Transcranial Brain Sonography Findings in Discriminating Between Parkinsonism and Idiopathic Parkinson Disease

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Background: In several pilot studies, transcranial brain sonography findings of substantia nigra and lenticular nucleus discriminated between idiopathic Parkinson disease (PD) and atypical parkinsonian disorders.

Objective: To study the use of transcranial brain sonography in excluding the diagnosis of idiopathic PD in patients with sporadic parkinsonism.

Design and Setting: All patients with parkinsonism admitted to our movement disorder clinic from January 1, 2003, through December 31, 2005, who fulfilled clinical diagnostic criteria for definite PD, probable parkinsonian variant of multiple-system atrophy (MSA-P), or probable progressive supranuclear palsy (PSP) were prospectively studied with transcranial brain sonography by an investigator blinded to clinical diagnoses.

Patients: Eligible patients included 138 with sporadic idiopathic PD (82 men and 56 women; mean±SD age, 67.1±9.8 years; mean±SD disease duration, 7.5±6.3 years; mean±SD motor score on the Unified Parkinson Disease Rating Scale, 32.6±18.1), 21 with MSA-P (10 men and 11 women; mean±SD age, 65.4±9.5 years; mean±SD duration of disease, 3.1±2.0 years; mean±SD motor score, 33.5±16.1), and 22 with PSP (13 men and 9 women; mean±SD age, 71.2±5.5 years; mean±SD duration of disease, 3.4±2.4 years; mean±SD motor score, 46.2±18.9). In 7 patients, transcranial brain sonography was not possible owing to insufficient temporal acoustic bone windows.

Main Outcome Measures: Sensitivity, specificity, and predictive value of transcranial brain sonography in indicating an atypical parkinsonian syndrome rather than idiopathic PD in patients with sporadic parkinsonism.

Results: Normal echogenic substantia nigra indicated MSA-P rather than PD (sensitivity, 90%; specificity, 98%; positive predictive value, 86%), whereas third-ventricle dilatation of more than 10 mm in combination with lenticular nucleus hyperechogenicity indicated PSP rather than PD (sensitivity, 84%; specificity, 98%; positive predictive value, 89%). Normal echogenic substantia nigra combined with lenticular nucleus hyperechogenicity indicated MSA-P or PSP (sensitivity, 59%; specificity, 100%; positive predictive value, 100%). In parkinsonism with age at onset younger than 60 years, normal echogenic substantia nigra alone indicated MSA-P or PSP (sensitivity, 75%; specificity, 100%; positive predictive value, 100%).

Conclusions: Distinct transcranial brain sonography findings can exclude the diagnosis of PD in patients with sporadic parkinsonism. Sonographic discrimination of atypical parkinsonian syndromes from PD is clearer in patients with onset of parkinsonism at younger than 60 years.

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diopathic Parkinson disease (PD) and atypical parkinsonian syndromes such as the parkinsonian variant of multiple-system atrophy (MSA-P) and progressive supranuclear palsy (PSP) differ in their prognosis and treatment options but may be difficult to differentiate clinically, especially in the early course of the disease. Also, levodopa sensitivity is not always conclusive in differentiating these diseases. Sophisticated neuroimaging methods such as routine magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography may help to discriminate between PD and atypical parkinsonian syndromes. Despite the high technical demands and costs of these techniques, sensitivity and specificity are not sufficiently high.

Recently, transcranial brain sonography (TCS) was reported to discriminate PD from MSA-P and PSP. The TCS finding of substantia nigra hyperechogenicity is characteristic of PD, whereas normal substantia nigra echogenicity in combination with lenticular nucleus hyperechogenicity suggests atypical parkinsonian syndromes. Substantia nigra hyperechogenicity is thought to reflect...
### Table 1. Demographic Data of Patients Undergoing TCS

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>PD60⁻ (n=59)</th>
<th>PD60⁺ (n=79)</th>
<th>MSA-P (n=21)</th>
<th>PSP (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>34/25</td>
<td>48/31</td>
<td>10/11</td>
<td>13/9</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.1±9.0</td>
<td>72.4±6.6</td>
<td>65.4±9.5</td>
<td>71.2±5.5</td>
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<tr>
<td>Age at disease onset, y</td>
<td>35-75</td>
<td>61-96</td>
<td>48-79</td>
<td>61-80</td>
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<tr>
<td>Mean±SD</td>
<td>49.9±7.6</td>
<td>66.9±5.7</td>
<td>62.2±9.5</td>
<td>67.8±4.7</td>
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<tr>
<td>Range</td>
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<td>60-86</td>
<td>46-77</td>
<td>59-77</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>10.1±7.5</td>
<td>5.6±4.3</td>
<td>3.1±2.0</td>
<td>3.4±2.4</td>
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<tr>
<td>Range</td>
<td>1-29</td>
<td>1-17</td>
<td>1-8</td>
<td>1-10</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>34.6±19.4</td>
<td>31.0±17.1</td>
<td>33.5±16.1</td>
<td>46.2±18.9</td>
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<td>UPDRS-III score, mean±SD</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

Abbreviations: MSA-P, multiple-system atrophy, parkinsonian variant; PD60⁻, idiopathic Parkinson disease with onset at younger than 60 years; PD60⁺, idiopathic Parkinson disease with onset at 60 years or older; PSP, progressive supranuclear palsy; TCS, transcranial sonography; UPDRS-III, motor part of the Unified Parkinson Disease Rating Scale.

aPatients could not undergo TCS owing to bilateral insufficient acoustic temporal bone windows.

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**Figure 1.** Magnetic resonance imaging (MRI) and transcranial sonography (TCS) studies of axial transsections of the brain at midbrain level in 1 patient with multiple-system atrophy (A and B) and 1 patient with idiopathic Parkinson disease (C and D). A, The MRI corresponding to the image in part B. The square denotes the area to be evaluated in sonography of midbrain structures, as shown in parts B and D. B, The TCS image shows normal substantia nigra (SN) echogenicity in multiple-system atrophy. Within the midbrain (encircled area), only some small echogenic dots in the area of the bilateral SN (arrows) can be visualized. C, Schematic illustration of the area shown in part D (a indicates aqueduct; d, dorsal; f, frontal; and r, raphe). D, The TCS image shows abnormal SN in Parkinson disease. In the area of the bilateral SN (arrows), a marked hyperechogenicity can be seen.
increased amounts of iron, bound to proteins other than ferritin in the substantia nigra, and remains unchanged during the course of PD. Also, lenticular nucleus hyperechogenicity is most likely to be caused by increased trace metal content. Because patients with PD and substantia nigra hyperechogenicity (>90% of all patients with PD) were found to have a younger age at disease onset (mean ± SD, 54 ± 7 years) compared with patients with PD and normal substantia nigra echogenicity (<10%; mean ± SD, 65 ± 6 years), we hypothesized that sonographic discrimination from atypical parkinsonian syndromes might be clearer in patients with PD who have onset at younger than 60 years compared with patients with later PD onset. To further assess the discriminative value of TCS, we studied a larger group of patients with PD, randomly mixed with patients with MSA-P or PSP.

METHODS

STUDY POPULATION

We prospectively studied all patients with sporadic parkinsonism admitted to our movement disorder clinic from January 1, 2003, through December 31, 2005, who fulfilled the British Brain Bank criteria for definite PD or the clinical consensus criteria for probable MSA-P or PSP. Computed tomography and/or magnetic resonance imaging of the brain and laboratory workup were performed in all patients to exclude other causes of parkinsonism. Altogether, we included the following 181 patients: 138 with idiopathic PD, 21 with MSA-P, and 22 with PSP. Fifty-nine patients with PD had disease onset at younger than 60 years (PD60− patients), and 79, at 60 years or older (PD60+ patients). The TCS findings of some of these patients (PD60−, n=10; PD60+, n=13; MSA, n=9; PSP, n=6) had contributed to results of a previously published study. Table 1 shows demographic data of the patients studied.

TRANSCRANIAL BRAIN SONOGRAPHY

We performed TCS through the preauricular acoustic bone windows using a phased-array ultrasound system with a 2.5-MHz transducer (Sonoline; Siemens, Erlangen, Germany). The ultrasound variables chosen were penetration depth of 16 cm, dynamic range of 50 dB, and high persistence. Substantia nigra echogenic size measurements were performed on axial TCS images automatically after manually encircling the outer circumference of the echogenic area of the substantia nigra. According to the normal values of substantia nigra echogenic size, obtained by examining 300 healthy adults, the substantia nigra echogenicity was classified into the following 3 groups: group 1, normal substantia nigra echogenicity (echogenic size, <75th percentile of the healthy control group, ie, <0.20 cm²); group 2, moderate substantia nigra hyperechogenicity (echogenic size, 75th-90th percentile); and group 3, marked substantia nigra hyperechogenicity (echogenic size, >90th percentile, ie, ≥0.25 cm²). For classification of patients with respect to their substantia nigra echogenicity, the greater value of bilateral measurements was used. For intergroup comparisons, bilateral substantia nigra echogenic sizes in each individual were used. In addition, echogenicity of the lenticular nucleus was investigated and classified as hyperechogenic when it was more intense than the surrounding white matter. Classification of patients with respect to lenticular nucleus echogenicity was based on the more affected side. Because third-ventricle dilatation was previously reported as a TCS finding characteristic of PSP, the minimal width of the third ventricle was measured. All TCS examinations were performed by 1 experienced sonographer (U.W.) who was unaware of the clinical diagnosis of the patients. The TCS images of brain structures of all patients were stored and analyzed off-line by a second investigator (T.P. or M.A.-M.) blinded to the diagnoses and clinical data. A given structure was regarded as abnormal on TCS only if the findings of both investigators agreed.

STATISTICS

Descriptive statistics are given as medians with lower (25th percentile) and upper (75th percentile) quartiles. For group comparison of substantia nigra echogenic sizes, we used the Mann-Whitney test. We analyzed categorical data by means of the χ² test. For comparison of echogenic sizes with age, disease duration, and disease severity, we performed the Spearman rank correlation test.

RESULTS

A temporal bone window sufficient for an adequate sonographic analysis of the substantia nigra at least on 1 side was found in 57 of 59 PD60− patients, 77 of 79 PD60+ patients, 21 of 21 patients with MSA-P, and 19 of 22 patients with PSP (96% of all patients). Lenticular nucleus TCS was possible in 54 of 59 PD60− patients, 71 of 79 PD60+ patients, 20 of 21 patients with MSA-P, and 19 of 22 patients with PSP (91% of all patients). Third-ventricle measurement was possible in 57 of 59 PD60− patients, 73 of 79 PD60+ patients, 19 of 21 patients with MSA-P, and 20 of 22 patients with PSP (93% of all patients).

In the patients with sufficient temporal acoustic bone windows, moderate or marked substantia nigra hyperechogenicity was found in all PD60+ patients, 74 PD60− patients (96%), 2 patients with MSA-P (10%), and 9 patients with PSP (47%) (Figure 1 and Figure 2). Substantia nigra echogenic sizes were larger in patients with PD than in those with MSA-P (Mann-Whitney test, P<.001) and PSP (P<.001). There was no correlation of substantia nigra echogenic sizes with age, disease severity, or disease duration in either group.
Lenticular nucleus hyperechogenicity was found in 10 PD60− patients (19%), 21 PD60+ patients (30%), 15 patients with MSA-P (75%), and 19 patients with PSP (100%). The patients with PD with and without lenticular nucleus hyperechogenicity did not differ with respect to disease duration, disease severity, age at PD onset, or motor subtype. Lenticular nucleus hyperechogenicity in combination with normal substantia nigra echogenicity was detected only in 13 patients with MSA-P (65%) and 10 patients with PSP (53%) (Figure 3). Lenticular nucleus hyperechogenicity in combination with normal or moderately hyperechogenic substantia nigra echogenicity was seen in none of the PD60− patients, 4 PD60+ patients (6%), 15 patients with PSP (79%), and 15 patients with MSA-P (75%). Third-ventricle dilatation of more than 10 mm was found in 5 PD60− patients (9%), 9 PD60+ patients (12%), 4 patients with MSA-P (21%), and 17 patients with PSP (85%). Combination of third-ventricle width of more than 10 mm with lenticular nucleus hyperechogenicity was exhibited in 1 PD60− patient (2%), 1 PD60+ patient (1%), 4 patients with MSA-P (21%), and 16 patients with PSP (84%) (Figure 4 and Figure 5). Third-ventricle width of more than 10 mm in combination with hyperechogenic lenticular nucleus discriminated PSP from PD with a positive predictive value of 89% (sensitivity, 84%; specificity, 98%). The finding of hyperechogenic lenticular nucleus in combination with normal echogenic substantia nigra or third-ventricle dilatation of more than 10 mm indicated MSA-P or PSP rather than PD, with a positive predictive value of 94% (Table 2).

The flow diagram in Figure 6 displays the diagnostic algorithm and accuracy of substantia nigra and lenticular nucleus TCS for excluding the diagnosis of idiopathic PD in patients with sporadic parkinsonism.

Data obtained in this study show that the combined TCS finding of normal substantia nigra echogenicity
and lenticular nucleus hyperechogenicity excludes the diagnosis of PD, indicating MSA-P or PSP, with a positive predictive value of 100%. In patients with onset of parkinsonism at younger than 60 years, normal substantia nigra echogenicity alone indicates MSA-P or PSP rather than PD, with a sensitivity of 75% and a positive predictive value of 100%. We found that MSA-P is best discriminated from PD by normal substantia nigra echogenicity, whereas PSP is best discriminated from PD by the combined finding of third-ventricle dilatation of more than 10 mm and lenticular nucleus hyperechogenicity.

A limitation of this study is that the diagnosis of MSA-P or PSP in our patients could not be confirmed by postmortem investigation, which is the diagnostic gold standard. We aimed to minimize the liability of a misdiagnosis by including only patients with clinically probable MSA-P or PSP according to current consensus criteria.

On the basis of the findings of 2 pilot studies that identified the substantia nigra, lenticular nucleus, and third ventricle as the brain structures of most value for sono graphic syndrome discrimination, in the present study these structures were systematically studied in a large sample of patients. In a recent study, only the substantia nigra and lenticular nucleus were investigated, and patients with clinically possible MSA-P and PSP were included. Frequency and distribution of TCS abnormalities of the substantia nigra, lenticular nucleus, and third ventricle found in the present study are in line with previous findings in patients with PD, MSA-P, and PSP. The group of patients with PD was subdivided according to onset of parkinsonism before 60 years or at 60 years or older because this cutoff value was found to differentiate patients with PD who had normal and hyperechogenic substantia nigra. Our hypothesis, namely that in
parkinsonian patients with age at onset younger than 60 years, the value of normal substantia nigra echogenicity in predicting MSA-P or PSP is higher than in patients with later onset, was confirmed by the present findings. Substantia nigra echogenicity in our patients with PD was independent of disease duration, which agrees with the findings of a previously reported 5-year follow-up study that demonstrated stable substantia nigra echogenic sizes in patients with PD. In recent studies, normal substantia nigra echogenicity also separated posttraumatic parkinsonism and essential tremor from idiopathic PD. However, the value of substantia nigra hyperechogenicity alone in predicting the diagnosis of idiopathic PD in parkinsonian patients is less specific because substantia nigra hyperechogenicity is also frequent in patients with corticobasal degeneration,10 dementia with Lewy bodies,20 and parkin-related hereditary parkinsonism.11,22 In these entities, the additional TCS findings of more pronounced and bilateral symmetric substantia nigra hyperechogenicity or of lenticular nucleus hyperechogenicity may be obtained and may help to discriminate them from PD.10,20

Data in this study suggest that distinct TCS findings in parkinsonian patients indicate an atypical parkinsonian syndrome rather than PD, with a high positive predictive value. Further studies are necessary that compare TCS findings with postmortem histopathological findings in parkinsonian patients. As TCS has the advantages of wide availability, noninvasiveness, and short investigation times, this method might become useful to improve diagnostic accuracy.

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