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Cerebral peduncle angle: Unreliable in differentiating progressive supranuclear palsy from other neurodegenerative diseases☆

Philip W. Tipton [a, 1], Takuya Konno [a, 1], Daniel F. Broderick [b], Dennis W. Dickson [c], Zbigniew K. Wszolek [a, *]

[a] Department of Neurology, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA
[b] Department of Radiology, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA
[c] Department of Neuroscience, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA

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ABSTRACT

Introduction: The significant symptom overlap between progressive supranuclear palsy (PSP) and other parkinsonian neurodegenerative diseases frequently results in misdiagnosis. However, neuroimaging can be used to quantify disease-related morphological changes and specific markers. The cerebral peduncle angle (CPA) has been shown to differentiate clinically diagnosed PSP from other parkinsonian diseases but this result has yet to be confirmed in autopsy-proven disease.
Methods: Magnetic resonance imaging (MRI) scans were obtained for 168 patients representing 69 medical facilities. Following randomization, the images were divided into two groups (Type 1 and Type 2) based upon midbrain morphological differences. Two readers were blinded and independently measured the CPA of 146 patients with autopsy-proven progressive supranuclear palsy (PSP; n = 54), corticobasal degeneration (n = 16), multiple system atrophy (MSA; n = 11) and Lewy body disease (n = 65).
Results: Applying two separate measurement techniques revealed no statistically significant differences in CPA measurements among any study groups regardless of classification measurement approach. The interobserver agreement showed significant differences in measurements using the Type 2 approach.
Conclusion: Measuring the CPA on MRI is not a reliable way of differentiating among patients with PSP, corticobasal degeneration, MSA, or Lewy body disease.

1. Introduction

Clinically diagnosing progressive supranuclear palsy (PSP) and other parkinsonian-like neurodegenerative diseases poses a challenge to practitioners. Clinical heterogeneity within disease populations makes reliance on the presence of pathognomonic features highly unreliable. For example, the absence of down-gaze palsy has been reported to result in the misdiagnosis in up to 60% of pathologically confirmed PSP patients [1–3]. Significant treatment differences among parkinsonian diseases have motivated the search for objective evidence to differentiate these diseases. Gross neuropathological changes including atrophy of the superior cerebellar peduncles and midbrain tegmentum are present in PSP but absent in multiple system atrophy (MSA) and Parkinson disease (PD) [4–7]. Previous imaging studies have attempted to quantify these changes [8–20]. However, many of these measurement techniques are cumbersome and time consuming [8–15]. The techniques that are more practical have been difficult to objectively quantify or have not been sufficiently confirmed with autopsy-proven subjects [17,18].

Atrophy of the midbrain tegmentum presents as changes in the interpeduncular cistern, which is the region between the cerebral peduncles. Yuki et al. observed that patients with PSP had interpeduncular cistern enlargement, which was later shown to be progressive [16,21]. Fatterpekar and colleagues quantified midbrain

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* Corresponding author.
E-mail addresses: tipton.philip@mayo.edu (P.W. Tipton), konno.takuya@mayo.edu (T. Konno), Broderick.daniel.f@mayo.edu (D.F. Broderick), dickson.dennis@mayo.edu (D.W. Dickson), wszolek.zbigniew@mayo.edu (Z.K. Wszolek).

[1] Both authors contributed equally.

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atrophy by calculating an angle between the cerebral peduncles on magnetic resonance imaging (MRI). They showed the cerebral peduncle angle (CPA) to be significantly larger in clinically diagnosed PSP-Richardson Syndrome (PSP-RS) patients compared to MSA patients and PD patients and healthy controls [22]. Their study included patients diagnosed with MSA and PD according to Gilman et al. and Gelb et al., respectively [23,24]. Given the difficulty of determining the clinical diagnosis of these diseases, their study groups may have consisted of heterogeneous conditions. We attempted to validate the CPA measurement technique for differentiating PSP from other neurodegenerative diseases by comparing magnetic resonance imaging (MRI) scans from autopsy-proven cases of PSP, corticobasal degeneration (CBD), MSA, and Lewy body disease (LBD).

2. Materials and methods

2.1. Image selection

Initial inclusion criteria required that all patients have pathologically confirmed disease. Medical records were acquired from 107 medical centers for 328 patients with autopsy-proven PSP (n = 121), CBD (n = 24), MSA (n = 28) and LBD (n = 155). Of these, MRIs of the brain were available for 168 patients; some had multiple MRIs, and in these cases, the most recent scan was used. T2-weighted imaging was the preferred MRI modality; however, in cases where T2-weighted imaging was not available, fluid attenuation inversion recovery (FLAIR) was preferred followed by Fast Spin Echo or Dual Echo. Axial images showing the midbrain were identified. In most cases, there were multiple levels at which the midbrain was visible. Slice level limits were used to specify and standardize the midbrain level for assessment. In the caudal direction, images where the pons was visible were excluded. In the rostral direction, images containing mammillary bodies were excluded. Images were also excluded if the midbrain interpeduncular cistern contour was too irregular for accurate measurement. Approval for this retrospective study was obtained from the Mayo Clinic institutional review board.

2.2. Measurement

Despite the aforementioned rostral and caudal slice limits, there remained variability among axial slice levels resulting in contour variation of the medial borders of the midbrain peduncles. While rostral images consistently have linear medial peduncular borders, the contour becomes increasingly curvilinear as the slice level moves caudally. Therefore, a method of classification was developed to direct the measurement approach. Midbrain sections were classified based on the presence of bilateral inflection points (where the degree of curvature visibly changes) on the medial sides of the cerebral peduncles. Midbrain sections without a bilateral inflection point (i.e. those with a unilateral inflection point, or those with no inflection point on either side) were classified as Type 1 (Fig. 1A, B) and those with a bilateral inflection point were classified as Type 2 (Fig. 1C, D). Rostral images had the tendency to meet the Type 1 criteria, while caudal images tended to meet Type 2 criteria. CPAs were obtained for Type 1 sections using an intersecting line method. Two lines were drawn by independent readers using a function of the QREADS imaging software (Mayo Clinic). Each line was parallel to a medial border of the midbrain peduncle, resulting in an angle (Fig. 1B). Due to the curvilinear nature of caudal slices (Type 2) two angles were obtained using three points for each angle (Fig. 1D). Type 2 θ1 was formed with a vertex at the posteriormost midline point of the interpeduncular cistern and the two remaining points on the anteriormost medial aspect of the cerebral peduncles. Type 2 θ2 was formed using the same vertex as θ1 and the bilateral inflections points on the medial aspect of the peduncles. Measurements were made at magnification of 200%. Two readers independently measured all images meeting inclusion criteria. Readers applied the techniques described above. Readers were blinded to the patient's diagnosis and the other reader's measurements. Reader 1 was a neurology trainee and reader two was a practicing neurologist. Readers practiced measuring the CPA together for several months prior to makes measurements for this study. Both readers agreed upon the type classification of each midbrain slice. The measuring approach was supervised and approved by a fellowship-trained practicing neuroradiologist.

2.3. Analysis

Data for both readers was analyzed separately. Mean angle measurements were calculated for each autopsy-proven neurodegenerative disease group and segregated by midbrain classification (Type 1, Type 2 θ1, Type 2 θ2). Mean angles were compared by an analysis of variance (ANOVA). The mean ages of each disease group were compared by ANOVA, and a Student's *t*-test was used for paired group comparison. We used the Bland-Altman method for interobserver analysis. All statistical analyses were performed using Microsoft Excel and JMP (SAS Institute Inc., Cary, NC, USA).

3. Results

Of the 168 patients with MRI scans, 22 were excluded for the following reasons: 17 did not have an axial image with a slice level rostral to the pons and caudal to the mammillary bodies, and five had poor image quality. The 146 patients analyzed were stratified by diagnosis: PSP (n = 54), CBD (n = 16), MSA (n = 11) and LBD (n = 65). The results from the ANOVA of the disease group ages revealed a significant difference (P = 0.027). Paired comparisons isolated this significance to only LBD vs. MSA (p = 0.021) and LBD vs. CBD (P = 0.020). Patients with PSP had a mean age of 71 years, which was not significantly different (P < 0.05) from any other disease group. Slice thickness and spacing was obtained for every patient except one for whom slice spacing was not available. The mean slice thickness was 4.31 mm (standard deviation [SD]: 0.91 mm) and mean slice spacing was 0.39 mm (SD: 1.02 mm). Among study participants, 83 and 63 midbrain sections were measured using either the Type 1 and Type 2 approach, respectively. Table 1 displays the measurements for autopsy-confirmed groups of PSP, CBD, MSA, and LBD patients. No significant differences existed between the means. A Bland Altman plot was constructed for each measurement type to assess interobserver agreement between the two readers (Fig. 2). There was no significant difference in interobserver measurements for Type 1, Type 2 θ2, or both types as a whole; however, the measurements for Type 2 θ1 were significantly different ($p < 0.044$).

4. Discussion

All of our study subjects had pathologically confirmed disease, and the number of subjects was larger than that of the Fatterpekar et al. (PSP-RS, n = 15; MSA, n = 15; PD, n = 22) [22]; however, we could not verify the utility of the CPA measurement for differentiating PSP from other neurodegenerative diseases. Although atrophy occurs in the tegmentum of the midbrain and the superior cerebellar peduncles in PSP patients [4,5], it is unclear if the CPA widens as atrophy progresses. If the pattern of tegmental atrophy was spatially heterogenous, then the resultant midbrain morphology could be heterogenous. Moreover, if the atrophy was more pronounced in the lateral tegmentum, then a widening CPA could be

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