A New Assessment Tool for Parkinson Disease

The Nigral Lesion Load Obtained by Transcranial Sonography

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Objectives—A sonographic method that provides for the measurement of a single frozen image and ignores the remaining portions of the midbrain has been used recently as a biological marker of Parkinson disease. We propose a new approach to evaluating the midbrain: obtaining the nigral lesion load, with which it is possible to acquire an estimate of the real damage to the substantia nigra.

Methods—We studied 60 patients with Parkinson disease and classified them according to the Hoehn and Yahr scale (Neurology 1967; 17:427–442). Magnetic resonance imaging of the brain, ioflupane-labeled single-photon emission computed tomography, and technetium Tc 99m–labeled single-photon emission computed tomography were performed. Assessment of the midbrain parenchyma was performed with transcranial sonography to quantify the extent of hyperechoic signals on 2 different scans (upper and lower substantia nigra).

Results—In 90% of patients (54), we found pathologic hyperechoic substantia nigra signals (>0.25 cm²). These data were similar to those described previously by other authors. However, the sum of the values obtained from each measurement (total of 4 per patient) showed that patients with severe disease had larger nigral lesion loads. In most cases, the study showed impairment of the nigrostriatal dopaminergic system when the hyperechoic pattern was more pronounced.

Conclusions—Transcranial sonography is a useful tool for Parkinson disease workup. A single measurement of substantia nigra echogenicity may be insufficient for an optimal definition of the stage of the disease. A study of the entire midbrain may deliver more information than a single measurement.

Key Words—Parkinson disease; single-photon emission computed tomography; sonography; substantia nigra; transcranial sonography

In the last decade, transcranial sonography became the traditional diagnostic approach to Parkinson disease in all studies performed to date, as described since 1999.1–7 The first article published by Becker et al8 in 1995 described only semiquantitative assessment of the substantia nigra. After image freezing, the midbrain is zoomed 2- or 3-fold, and the hyperechoic area is measured at its largest extension. Finding a value greater than 0.25 cm² can validate the diagnosis. Therefore, this value reflects a structural change in the substantia nigra, leading to functional impairment of the nigrostriatal dopaminergic system. A recent study reported high interobserver reliability of traditional transcranial sonography.9
Thus, substantia nigra hyperechogenicity has been proposed as a biological marker to indicate an increased risk for developing Parkinson disease or a subclinical stage of the disease but, to our knowledge, has not been mentioned as a tool for indicating the specific stage of the disease. In fact, almost all studies show that if the size of this area is increased, we do not observe a correlation with the clinical severity of disease. So far, measurement is obtained by a single scan in which the hyperechoic area is most evident. The aim of our study was to investigate whether changes could be detected with transcranial sonography in the upper and lower planes because we believed that relying on a single scan was limited. Indeed, the midbrain is about 2 cm long, and when exploring it, we found that to achieve better results, it was necessary to change the diagnostic approach (Figure 1).

Materials and Methods

Patients

Over a 2-year period, our investigation involved 60 patients (15 female and 45 male) with Parkinson disease (age range, 45–85 years). All patients underwent a neurologic assessment. Diagnosis was established according to the UK Parkinson’s Disease Society Brain Bank.10 Eight patients were graded as Hoehn and Yahr stage I,11 32 as Hoehn and Yahr stage II, and 20 as Hoehn and Yahr stage III. The scale was rated 12 hours after drug suspension. We excluded patients who had gaze palsy and pyramidal or cerebellar signs. None of the patients had a history of neuroleptic therapy or other identifiable possible causes of secondary Parkinsonism. Patients with cerebrovascular diseases, psychiatric disorders, and any other diseases that might affect ioflupane uptake (DaTscan) were excluded. An insufficient bone window was an exclusion criterion for 12 patients, in 5 of whom we could observe only a part of the midbrain. Clinical assessments including clinical scores, single-photon emission computed tomography (SPECT), and transcranial sonography were performed independently by physicians, who were blinded to the results of the other examinations.

Participants enrolled were consecutive patients recruited from those of the Department of Neurology, Hospital of Vittoria, Ragusa, Italy. This work came from daily hospital activity, in which patients undergo various medical tests. For this reason, we did not require permission from our institution’s Ethics Committee. All patients provided informed consent before participation in the study.

Transcranial Sonography

All examinations were performed by a sonographer with more than 15 years of clinical experience. The investigator was not blinded to the patients while scanning but was not explicitly informed about the groups to which the patients belonged. For transcranial sonography, a commercial ultrasound device (LOGIQ 7 Pro; GE Healthcare, Milwaukee, WI) with a 2–4-MHz phased array sector transducer was used. Imaging was performed through the right and left temporal acoustic bone windows with a penetration depth of 15 to 16 cm, a dynamic range of 45 to 50 dB, and a mechanical index of 1.5. Postprocessing parameters were set for moderate suppression of low echo signals. The image brightness was adapted as needed. The midbrain was imaged in standardized axial scanning planes, parallel to the orbitomeatal line and identified by its butterfly shape, surrounded by the echogenic basal cisterns. From this position, by tilting the ultrasound beam upward, with an angle of approximately 10° to 15° until the third ventricle, the echogenicity of the ipsilateral substantia nigra could be assessed, scanned across its length, and stored. The first half of the clip showed the region of the inferior colliculus (lower substantia nigra), and the second half showed the region of the superior colliculus (upper substantia nigra; Figures 2 and 3 and Video 1). To ensure the reliability of the examination, it was absolutely necessary to maintain a constant scanning speed.

We know that the red nucleus is located in the rostral midbrain and lies just dorsal to the substantia nigra at the level of the superior colliculus.12,13 To avoid the risk of...
Figure 2. Patient 56 (Hoehn and Yahr stage, II; nigral lesion load, 1.02 cm²). From the orbitomeatal line, by tilting the ultrasound beam upward, with an angle of approximately 10° to 15° until the third ventricle, the echogenicity of the ipsilateral substantia nigra could be assessed, scanned across its length, and stored. The first half of the clip showed the region of the inferior colliculus (lower substantia nigra), and the second half showed the region of the superior colliculus (upper substantia nigra). Substantia nigra echogenicity was quantified by a planimetric measurement of the maximum extension of hyperechoic signals at the level of the inferior and superior colliculus to achieve what we defined as the nigral lesion load. In this example, the clip of the left midbrain contained 171 frames, whereas the clip of the right side contained 135 frames. Frames 65 (left) and 57 (right) showed the greatest hyperechoic areas in the lower regions of the midbrain; frames 123 (left) and 85 (right) showed the greatest hyperechoic areas in the upper regions.

Figure 3. Patient 5 (Hoehn and Yahr stage, III; nigral lesion load, 1.55 cm²). In this patient, all of the findings were higher than the cutoff (>0.25 cm²).
unknowingly measuring it, we looked carefully at the transition between the lower and upper substantia nigra, avoiding assessment errors as much as possible. After the image was frozen, the measurements were made after optimization of the signal at its greatest extension. Substantia nigra echogenicity was quantified by a planimetric measurement of the maximum extension of hyperechoic signals at the level of the inferior and superior colliculi to achieve what we defined as the nigral lesion load, which was the sum of 4 measurements, 2 on each side (Table 1). In our ultrasound laboratory, the cutoff value (90th percentile) for the substantia nigra area was found to be equivalent to the cutoff values from other studies using different ultrasound devices, and high intrarater correlation was reported.14 Then, echogenic sizes smaller than 0.25 cm² were classified as normal and measurements of 0.25 cm² and larger as pathologic.

Single-Photon Emission Computed Tomography
Perfusion SPECT data were obtained 1 hour after injection of technetium Tc 99m. After 7 to 10 days, cerebral SPECT was performed with ioflupane (DaTscan), and measurements were obtained 4 hours after intravenous injection of this radioactive substance. Cerebral striatal/posterior lobe binding of ioflupane was assessed semiquantitatively by using a region-of-interest technique, after registration of the patient’s SPECT images with a pattern of the mean activity distribution obtained from a control group.

Magnetic Resonance Imaging
Data from 1.5-T magnetic resonance imaging were acquired by using different sequences (T1 weighted, T2 weighted, and fluid-attenuated inversion recovery) to exclude cerebrovascular diseases, tumors, and other causes of secondary parkinsonism.

Statistical Analysis
Statistical analysis was performed with the Spearman rank correlation test (nonparametric measure of statistical dependence between variables) and the Pearson correlation coefficient (sensitive to a linear relationship between variables).

Results
Cerebral magnetic resonance imaging findings excluded secondary parkinsonism in all patients. Transcranial sonography was performed in 60 consecutive patients with sufficient bone windows. Ninety percent of the patients (54) showed highly characteristic enlargement of the echogenic substantia nigra signal. According to the previous...
Studies have shown no change in substantia nigra sizes over the course of the disease and emphasize that if the extent of the hyperechoic substantia nigra signal increases, we often do not observe a more severe clinical picture. There may be an explanation for this lack of correlation. So far, in fact, measurements have been obtained with a single scan in which the hyperechoic area is more evident. We thought that relying on a single scan was limited, and that it was necessary to change the diagnostic approach to study the entire midbrain. Only in this way can we have a clear estimate of the lesion load, which may reflect the different presentations and severity of Parkinson disease.

It happens frequently that 2 or more patients have the same hyperechoic area values, considering the segment with the maximum signal extent but different nigral lesion loads. This finding could explain why some patients show the same pathologic area in one segment but different disease severity. In those cases, a single scan may be useful for diagnosis, whereas several scans may reflect the real damage to the substantia nigra. We found that multiple scans were able to show a significant correlation between the level of echogenicity in the substantia nigra and the clinical stage.

Our results emphasize the importance of this new approach, and we have confirmed the usefulness of transcranial sonography for evaluation of Parkinson disease with regard to the correlation between the level of echogenicity in the substantia nigra and the clinical stage of the disease.18 Tissue iron content stores probably increase gradually and irregularly in the different regions of the substantia nigra, leading to functional impairment of the nigrostriatal dopaminergic system. It is supposed that substantia nigra hyperechogenicity reflects an increased amount of iron in the substantia nigra, which is bound to proteins.19-21 Therefore, it is correct to think that this slow, gradual, and relentless process is able to indicate progressive worsening of the disease, and by measuring the area of hyperechogenicity, we can obtain a more precise analysis of the course of Parkinson disease. Furthermore, our data were corroborated by the results derived from SPECT: in about 70% of patients with a nigral lesion load exceeding 1.30 cm², we found markedly low ioflupane uptake. Statistical analysis confirmed a significant correlation between the nigral lesion load and Hoehn and Yahr stage, as shown by the Spearman ρ (0.74), the Pearson correlation coefficient (0.73), and the high value (1.52) of the parameter that determined the slope of the line.

In conclusion, nowadays, transcranial sonography is universally accepted as a reliable and highly sensitive tool for differentiation of patients with Parkinson disease from individuals without central nervous system disorders.22 It is known that a hyperechoic substantia nigra signal and reduced striatal uptake on DaTscan are common findings in Parkinson disease. In our patients, substantia nigra echogenicity correlated with striatal ioflupane uptake and significantly with the Hoehn and Yahr stage, suggesting that substantia nigra echogenicity is a quantitative marker of substantia nigra degeneration. Previous longitudinal studies indicate that the ultrasound signal does not change in the course of Parkinson disease, and the same substantia nigra echogenicity could be found in early as well as late stages of disease.

Table 2. Nigral Lesion Loads, Hoehn and Yahr Stages, and SPECT Findings for the 60 Patients

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Pearson correlation showed that there was a positive linear relationship between the nigral lesion load (NLL) and Hoehn and Yahr scale (r = 0.73; r² = 0.53). Regression analysis with the parameter that determined the slope of the line (b = 1.52) confirmed the correlation. The Spearman rank correlation coefficient (0.74) was greater than the critical ρ (<0.3); therefore we rejected the hypothesis of no correlation between the variables. For SPECT findings, + indicates mild reduction in tracer uptake; ++, moderate reduction; and ++++, severe reduction.
stages of the disease, whereas parkinsonian symptoms clearly progress over time. However, in previous studies, measurements were performed by using only a single section of the midbrain at the maximum extension of the hyperechoic signal. From our data, multiple scans could indicate a significant correlation between the amount of hyperechoic deposits in the substantia nigra and the clinical stage. The most important and central point remains the nigral lesion load, obtained by 4 captured images in the predefined planes of superior and inferior colliculi. The limitations of the method are almost the same as described previously (inadequate acoustic window, poor-quality ultrasound equipment, and lack of operator experience). In fact, in 5 patients, we could not study all of the midbrain, but only a part of it. We were able to define the diagnosis but not the nigral lesion load.

References