Transcranial Sonography of the Substantia Nigra in Japanese Patients with Parkinson’s Disease or Atypical Parkinsonism: Clinical Potential and Limitations

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Abstract

Objective There is growing interest in the use of transcranial sonography (TCS) of the substantia nigra (SN) in patients with Parkinson’s disease (PD), as it has been reported that SN hyperechogenicity may be present in about 90% of PD patients. However, TCS of the SN has not been applied in Japanese patients, and its clinical potential has not been determined.

Patients and Methods TCS of the SN was performed in patients with PD, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and essential tremor (ET), and age-matched controls. Ultrasound images of the SN were assessed using semi-qualitative estimation criteria by two investigators unaware of clinical diagnosis.

Results SN hyperechogenicity was observed in approximately 83% of accessible SNs in Japanese PD patients. In comparison, SN hyperechogenicity was less frequently observed in healthy subjects or in patients with PSP, MSA, and ET. However, the rate of successful recording of the SN by TCS decreased prominently with advancing age, particularly in females.

Conclusion The present study confirmed that TCS of the SN is potentially useful in the investigation of Japanese patients, and it provides a better differential diagnosis between PD and atypical parkinsonism. The recording failure of TCS in aged, particularly female subjects, may limit the clinical potential of TCS of the SN in Japanese patients.

Key words: transcranial sonography, substantia nigra, Parkinson’s disease, progressive supranuclear palsy, essential tremor

Intervention

In 1995, Becker and colleagues first reported hyperechogenicity of the substantia nigra (SN) by transcranial sonography (TCS) in patients with Parkinson’s disease (PD) (1). Since then, there has been continued research on this finding, both clinically and experimentally (2-11), although only to a limited extent. More recently, there is growing interest on the clinical potential of TCS of the SN in patients with PD or related disorders, and is regarded as one of the most important topics in neuroimaging of PD. However, there has been no systematic study that addresses TCS of the SN in Japanese subjects. Since there may be a difference in permeability of transcranial ultrasound between eastern and western people, it is of clinical relevance to determine whether TCS of the SN is also applicable in Japanese subjects. Therefore, the aim of the present study was to examine the clinical potential of TCS of the SN in Japanese subjects, particularly in patients with PD and related disorders.

Subjects and Methods

Subjects

Subjects were patients with PD, atypical parkinsonism...
Table 1. Demographic Data of Patients Studied

<table>
<thead>
<tr>
<th>Disease*</th>
<th>PD</th>
<th>PSP</th>
<th>MSA</th>
<th>ET</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
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<td>17</td>
<td>14</td>
<td>19</td>
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<tr>
<td>Men</td>
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<td>15</td>
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<tr>
<td>Age (year)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
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<td>71.1</td>
<td>67.4</td>
<td>68.6</td>
<td>67.6</td>
</tr>
<tr>
<td>(SD)</td>
<td>(9.3)</td>
<td>(6.8)</td>
<td>(9.3)</td>
<td>(10.9)</td>
<td>(10.1)</td>
</tr>
<tr>
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<td>58-83</td>
<td>50-78</td>
<td>39-81</td>
<td>51-89</td>
</tr>
<tr>
<td>Disease duration (year)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>4.3</td>
<td>7.46</td>
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<tr>
<td>(SD)</td>
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<td>(3.8)</td>
<td>(4.2)</td>
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<td>0.5-12</td>
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<td></td>
<td></td>
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<tr>
<td>Mean</td>
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<td>3.9</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD)</td>
<td>(1.1)</td>
<td>(0.9)</td>
<td>(1.4)</td>
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</table>

* PD, Parkinson disease; PSP, Progressive supranuclear palsy; MSA, Multiple system atrophy; ET, Essential tremor.

that included progressive supranuclear palsy (PSP) and multiple system atrophy (MSA), and essential tremor (ET). Age-matched healthy controls also were studied. Patients’ demographic data are shown in Table 1. Experienced, board-certified neurologists made the clinical diagnoses. Diagnosis of PD was made on the basis of the criteria of the United Kingdom Brain Bank (12). The diagnosis of PSP was made in accordance with the NINDS criteria (13). The clinical diagnosis of MSA was made in accordance with the consensus criteria for probable MSA (14). The diagnosis of ET was made on the basis of the Tremor Investigation Group Criteria (15). All patients provided informed consent.

Transcranial sonography

TCS was performed by using a conventional transcranial Doppler sonographer equipped with a 2.5 MHz phased array transducer (Aplio®, Toshiba Medicals, Japan). TCS was performed in subjects lying in a supine position. Ultrasound scanning was performed through bilateral acoustic bone window using standard techniques as described previously (9-11). In TCS, the midbrain can be depicted as a butterfly-shaped structure of low echogenicity surrounded by hyperechogenic basal cistern. First, to determine whether or not an ultrasound image with sufficient resolution could be obtained in each patient, ultrasound images of the midbrain were graded into three grades (A, B and C) by visual inspection; grade A: midbrain was observed clearly with sufficient resolution for quantitative measurement of the size of hyperechogenicity corresponding to the SN; grade B: midbrain was identifiable, and the SN signals appeared grainy, but sufficient to be quantitatively assessed; grade C: midbrain was identifiable but without sufficient resolution for analysis of the SN, or midbrain was unidentifiable. When the SN was assessable (Grade A or B), SN hyperechogenicity was scored by two investigators who were unaware of clinical diagnosis, using a four-point scale as follows: I = none or faint, II = equivocal, III = definite, IV = marked (Fig. 1). In the present study, when ultrasound signals corresponding to the SN showed a III/IV score, SN hyperechogenicity was defined as significant. In our preliminary study, an inter-rater variability in the evaluation of SN hyperechogenicity was assessed, and a significant concordance in judgment of SN hyperechogenicity between two investigators was found if they estimated SN signals using the above semi-qualitative estimation criteria (the concordance rate of judgment for the presence or absence of SN hyperechogenicity was more than 80%).
Figure 1. SN hyperechogenicity was scored using four-point scale, as follows: I=none or faint, II=equivocal, III=definite, IV=marked.

Figure 2. The rate (%) of successful recording of SN decreases with advancing age, especially in female patients.

Figure 3. In PD patients, significant SN hyperechogenicity (II and IV) was observed in 83% of assessable SNs. In comparison, in other neurological disorders and controls the frequencies of SN hyperechogenicity were generally low: CONT, Control; ET, Essential tremor; MSA, Multiple system atrophy; PSP, Progressive supranuclear palsy; PD, Parkinson’s disease.

Results

Accessibility of SN in Japanese subjects

There was a high rate of recording failure of the SN, judged as grade C, in Japanese subjects (Fig. 2). In aged subjects, particularly in females, it was difficult to obtain clear sonographic images of not only the SN, but also brain parenchyma of the other anatomical sites. In women over 60 years old, 59% of the more of the SN could not be observed by TCS. Comparatively, in subjects under 55 years old the SN could be visualized clearly by TCS in both males and females.

SN hyperechogenicity in parkinsonism

The rates of SN hyperechogenicity in diseased and control subjects in whom the SN was assessable are demonstrated in Fig. 3. The frequency of SN hyperechogenicity, judged as III and IV scales, was significantly increased in PD patients, and observed in 83% of assessable SN (52/63; qui-squire; p<0.001, vs. controls). In addition, marked SN hyperechogenicity was observed only in patients with PD. Simultaneously, the frequency of faint or no SN hyperechogenicity, judged as I scale, was exceptionally low (Fig. 3). There was no correlation between the degree of SN hyperechogenicity and disease stage (Hoehn-Yahr stage; P=0.449), or the degrees of SN hyperechogenicity and duration of illness (P=0.426). In other neurological disorders, the frequencies of SN hyperechogenicity were generally low, as follows: PSP (1/13; 8%); MSA (1/11; 9%); ET (0/13; 0%). The frequency of SN hyperechogenicity in each disease state did not significantly differ to that of healthy controls (1/15; 7%).

Discussion

The present study showed that 83% of subjects who were clinically diagnosed as having PD had SN hyperechogenic-
ity. In comparison, one of 15 healthy subjects (7%) had SN hyperechogenicity. These findings were similar to those of previously published reports demonstrating that SN hyperechogenicity was present in 81% to 100% of examined PD patients (2), and in less than 10% of control subjects (6). Thus, the present study confirmed that SN hyperechogenicity is also a characteristic finding in Japanese patients, although SN hyperechogenicity was assessed semi-quantitatively. Previous studies have shown that there is no significant relationship between the severity of PD and the size of SN hyperechogenicity (3, 8). In addition, it was reported that the size of SN hyperechogenicity did not change during a five-year follow-up period (4), suggesting that SN hyperechogenicity may not be related to disease progression. Our data also confirmed that SN hyperechogenicity had no correlation with disease stage or duration of illness. Thus, as proposed, SN hyperechogenicity may not be a result of neurodegeneration itself, but rather it is a risk marker for nigral injury (16).

TCS has been suggested to be a useful tool for improving the differential diagnosis of parkinsonism as it is often difficult to precisely differentiate PD, PSP, MSA, and ET clinically. Walter et al (7) reported that SN hyperechogenicity was not observed in patients with MSA and PSP. Our study also confirmed a low frequency of SN hyperechogenicity in patients with PSP and MSA, suggesting that TCS of the SN may improve the differential diagnosis between PD and atypical parkinsonism, such as PSP and MSA.

In the present study, SN hyperechogenicity was not observed in ET patients. This is an interesting finding as there is no consensus about SN hyperechogenicity in ET patients. One study reported that ET patients did not have SN hyperechogenicity more often than in healthy controls (17). However, Stockner et al recently reported that 16% of ET patients, but only 3% of controls, had SN hyperechogenicity (18), suggesting that the frequency of SN hyperechogenicity may be slightly higher in ET patients. Since ET patients may have an increased risk of future development of PD, or a subset of tremor-dominant PD patients may be misdiagnosed as having ET in the early phase of their illness, it will be clinically important in the future to determine whether or not ET patients have more SN hyperechogenicity than controls.

The present study also demonstrated a relevant limitation of TCS in Japanese subjects. Unfortunately, the rate of successful recording of the SN decreased prominently with advancing age, particularly in females. This is a practical disadvantage in using TCS as a diagnostic tool for Japanese patients. It is possible that technical problems may contribute to the high frequency of recording failure of the SN; however, we consider this unlikely as our two investigators in TCS had more than at least two years experience, and there was no prominent inter-rater variability between the two investigators in qualitative identification of the midbrain by TCS (our preliminary data). In addition, the high frequency of recording failure in TCS in Japanese subjects has been already noted in the case of examination of the middle cerebral artery (19, 20). Thus, the high incidence of recording failure of TCS in Japanese patients is likely to be an unfortunate limitation of TCS, possibly because of postmenopausal osteoporosis in Japanese female subjects.

Finally, the present study showed that 83% of Japanese PD patients had SN hyperechogenicity, suggesting that SN hyperechogenicity is also a typical, stable finding in Japanese PD patients. In addition, it is expected that TCS of the SN will be useful for the differential diagnosis between PD and atypical parkinsonism, such as PSP and MSA. However, unfortunately, the rate of successful recording of the SN decreased remarkably with advancing age, particularly in female patients. This may prove a practical disadvantage in the clinical application of TCS in Japanese patients. In contrast, since the SN is easily visible by TCS in subjects less than 60 years old, TCS is likely to be useful for the pre-clinical evaluation of the risk for developing PD in the future in relatively younger subjects.

References


