How to Measure Substantia Nigra Hyperechogenicity in Parkinson Disease

Detailed Guide With Video

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The detection of an enlarged echogenic size ("hyperechogenicity") of the substantia nigra on transcranial sonography has become increasingly used for the early and differential diagnosis of Parkinson disease. However, the diagnostic value of substantia nigra sonography depends on the quality of its execution. This article with an accompanying video presents a step-by-step description and demonstration of ultrasound system settings, typical errors in assessment of the substantia nigra, planimetric measurement of substantia nigra echogenicity according to current guidelines, and its diagnostic implications in 2 exemplary patients with parkinsonism. Published cutoff values for grading substantia nigra hyperechogenicity with different ultrasound systems and novel technologies are reviewed.

Key Words—methodological standard; Parkinson disease; parkinsonism; substantia nigra; transcranial sonography

Since its first description, the detection of an enlarged echogenic size ("hyperechogenicity") of the substantia nigra on transcranial sonography has become a widely recognized diagnostic tool in Parkinson disease. The finding of a hyperechoic substantia nigra supports the discrimination of Parkinson disease from atypical parkinsonian syndromes and essential tremors. Its clinical use could be recommended provided the adherence to methodological guidelines. An evolving application of substantia nigra transcranial sonography is the detection of Parkinson disease at premotor stages.

To date, the best-validated method to grade substantia nigra echogenicity is the planimetric measurement of the substantia nigra's echogenic signals in the axial plane. Semiquantitative visual grading was less reliable. Efforts to quantify substantia nigra echogenicity in a less rater-dependent way, eg, by measuring the echo intensity of the substantia nigra relative to surrounding parenchyma, volumetry, semiautomatic substantia nigra detection, and complex mathematical echo signal analysis, have either failed or are not ripe for clinical application. To rate the substantia nigra as normoechoic or hyperechoic on the basis of planimetric measurements, cutoff values need to be established for each different ultrasound system and each different ultrasound laboratory even if using the same system. The following ultrasound system settings are recommended: penetration depth, 14 to 16 cm; dynamic range, 45 to 55 dB; and, if selectable, a postprocessing preset with...
moderate suppression of hypoechoic signals. Image brightness and time-gain compensation are adapted visually or by automated image optimization (available on high-end ultrasound systems). The substantia nigra’s echo signals may have a patchy, bandlike, or sometimes a wide oval appearance, which may slightly vary even in the same individual if different transducer angulations or various ultrasound systems are used (Figure 1). This variation is caused by the following: (1) the arched anatomic structure of the substantia nigra, (3) the transcranial sonographic image composition from an approximately 2-mm-thick “slice” of the brain, (3) the 1.5- to 3-fold higher axial than lateral transcranial sonographic image resolution, and (4) different imaging technologies of diverse ultrasound systems.

According to consensus guidelines, marked substantia nigra hyperechogenicity is considered if the measured echogenic area exceeds a cutoff value defined by the 90th percentile of measurements in a normal population, and moderate hyperechogenicity is considered if the measured area ranges between the 75th and 90th percentiles of measurements in a normal population. Most authors use the larger of bilaterally measured sizes for rat-

Table 1 displays cutoff values for different ultrasound systems. Although methodological recommendations for transcranial sonography have been published, there is a lack of detailed, video-supported instructions. This article with a video presents measurement of substantia nigra echogenicity in more detail and its diagnostic implications in 2 exemplary patients with parkinsonism.

Technique

Patient 1

A 67-year-old man presented with akinetic rigid parkinsonism slightly pronounced in the right extremities, which responded initially to l-3,4-dihydroxyphenylalanine (levodopa). His symptoms deteriorated gradually over 6 years, eventually with a predominating gait disorder and frequent falls. At 73 years, dysarthrophonia and hypometric vertical eye saccades became evident. He was referred for transcranial sonography to differentiate between Parkinson disease and atypical parkinsonian syndrome.

Transcranial sonography was performed with an Acuson Antares ultrasound system (see Table 1 for detailed system settings) equipped with a 2.5-MHz phased array transducer (Figure 1), as also shown in Video 1, section 1:

1. The patient was placed in the supine position on an examination chair.
2. The transcranial ultrasound probe was placed on the right temple near the ear and parallel to the orbitomeatal line to obtain a standardized axial view of intracranial structures.
3. The optimum transtemporal bone window was located by moving the probe near the anterior helix of the ear conch and searching for the probe position with best available visualization of brain structures and the contralateral skull bone. The stability of the probe position was controlled by pressing the probe and also the small finger/ulnar edge of the hand firmly on the patients’ head throughout the examination.
4. The butterfly-shaped midbrain surrounded by the highly echogenic basal cisterns was identified on the monitor. Image brightness was adapted at a moderate level.
5. The whole rostrocaudal dimension of the midbrain was scanned by tilting the probe up and down. Thereby, the investigator focused his attention on the monitor to identify the echo signals of the substantia nigra, midbrain raphe, and red nucleus in their referring anatomic locations by their brightness, which was similar to that of the basal cisterns surrounding the midbrain.
6. The axial midbrain transection showing the echo signals of the ipsilateral substantia nigra in its largest extension was located by slight tilting of the probe.
7. The clearest, most compact view of the substantia nigra’s echogenic signals was located by very slight probe movements. Once the substantia nigra was seen very clearly, even if only shortly, the image was frozen immediately. After moving back to the optimum frame using the cine mode, the midbrain was zoomed out 2- to 3-fold. The substantia nigra’s echogenic signals were surrounded manually by the cursor using the trackball, resulting in automatic calculation of the echogenic area (here, 0.16 cm²).
8. After rescanning as described in 6 and 7, a second measurement was obtained (0.14 cm²). Since both measurements were similar, their mean value (0.15 cm²) was considered to represent the right-sided substantia nigra echogenic size, which was normal.
9. Tilting the probe more cranially, the third ventricle, thalami, basal ganglia, and frontal horns were assessed (not shown). Third ventricle dilatation (10.5 mm) and a hyperechoic lesion of the lenticular nucleus were detected.
10. The procedures described in 2 through 9 were performed through the left transtemporal bone window (not shown). The left substantia nigra echogenicity...
Figure 1. Images of the substantia nigra. A. Axial transcranial sonogram of the brain at the midbrain level obtained from patient 1. In the center of the image, the butterfly-shaped weakly echogenic midbrain is displayed, which is surrounded by the highly echogenic basal cisterns. The rectangle corresponds to the zoomed image of the midbrain shown in the inset panel in the top right corner; in this panel, the echo signals of the substantia nigra are surrounded (here, normal echogenic area). Note the typical imaging artifact from the basal cistern (arrows) that should not be mistaken for substantia nigra echo signals. For comparison, an exemplary image obtained from patient 2 with a markedly hyperechoic substantia nigra is shown in the inset in the top left corner. B. Transducer position for substantia nigra transcranial sonography. C. Magnetic resonance image corresponding to the transcranial sonographic plane shown in A. D. Transcranial sonogram of the midbrain corresponding to the rectangle in A. The midbrain was surrounded for better recognition. The transcranial sonograms shown in A and D were obtained with an Acuson Antares ultrasound system. E. Corresponding image of the substantia nigra in patient 1 obtained with a Sonoline Elegra ultrasound system. F. Corresponding image of the substantia nigra in patient 1 obtained with a MyLab 25 Gold ultrasound system. G. Schematic illustration of the transcranial sonograms shown in A, D, E, and F. 1 indicates substantia nigra echo signals; 2, red nucleus echo signals; 3, midbrain raphe and aqueduct echo signals; and arrows, imaging artifact from the basal cistern in a typical location.
was normal. Bilateral lenticular nucleus hyperechogenicity was found.

11. In the report, the findings on midbrain structures, basal ganglia, and ventricles were described. In conclusion, the transcranial sonographic findings were compatible with the diagnosis of progressive supranuclear palsy rather than multiple-system atrophy but not Parkinson disease.3

**Patient 2**

A 70-year-old woman developed a slowly progressive gait disturbance with occasional falls and bradykinesia more pronounced on her left extremities. At 71 years, she presented with hypomimia, generalized bradykinesia, and postural instability. She was referred for transcranial sonography to support the differentiation of Parkinson disease versus atypical parkinsonian syndrome.

Transcranial sonography was performed as described above and shown in Video 1, section 2. The right substantia nigra was found to be moderately hyperechoic (0.25 cm²), and the left substantia nigra was markedly hyperechoic (0.31 cm²). Other brain structures were unremarkable. The transcranial sonographic findings were characteristic of Parkinson disease.3

**Discussion**

The patients presented here are typical of cases from a movement disorder clinic referred for diagnostic transcranial sonography. Transcranial sonography supports the discrimination of Parkinson disease from the 2 most frequent atypical parkinsonian syndromes: progressive supranuclear palsy and multiple-system atrophy, already at early disease stages.4,31 The key finding arguing against the diagnosis of Parkinson disease is normal substantia nigra echogenicity (positive predictive value, >80%),4,31–34 especially if combined with lenticular nucleus hyperechogenicity and, in progressive supranuclear palsy, a third ventricle width greater than 10 mm (positive predictive value, >90%; Figure 2).2,3

High intra- and inter-rater reliability and diagnostic accuracy of planimetric substantia nigra echogenicity measurements have been demonstrated by numerous groups.7,14,20,22,26–28,35–38 Another group reported less favorable reliability; however, no transcranial sonograms were presented in their publications.39,40 A number of investigator- and laboratory-related pitfalls can impair the reliability of transcranial sonography and need to be excluded before diagnostic application (Table 2).2,7,13,35,41

<table>
<thead>
<tr>
<th>Manufacturer/ Ultrasound System</th>
<th>Probe / Frequency, MHz</th>
<th>Cutoff Value, cm²</th>
<th>Reference</th>
</tr>
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<tbody>
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<td>Aloka/ProSound SSD-5500</td>
<td>Cardiac/2.5</td>
<td>≥0.20</td>
<td>Budisic et al22</td>
</tr>
<tr>
<td>Aloka/ProSound Alpha 10</td>
<td>UST-5210/5.2/5</td>
<td>≥0.19, ≥0.25</td>
<td>Mijajlovic et al23</td>
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<td>≥0.20</td>
<td>Ressner et al24</td>
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<td>≥0.20</td>
<td>Go et al25</td>
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<tr>
<td>ESAOTE/Technos MP</td>
<td>Sector/2.5</td>
<td>≥0.19, ≥0.25</td>
<td>Mijajlovic et al26</td>
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<td>GE/LOGIQ 7</td>
<td>35/2.5</td>
<td>≥0.20</td>
<td>Stockner et al27</td>
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<td>GE/LOGIQ 9</td>
<td>35/2.5</td>
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<td>Kim et al28</td>
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<td>≥0.20</td>
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<td>Mehner et al30</td>
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<td>≥0.20</td>
<td>Hagenah et al31</td>
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<tr>
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<td>≥0.24</td>
<td>van de Loo et al32</td>
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<tr>
<td>Siemens/Sonoline Elegra</td>
<td>2.5PL20/2.6</td>
<td>≥0.20</td>
<td>Glaser et al33</td>
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</table>

SN-h indicates substantia nigra hyperechogenicity.

*Hitachi Aloka Medical, Ltd (Tokyo, Japan), ESAOTE SpA (Genoa, Italy), GE Healthcare (Waukesha, WI), Philips Healthcare (Best, the Netherlands), and Siemens Medical Solutions (Mountain View, CA).

The cutoff values for the Sonoline Elegra and LOGIQ 7 systems were obtained by studying large normal populations. With most other transcranial Doppler systems, the cutoff values were derived from receiver operating characteristic curve analysis of diagnostic discrimination between patients with Parkinson disease and healthy individuals and/or by direct comparison of 2 different ultrasound systems in the same study cohort.

Substantia nigra hyperechogenicity was regarded present if a substantia nigra echogenic size of 0.20 cm² or larger was found bilaterally.

*Mean of bilateral measurements.

**Table 1** Reported Cutoff Values for Discrimination Between a Normoechogenic and Hyperechoic Substantia Nigra on Different Ultrasound Systems
After resolving these issues, substantia nigra transcra-
nial sonography can be learned by physicians within 2 to 8
weeks depending on their previous sonography experi-
ence2 and can be reliably performed even by adequately
trained doctoral students and medical technicians.8,25,36
In 4 adequately trained raters independently investigating
the same study cohort with transcranial sonography, the
intra-rater reliability (intraclass correlation coefficients) of
substantia nigra planimetry was found to range between
0.75 and 0.95, and inter-rater reliability ranged between
0.84 and 0.89.14 To maintain high inter-rater reliability of
substantia nigra transcranial sonography with increasing
worldwide use, strict methodological standards need to be
communicated, which was also the intention of this report.
The upcoming transcranial sonography and magnetic reso-
nance imaging fusion technologies promise an easier assess-
ment of substantia nigra echogenicity in the near future,
which will further improve its diagnostic application.

Table 2: Pitfalls and Recommendations for Their Avoidance in Sonographic Assessment of the Substantia Nigra

<table>
<thead>
<tr>
<th>Pitfalls</th>
<th>Recommendations to Avoid Pitfalls</th>
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<tbody>
<tr>
<td>Investigator related</td>
<td></td>
</tr>
<tr>
<td>Inadequate qualification in interpreting sonograms35</td>
<td>Attend transcranial sonography courses</td>
</tr>
</tbody>
</table>
| Inadequate qualification in understanding brain anatomy26             | Receive initial supervision by an expert sonologist experienced in transcranial
|                                                          | sonography in movement disorders5                                             |
| Errors in inclusion of highly echogenic signals of structures          | Publish data only of investigators who had performed and analyzed transcranial
| neighboring the substantia nigra, ie, red nucleus and                  | sonographic examinations of >200 patients41                                   |
| basal cisterns7                                                       |                                                                               |
| Laboratory related                                                     |                                                                               |
| Use of former-generation, low-standard ultrasound systems              | Use a contemporary ultrasound system                                          |
| Inappropriate or changing ultrasound system settings27                 | Apply recommended system settings (usually frequency, 2.5 MHz, dynamic range,
|                                                          | 40–50 dB, contour amplification, medium to high, postprocessing function, moderate suppression of low-echo signals)23 |
| Missing establishment of normal ranges of substantia nigra echogenic   | Investigate 50, better, 100–200, healthy individuals to establish normal ranges
| sizes in the referring ultrasound laboratory2                          | of substantia nigra echogenic sizes2                                           |
References


Walter—How to Measure Substantia Nigra Hyperechogenicity in Parkinson Disease


