Progressive Supranuclear Palsy: Brainstem Measurement and its Clinical Implication

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ABSTRACT

Background: Accurate clinical differentiation of progressive supranuclear palsy (PSP) from other extrapyramidal syndromes may be difficult. Objective: To detect the value of mid-sagittal MRI measurements of the midbrain and pons in the diagnosis of progressive supranuclear palsy (PSP) and to differentiate it from mimics [Parkinson Disease (PD) and Multiple-System Atrophy of Parkinson Type (MSA-P)], and to what extent these radiological measurements correlate with the clinical aspects of PSP. Methods: MRI of 11 patients with PSP, 25 patients with PD, and 8 patients with MSA-P as well as 20 age-matched controls were prospectively studied. The areas of the midbrain tegmentum and the pons were measured on mid-sagittal MRI. Patients were also evaluated clinically using Hoehn and Yahr Scale, Unified Parkinson's Disease Rating Scale (UPDRS) and Mini-Mental State Examination (MMSE) scale in addition to full general and neurological assessment and routine laboratory investigations. Results: The mean midbrain area and the ratio of midbrain area to the pontine area of PSP patients were significantly smaller than that of the PD patients, MSA-P patients and the age matched control group. In PSP patients, the radiological measurements studied correlated significantly with disease duration, staging and severity. Conclusion: Mid-sagittal MRI measurements of the midbrain area are reliable diagnostic criteria that can differentiate progressive supranuclear palsy from other common extrapyramidal syndromes and normal aging.

Keywords: Progressive supranuclear palsy (PSP), Magnetic resonance imaging (MRI), Clinical assessment.

INTRODUCTION

Progressive supranuclear palsy (PSP) is a neurodegenerative disease that results in severe disability. It is characterized by supranuclear vertical gaze palsy, pseudo-bulbar palsy, dystonic rigidity of the neck and upper extremities, and frequent falls. In addition to their movement disorder, patients with PSP have a variety of behavioral disturbances, often in association with impairment of executive function. Disruption of cortical-subcortical brain circuits is postulated to be responsible for these clinical features.

The main neuropathology characteristics of PSP are neuronal degeneration and loss in the tegmentum of the midbrain, atrophy of the substantial Ingra (SN), and changes in the red nucleus and globes pallid us.

An accurate method is needed for diagnosing PSP as the clinical differentiation of PSP from PD and Multiple-System Atrophy of Parkinson Type (MSA-P) may be difficult, particularly in the early stages of the disease.

MRI studies on PSP emphasized the utility of mid-sagittal MRI in its diagnosis. Atrophy of the midbrain and pons and dilatation of their surrounding cisterns are more clearly observed on mid-sagittal images, especially in the upper midbrain, than on axial images.

The aim of this study is to evaluate the area of the midbrain and pons on mid-sagittal MRI in patients with PSP, PD and MSA-P to reach and establish reliable MRI diagnostic criteria for PSP and to correlate these MRI measurements with the clinical aspects of PSP.

SUBJECTS AND METHODS

Eleven patients satisfied the diagnostic criteria established by the National Institute of Neurological Disorders and Stroke (NINDS) and Society for Progressive Supranuclear palsy (6 probable and 5 possible). All PSP cases had progressive symmetric Parkinsonism (axial greater than limb) with postural instability and vertical supranuclear palsy. Twenty-five patients satisfying clinical criteria for Parkinson’s disease (20 probable and 5 possible), as defined by the United Kingdom Parkinson’s Disease Brain Bank were selected. All Parkinson’s disease cases had a kinetic-rigid syndrome (limb greater
than axial) in the absence of supranuclear ophthalmoplegia\(^7,8\). Eight cases satisfying clinical features of multiple system atrophy syndrome (4 probable and 4 possible) as defined by the consensus statement on the diagnosis of MSA-P\(^11\) and the criteria set by the research committee on spino-cerebellar degenerations at the Japanese Ministry of Welfare and Health\(^12\). All cases with MSA had a kinetic rigid syndrome and obvious clinical evidence of ataxia and autonomic dysfunction in the absence of supranuclear ophthalmoplegia\(^7,8\).

For comparison 20 age-matched normal healthy individuals were included as a control group.

**Excluded from the study:**

Patients or control cases with history of major head injury, drugs or alcohol abuse, major psychiatric or focal neurological disorders. Patients with known medical disorders e.g. hypothyroidism, D.M, renal or liver impairment, and structural brain lesions including substantial white matter changes on MRI brain images.

All diseased and control subjects underwent the following:

- Full general, physical and neurological assessment as well as routine laboratory tests.
- Disease severity (for patients only) was quantified using the Hoehn and Yahr scale\(^13\). Mutation, ADL, and Motor examination components of the Unified Parkinson's Disease Rating Scale (UPDRS)\(^14,15\), and cognitive examination using Mini-Mental State Examination (MMSE) test\(^16\).

**MRI analysis of the midbrain and Pons:**

All MRI examinations were done using 1.5 – T units (Philips Gyroscan Intera, Superconducting magnet). 3 mm thick sagittal images, including mid-sagittal images were obtained.

The mid-sagittal images were prescribed from the axial images at the level of the midbrain to pass through the center of the interpeduncular cistern and the center of the aqueduct.

Using display tools the areas of the midbrain (measuring the tegmentum but not the tectum) and Pons were measured on the mid-sagittal MRI. The areas of midbrain and Pons were defined as described below and illustrated in Figure1. All mid-sagittal MR images were magnified four times. Two additional straight lines were drawn. The first line was drawn so as to pass through the superior pontine notch and the inferior edge of the quadrigeminal plate (line 1 on Fig. 1 A and B). The second line was drawn parallel to the first line so as to pass through the inferior pontine notch (line 2 on Fig. 1, A and B). The area of the midbrain was traced plotting the delta-shaped part above the first line (excluding the tectum; Fig. 1A). The area of the Pons was traced as the area between the ventral margin of the Pons, the dorsal margin of the Pons, and lines 1 and 2 (Fig. 1B). The measurements were performed four times in each patient, and the mean values of these measurements were used in the statistical analysis.

**Figure 1.** Scheme for measurement of the area of the midbrain and pons on mid-sagittal MRI. On the workstation, mid-sagittal MR images were magnified. Two straight lines were drawn. The first line was drawn to pass through the superior pontine notch and inferior edge of the quadrigeminal plate. The second line was drawn parallel to the first line so as to pass through the inferior pontine notch. The area of the midbrain (A) was traced around the edges of line 1 and the delta-shaped midbrain tegmentum above it. The area of the pons (B) was the area inside the line traced along the anterior and posterior margins of the pons and along lines 1 and 2.
Statistical Analysis
For statistical analysis SPSS (version 11) was used. Simple descriptive statistical tests (mean and standard deviation) were used.

The Mann-Whitney rank sum test was used to compare the individual groups. For the evaluation of correlation between the area of midbrain tegmentum and the area of Pons and various clinical features, the Spearman's rank order test was used.

RESULTS
Demographic data of the patients and control subjects are illustrated in Table (1) and revealed a non-significant differences regarding the sex, age of patients and control subjects and disease duration and staging (using Hoehn and Yahr Scale) of the patients.

MRI measurements were illustrated in Table 2 and revealed that: the area of the midbrain in patients with PSP was about half of the area of the midbrain area in patients with PD, MSA-P and age-matched control group. So a highly statistically significant difference was observed between the midbrain area in patients with PSP compared to PD group, MSA-P group and normal control group (p<0.01).

The area of the Pons was significantly smaller in MSA-P patients than that in the PSP group, PD group and control group, but still the area of the Pons was significantly smaller than that of PD patients and normal control subjects (p<0.01). There was some overlap between the PSP patients and MSA-P patients.

The ratio of the area of the midbrain to the area of the Pons in patients with PSP was significantly smaller than that in those with PD, MSA-P and control groups (p<0.01).

Correlation between various demographic and clinical features and radiological findings (Table 3) revealed a significant correlation between disease staging by H and Y. Disease severity ADL scores of UPDRS, motor examination of UPDRS and midbrain area, pontine area and midbrain/pontine ratio and significant correlation between disease duration and midbrain area and midbrain/pontine ratio only. While non-significant correlations were observed between age, mental state and all radiological data studied.

Table 1. Demographic data in 44 patients and 20 control subjects

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>PSP (n=11)</th>
<th>PD (n=25)</th>
<th>MSA (n=8)</th>
<th>Control (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Male/Female</td>
<td>6/5</td>
<td>16/9</td>
<td>5/3</td>
<td>12/8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Age in years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean±SD</td>
<td>70.3±6.5</td>
<td>69.9±7.3</td>
<td>68.3±6.2</td>
<td>70.1±6.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>- Range</td>
<td>60-80</td>
<td>60-81</td>
<td>58-81</td>
<td>61-82</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Disease duration (months):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean±SD</td>
<td>35.7±16.7</td>
<td>39.3±17.5</td>
<td>40.1±16.2</td>
<td>NA</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>- Range</td>
<td>10-60</td>
<td>14-86</td>
<td>15-60</td>
<td>NA</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hoehn and Yahr Scale:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean±SD</td>
<td>2.7±0.39</td>
<td>2.6±0.41</td>
<td>2.7±0.42</td>
<td>NA</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>- Range</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
<td>NA</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

MSA Multiple system atrophy, NA Not applicable, PD Parkinson disease, PSP Progressive supranuclear palsy, SD standard deviation

Table 2. MRI measurements of the patients and control subjects

<table>
<thead>
<tr>
<th>MRI Measurements</th>
<th>PSP (n=11)</th>
<th>PD (n=25)</th>
<th>MSA (n=8)</th>
<th>Control (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midbrain area:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean (mm²)±SD</td>
<td>57.5±4.8</td>
<td>110.4±12.2</td>
<td>95.6±13.5</td>
<td>117.8±17.4</td>
</tr>
<tr>
<td>- Range (mm²)</td>
<td>33-62</td>
<td>87-125</td>
<td>65-130</td>
<td>101-156</td>
</tr>
<tr>
<td>Pontine area:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean (mm²)±SD</td>
<td>397.9±38.4</td>
<td>497.9±49.6</td>
<td>312.0±42.5</td>
<td>521.0±31.5</td>
</tr>
<tr>
<td>- Range (mm²)</td>
<td>355-430</td>
<td>469-583</td>
<td>207-420</td>
<td>482-611</td>
</tr>
<tr>
<td>Midbrain/Pons ratio:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean±SD</td>
<td>0.123±0.15</td>
<td>0.207±0.13</td>
<td>0.265±0.11</td>
<td>0.235±0.9</td>
</tr>
<tr>
<td>- Range</td>
<td>0.09-0.15</td>
<td>0.17-0.3</td>
<td>0.18-0.49</td>
<td>0.18-0.32</td>
</tr>
</tbody>
</table>

MSA Multiple system atrophy, PD Parkinson disease, PSP Progressive supranuclear palsy, SD standard deviation
The present study showed that the midbrain tegmentum area and midbrain/pons ratio in PSP patients were significantly smaller than those in patients with PD, MSA-P and normal control subjects, these findings were in concordance with that many recent studies\textsuperscript{3,5,17-21}.

Although the area of the pons of PSP patients in this study was significantly smaller than that of PD patients and normal control subjects, still MSA-P patients had a significantly smaller Pons area than PSP patients a finding which was also reported by Emam et al.\textsuperscript{18}.

Although both the midbrain and the pons diminish in size in PSP patients, still midbrain atrophy appears to be more severe than pontine atrophy. Moreover, there was no overlap between PSP midbrain findings and that of PD, MSA-P and control subjects. On the other hand, there was an overlap between the PSP pontine findings and that of MSA-P and the use of the midbrain area/pons area ratio avoided this overlap and hence implies a more accurate differentiation.

These previously observed results confirmed the superiority of sensitivity and specificity of midbrain atrophy over that of pontine atrophy in PSP a finding which was supported by Quattrone et al.\textsuperscript{1}, who reported that a midbrain area <70 mm\textsuperscript{2} strongly suggests the diagnosis of PSP and the sensitivity on using this cut point of 70 mm\textsuperscript{2} is 100% and the specificity is 91.3%. They added that a ratio of midbrain tegmentum to pons of <0.15 strongly argues against the diagnosis of PD and suggest that of PSP and the sensitivity and specificity on using this cut point of 0.15 are both 100%.

Most MRI studies of PSP confirm the diagnostic value of midbrain atrophy in it, but the methods vary widely and include subjective estimates or measurement of the transverse, craniocaudal or anteroposterior diameter of the midbrain in planes that are not reproducible\textsuperscript{18-24}.

Axial MRI is not accurate for the objective evaluation of midbrain atrophy because the lack of reproducibility of the MR plane causes variations of measurement value due to scanning angle\textsuperscript{19,24}.

Atrophy of the midbrain and pons and dilatation of the cisterns are more clearly observed on mid-sagittal images than axial images, especially in the upper midbrain\textsuperscript{16,18}. Mid-sagittal MRI can precisely show atrophic changes that can be reproducibly documented by objective measurements that are not subject to the influence of the scanning angle\textsuperscript{5,25,26}.

Warmuth-Metz et al.\textsuperscript{24} have evaluated the AP diameter of the mesencephalic tectum on mid sagittal MRI. However, the colliculi are very small structures that are located in the para midline of the tectum. Therefore, mid-sagittal images do not accurately evaluate atrophy of the colliculi. Indeed, accurate evaluation of the tectal atrophy is difficult, even using the most recent MRI techniques.

The duration and staging of the disease and manifestations of disease severity were significantly correlated with the reduction of the midbrain area, pontine area and midbrain pontine ratio a findings which were supported by that of Halliday et al.\textsuperscript{27}, who reported that PSP like Parkinsonism, subcortical and brainstem degenerations has been primarily implicated in the gaze palsy of PSP, motor impairment and ADL disturbances suggesting the role of brainstem area in predicting the clinical presentation and staging of patients with PSP. Similar observations were reported by other authors\textsuperscript{1,2,28-30}, who also reported good correlation between brain stem atrophy and cognitive impairment and behavioral changes.

**Table 3.** Correlation between demographic and clinical features and radiological findings in PSP patients

<table>
<thead>
<tr>
<th>Demographic and Clinical Features</th>
<th>Midbrain area (mm\textsuperscript{2})</th>
<th>Pontine area (mm\textsuperscript{2})</th>
<th>Midbrain/pontine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
<td>r</td>
</tr>
<tr>
<td>Age in years</td>
<td>-0.172</td>
<td>&gt;0.05</td>
<td>-0.187</td>
</tr>
<tr>
<td>Disease duration in years</td>
<td>-0.531</td>
<td>&lt;0.05\textsuperscript{*}</td>
<td>-0.232</td>
</tr>
<tr>
<td>Hoehn and Yahr scale</td>
<td>-0.522</td>
<td>&lt;0.05\textsuperscript{*}</td>
<td>-0.532</td>
</tr>
<tr>
<td>MMSE</td>
<td>+0.231</td>
<td>&gt;0.05</td>
<td>+0.167</td>
</tr>
</tbody>
</table>

**ADL** activity of daily living, **MMSE** minimental state examination, **PSP** progressive supranuclear palsy, **r** Pearson’s correlation, **UPDRS5** Unified Parkinson disease rating scale

* Significant at p <0.05
Conclusion
The mid-sagittal MRI measurements of the midbrain area can differentiate PSP from PD, MSA-P and normal aging and these radiological measurements correlated well with the clinical aspects of the PSP syndrome.

[Disclosure: Authors report no conflict of interest]

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الملخص العربي
الشلل فوق النووي المتزايد: قياس جذع الدماغ و أهميته الإكلينيكية

الهدف من هذه الدراسة هو تحديد أهمية قياسات جذع الدماغ في التشخيص الشلل فوق النووي المتزايد وتفاقمها عن الأمراض المشابهة (مرض شلل الرعاش (باركنسون)) ومرض ضمور الأجزاء المتعددة من نوع شلل الرعاش (باركنسون) إلى أي درجة ترتبط هذه القياسات بالجوانب الإكلينيكية لمراض الشلل فوق النووي المتزايد.

تمت هذه الدراسة على 44 مريض [(11 مريض يعانون من مرض الشلل فوق النووي المتزايد، 25 مريض يعانون من مرض شلل الرعاش و 8 مريض يعانون من مرض ضمور الأجزاء المتعددة من نوع شلل الرعاش (باركنسون)] و 20 من الأشخاص الأصحاء كمجموعة مقارنة.

تم إجراء رنين مغناطيسي على المخ قياسات مساحة الدماغ الأسيط والجسم كما تم التقنيات الإكلينيكية للمرض باستخدام مقياس هوني ويار وقياس مريض باركنسون الموثوق وقياس القدرة المعرفية لفولشتين وكذلك التقنيات الإكلينيكية العام والعصبي وتم إجراء الفحوصات المعملية الروتينية.

وقد أظهرت نتائج البحث أن مساحة الدماغ الأسيط والنسبة بين مساحة الدماغ الأسيط والجسم في مرضى الشلل فوق النووي المتزايد أقل بدرجة ذات إحصائية من هذه القياسات لمريض شلل الرعاش ومرض ضمور الأجزاء المتعددة من نوع شلل الرعاش.

ومن هنا يتضح أن قياسات الدماغ الأسيط يمكنها المساعدة في التشخيص المبكر لمريض الشلل فوق النووي المتزايد وتوفيره من الأمراض المشابهة في الأعراض وهذا القياس ترتبط ارتباطًا متزايدًا بالجوانب الإكلينيكية لهذا المرض.