9 (2018) 1020–1030, https://doi.org/10.14336/AD.2018.0125.

[9] T. Yamanaka, Y. Uchida, K. Sakurai, D. Kato, M. Mizuno, T. Sato, Y. Madokoro, Y. Kondo, A. Suzuki, Y. Ueki, F. Ishii, C.V. Borlongan, N. Matsukawa, Anatomical links between white matter Hyperintensity and medial temporal atrophy reveal impairment of executive functions, Aging Dis. 10 (2019) 711–718, https://doi.org/10.14336/AD.2018.0929.

[10] S. Zhu, X. Wei, X. Yang, Z. Huang, Z. Chang, F. Xie, Q. Yang, C. Ding, W. Xiang, H. Yang, Y. Xia, Z.-P. Feng, H.-S. Sun, M.A. Yenari, L. Shi, V.C. Mok, Q. Wang, Plasma lipoprotein-associated phospholipase A2 and superoxide dismutase are independent predicators of cognitive impairment in cerebral small vessel disease patients: diagnosis and assessment, Aging Dis. 10 (2019) 834–846, https://doi.org/10.14336/AD.2019.0304.

[11] J. Zou, Z. Chen, C. Liang, Y. Fu, X. Wei, J. Lu, M. Pan, Y. Guo, X. Liao, H. Xie, D. Wu, M. Li, L. Liang, P. Wang, Q. Wang, Trefoil factor 3, cholinesterase and Homocysteine: potential predictors for Parkinson's disease dementia and vascular parkinsonism dementia in advanced stage, Aging Dis. 9 (2018) 51–65, https://doi.org/10.14336/AD.2017.0416.

[12] H. Oba, A. Yagishita, H. Terada, A.J. Barkovich, K. Kutomi, T. Yamauchi, S. Furui, T. Shimizu, M. Uchigata, K. Matsumura, M. Sonoo, M. Sakai, K. Takada, A. Harasawa, K. Takeshita, H. Kohtake, H. Tanaka, S. Suzuki, New and reliable MRI diagnosis for progressive supranuclear palsy, Neurology. 64 (2005) 2050–2055, https://doi.org/10.1212/01.WNL.0000165960.04422.D0.

[13] J.L. Whitwell, G.U. Höglinger, A. Antonini, Y. Bordelon, A.L. Boxer, C. Colosimo, T. van Eimeren, L.I. Golbe, J. Kassubek, C. Kurz, I. Litvan, A. Pantelyat, G. Rabinovici, G. Respondek, A. Rominger, J.B. Rowe, M. Stamelou, K.A. Josephs, Movement Disorder Society-endorsed PSP Study Group, Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? Mov. Disord. Off. J. Mov. Disord. Soc. 32 (2017) 955–971, https://doi.org/10.1002/mds.27038.

[14] A. Quattrone, G. Nicoletti, D. Messina, F. Fera, F. Condino, P. Pugliese, P. Lanza, P. Barone, L. Morgante, M. Zappia, U. Aguglia, O. Gallo, MR imaging index for differentiation of progressive Supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy, Radiology. 246 (2008) 214–221, https://doi.org/10.1148/radiol.2453061703.

[15] Y.-H. Kim, H.-I. Ma, Y.J. Kim, Utility of the midbrain Tegmentum diameter in the differential diagnosis of progressive Supranuclear palsy from idiopathic Parkinson's disease, J. Clin. Neurol. Seoul Korea. 11 (2015) 268–274, https://doi.org/10.3988/jcn.2015.11.3.268.

[16] L.A. Massey, H.R. Jäger, D.C. Paviour, S.S. O'Sullivan, H. Ling, D.R. Williams, C. Kallis, J. Holton, T. Revesz, D.J. Burn, T. Yousry, A.J. Lees, N.C. Fox, C. Micallef, The midbrain to pons ratio, Neurology. 80 (2013) 1856–1861, https://doi.org/10.1212/WNL.0b013e318292a2d2.

[17] M. Hwang, H. Yang, Y. Kim, J. Youn, J. Park, Y.E. Huh, H.-T. Kim, J.W. Cho, Differential progression of midbrain atrophy in parkinsonism: longitudinal MRI study, Neurodegener. Dis. 17 (2017) 31–37, https://doi.org/10.1159/000448174.

[18] K. Sakurai, A.M. Tokumaru, K. Shimoji, S. Murayama, K. Kanemaru, S. Morimoto, I. Aiba, M. Nakagawa, Y. Ozawa, M. Shimohira, N. Matsukawa, Y. Hashizume, Y. Shibamoto, Beyond the midbrain atrophy: wide spectrum of structural MRI finding in cases of pathologically proven progressive supranuclear palsy, Neuroradiol. Heidelb. 59 (2017) 431–443, https://doi.org/10.1007/s00234-017-1812-4.

[19] M. Morelli, G. Arabia, F. Novellino, M. Salsone, L. Giofrè, F. Condino, D. Messina, A. Quattrone, MRI measurements predict PSP in unclassifiable parkinsonisms: a cohort study, Neurology. 77 (2011) 1042–1047, https://doi.org/10.1212/WNL.0b013e31822e55d0.

[20] I. Litvan, Y. Agid, D. Calne, G. Campbell, B. Dubois, R.C. Duvoisin, C.G. Goetz, L.I. Golbe, J. Grafman, J.H. Growdon, M. Hallett, J. Jankovic, N.P. Quinn, E. Tolosa, D.S. Zee, Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop, Neurology. 47 (1996) 1–9.

[21] S. Zanigni, G. Calandra-Buonaura, D.N. Manners, C. Testa, D. Gibertoni, S. Evangelisti, L. Sambati, M. Guarino, P. De Massis, L.L. Gramegna, C. Bianchini, P. Rucci, P. Cortelli, R. Lodi, C. Tonon, Accuracy of MR markers for differentiating progressive Supranuclear palsy from Parkinson's disease, NeuroImage Clin. 11 (2016) 736–742, https://doi.org/10.1016/j.nicl.2016.05.016.

[22] E. Owens, K. Krecke, J.E. Ahlskog, R. Fealey, A. Hassan, K.A. Josephs, B. Klassen, J. Matsumoto, J. Bower, Highly specific radiographic marker predates clinical diagnosis in progressive supranuclear palsy, Parkinsonism Relat. Disord. 28 (2016) 107–111, https://doi.org/10.1016/j.parkreldis.2016.05.006.

[23] M. Cosottini, R. Ceravolo, L. Faggioni, G. Lazzarotti, M.C. Michelassi, U. Bonuccelli, L. Murri, C. Bartolozzi, Assessment of midbrain atrophy in patients with progressive supranuclear palsy with routine magnetic resonance imaging, Acta Neurol. Scand. 116 (2007) 37–42, https://doi.org/10.1111/j.1600-0404.2006.00767.x.

[24] S. Price, D. Paviour, R. Scahill, J. Stevens, M. Rossor, A. Lees, N. Fox, Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease, NeuroImage. 23 (2004) 663–669, https://doi.org/10.1016/j.neuroimage.2004.06.013.

[25] J.L. Whitwell, J. Xu, J.N. Mandrekar, J.L. Gunter, C.R. Jack, K.A. Josephs, Rates of brain atrophy and clinical decline over 6 and 12-month intervals in PSP: determining sample size for treatment trials, Parkinsonism Relat. Disord. 18 (2012) 252–256, https://doi.org/10.1016/j.parkreldis.2011.10.013.

[26] U. Saeed, J. Compagnone, R.I. Aviv, A.P. Strafella, S.E. Black, A.E. Lang, M. Masellis, Imaging biomarkers in Parkinson's disease and Parkinsonian syndromes: current and emerging concepts, Transl. Neurodegener. 6 (2017) 8, https://doi.org/10.1186/s40035-017-0076-6.