Transcranial Brain Parenchymal Sonography in Neurodegenerative and Psychiatric Diseases

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Transcranial sonography is a highly sensitive noninvasive sonographic method for detection of early and specific echogenic changes in basal ganglia of patients with some neurodegenerative diseases. Transcranial sonography showed substantia nigra hyperechogenicity as a typical echo feature in idiopathic Parkinson disease and lenticular nucleus hyperechogenicity as a characteristic finding in atypical parkinsonian syndromes. Brain stem raphe hypoechogenicity or interruption has been shown to be highly prevalent in patients with unipolar depression as well as depression associated with certain neurodegenerative diseases. Transcranial sonography also revealed basal ganglia hyperechoic changes in movement disorders with trace metal accumulation such as Wilson disease, some entities of neurodegeneration with brain iron accumulation, as well as several forms of spinocerebellar ataxia. Transcranial sonography is a valuable neuroimaging method for early and differential diagnosis and follow-up of patients with neurodegenerative and psychiatric diseases.

Key Words—basal ganglia echogenicity; neurodegenerative diseases; psychiatric diseases; transcranial sonography; ultrasound education

Transcranial Sonographic Method

Transcranial sonography is a relatively new sonographic modality that can display the echogenicity of human brain tissue through the intact skull. In addition to the characteristic finding of substantia nigra hyperechogenicity, which is present in about 90% of patients with Parkinson disease (PD) and was first described in 1995 by Becker et al,1 a series of studies using transcranial sonography have reported other specific sonographic features in other neurodegenerative diseases besides PD.

A structural abnormality of the midbrain raphe, depicted as reduced echogenicity or an invisible brain stem raphe in patients with unipolar depression compared with healthy individuals, was also shown by transcranial sonography.2-3 The same sonographic brain stem raphe changes have been shown in depression associated with some other neurologic diseases, eg, PD,4 idiopathic dystonia,5 and Wilson disease (WD),6 but this finding was not confirmed in multiple sclerosis with or without depression.7,8 High-tech transcranial sonographic machines have the possibility of displaying deep brain structures (eg, basal ganglia) with a very high lateral and axial resolution similar to that of magnetic resonance imaging (MRI) in clinical applications.9-10

Abbreviations
ADHD, attention deficit hyperactivity disorder; MRI, magnetic resonance imaging; PD, Parkinson disease; WD, Wilson disease

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Due to high interest in transcranial sonography in recent years, consensus guidelines for uniform transcranial sonographic scanning procedures for midbrain and basal ganglia structures, as well as the ventricular system, have been established. These transcranial sonographic protocols provide standardized scanning procedures and comparability of transcranial sonographic findings between different research groups and various ultrasound systems.

For the insonation of the brain parenchymal structures, it is suggested to perform transcranial sonographic scanning through the anterior or middle temporal acoustic bone windows, as suggested for transcranial vascular sonography. Guidelines suggest using modern clinical ultrasound systems equipped with 2.0–3.5-MHz phased array transducers. For the optimal insonation of brain structures, transcranial sonographic parameters should be set as follows: dynamic range between 45 and 60 dB, insonation depth of 14 to 16 cm, and individualized adaptation of the time-gain compensation and brightness of the sonogram to achieve the best possible visualization.

After clear sonographic depiction of the basal ganglia structures, it is suggested to fix and zoom the image at least 3 times to provide the optimal and most appropriate conditions for further sonographic measurements. The scanning is performed at several axial levels through the brain stem and thalamus.

The butterfly-shaped mesencephalic brain stem can be visualized as a hypoechoic region, which is surrounded by highly hyperechoic areas representing basal cisterns. At this axial scanning level, the echogenicity of the ipsilateral substantia nigra, red nucleus, and brain stem raphe can be evaluated (Figure 1). The best-validated method for measuring and grading substantia nigra echogenicity is planimetric measurement of the substantia nigra echogenic area in the axial plane. The hyperechoic area is measured by encircling the outer circumference and is automatically displayed in square centimeters. Other substantia nigra echogenicity scoring methods, such as semiquantitative visual grading, volumetry, semiautomatic substantia nigra detection, and complex mathematical echo signal analysis, were less reliable and are not validated.

Figure 1. Axial transcranial sonograms (mesencephalic level). The butterfly-shaped midbrain was encircled for better visualization (solid lines). The solid arrows indicate the brain stem raphe; the dotted arrows depict the red nucleus; the substantia nigra is encircled with a dotted line.
A. Mesencephalic brain stem of a healthy individual with a normal, nearly invisible substantia nigra and a normal, highly echogenic brain stem raphe, which has the same echogenicity as the red nucleus. B. Mesencephalic brain stem of a patient with unipolar depression with normal, nearly invisible substantia nigra and abnormal, reduced echogenicity of the brain stem raphe. C. Mesencephalic brain stem of a patient with PD and depression showing marked unilateral hyperechogenicity of the substantia nigra and abnormal, reduced echogenicity of the brain stem raphe.
According to consensus guidelines,\textsuperscript{11,12} "marked substantia nigra hyperechogenicity is considered, if the planimetrically measured echogenic area exceeds a cutoff value defined by the 90\% percentile of measures in a normal population, and moderate substantia nigra hyperechogenicity, if the measured area ranges in between the 75\% and 90\% percentiles of measures in a healthy population." The larger or sum of bilaterally measured hyperechoic sizes for rating substantia nigra echogenicity could be used for further comparisons. Planimetrically measured reference values of hyperechoic substantia nigra areas range between 0.18 and 0.24 cm\textsuperscript{2} depending on the ultrasound systems used.

In normal conditions, the brain stem raphe is depicted as a highly echogenic continuous line, which has echogenicity similar to that of the red nucleus or surrounding cerebral white matter (Figure 1).\textsuperscript{13–15} Based on the transcranial sonographic guidelines, brain stem raphe echogenicity is rated semiquantitatively. A 3-point grading system (1, raphe invisible; 2, hypoechoic or interrupted brain stem raphe; and 3, hyperechoic brain stem raphe) or, better, a 2-point grading system (0, invisible, hypoechoic, or interrupted brain stem raphe representing a pathologic finding; and 1, a highly echogenic continuous brain stem raphe, as a normal finding) is suggested.\textsuperscript{13–15} Due to variations in the transparency of temporal bone windows, it is suggested to insonate the brain stem raphe from both sides. If the brain stem raphe can be depicted as a continuous hyperechoic line from at least one side, then it is rated as normal: that is, a hyperechoic, noninterrupted continuous line (Figure 1).\textsuperscript{15}

To display the thalamic axial plane level, the ultrasound probe should be tilted 10° to 20° upward. A very important landmark of the thalamic or ventricular level is the usually highly echogenic pineal gland (Figure 2).\textsuperscript{13,14} At this insonation plane, the thalami, the anatomic site of the basal ganglia, and the ventricular system (third ventricle and frontal horns of the lateral ventricles) are displayed.

The thalami are normally depicted as isoechoic or hypoechoic round structures next to the third ventricle. Hypoechoic structures of the thalami and ventricles help differentiate the anatomic site of the basal ganglia: caudate

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure2}
\caption{Sonograms at the level of thalami (ventricular system).}
\textbf{A.} Normal finding at the thalamic level. The basal ganglia and thalami are invisible (ie, isoechoic with surrounding cerebral white matter). Normal diameters of the third ventricle (white line) and frontal horn of the lateral ventricle (dotted line) are shown. The thick white line represents enlargement of the third ventricle. \textbf{B.} Hyperechogenicity of the caudate nucleus (encircled with dotted line), located next to the frontal horn of the lateral ventricle (gray dotted line, normal diameter). \textbf{C.} Hyperechogenicity of the lenticular nucleus (encircled with dotted line), located close to the third ventricle (arrow, normal diameter).}
\end{figure}

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nucleus and lenticular nucleus. At the same level, the transverse diameters of the third ventricle, which is depicted between the two hyperechoic lines representing ependyma, as well as the diameter of contralateral frontal horn of the lateral ventricle can be measured (Figure 2). Normal transcranial sonographic values for the ventricular system diameters depend on age, but it could be roughly accepted that the normal diameter of the third ventricle is up to 10 mm, and that of the frontal horns of the lateral ventricle is up to 20 mm. The echogenicity of the contralateral thalamus, contralateral lenticular nucleus, and contralateral caudate nucleus should be evaluated semi-quantitatively at this level.

In normal conditions, these basal ganglia have the same echogenicity as surrounding brain parenchyma (Figure 2), which is why they are invisible. If hyperechoic areas at the anatomic sites of the caudate nucleus and lenticular nucleus can be detected, we can mark this finding as pathologic. In that case, hyperechoic basal ganglia signals could be measured planimetrically, as described for the substantia nigra (Figure 2). The most frequent causes of deep brain structure hyperechogenicity are trace metal accumulation and calcification.

Transcranial Sonography in PD and Atypical Parkinsonian Syndromes

Substantia nigra hyperechogenicity above the cutoff value as a typical finding in patients with PD (Figure 1) was first described by Becker et al. Substantia nigra hyperechogenicity could be found unilaterally or asymmetrically bilaterally. This finding has been also been shown by many other research groups over the last decades (for reviews, see Gaenslen and Berg and Bor-Seng-Shu et al). This transcranial sonographic finding that is present in up to 90% of PD patients was found to be independent from PD duration and severity, and was found to be stable in an at least 5-year follow-up of PD patients. Also, there was no correlation found between the degree of substantia nigra hyperechogenicity and degeneration of presynaptic dopaminergic neurons in PD represented by the striatal uptake measured by N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane single-photon emission computed tomography. These transcranial sonographic findings suggest that the occurrence and degree of a hyperechoic signal in the substantia nigra do not represent the extent of dopaminergic neurons’ progressive degeneration in patients with PD. Substantia nigra hyperechogenicity has also been detected in 8% to 10% of healthy people. Healthy individuals with substantia nigra hyperechogenicity may show functional deficits in the nigrostriatal dopaminergic pathways, with "soft motor sign and symptom" occurrence. Substantia nigra hyperechogenicity on transcranial sonography in healthy individuals has been shown to reveal up to a 20-fold increased risk of developing PD during a follow-up period of up to 5 years. This finding was confirmed not only in a hospital-based setting but also in the general population.

The reasons for substantia nigra hyperechogenicity in PD are not entirely clear. However, it is possible that an increased substantia nigra echogenic area reflects pathologic alterations related to an increased substantia nigra iron content and may represent a susceptibility marker of basal ganglia dopaminergic system vulnerability. Increased substantia nigra iron content possibly causes acoustic impedance changes that are displayed as different patterns of echogenic areas. The typical finding of substantia nigra hyperechogenicity in patients with idiopathic PD is not frequent in atypical (multiple-system atrophy and progressive supranuclear palsy), posttraumatic, or vascular parkinsonism.

A meta-analysis of 5 independent transcranial sonographic studies showed that substantia nigra hyperechogenicity discriminates PD from atypical parkinsonian syndromes (multiple-system atrophy and progressive supranuclear palsy) with a sensitivity of 92% and a specificity of 80%. Contrarily, basal ganglia hyperechogenicity (primarily lenticular nucleus) could be specifically seen in atypical parkinsonian syndromes but was very rare in PD. The finding of basal ganglia hyperechogenicity with normal echogenicity of the substantia nigra could be very helpful in discriminating PD from atypical parkinsonian syndromes. An increase in the diameter of the third ventricle (>10 mm) usually without substantia nigra hyperechogenicity but occasionally with lenticular nucleus hyperechogenicity has been described in progressive supranuclear palsy but not frequently in patients with PD.

Furthermore, on the basis of transcranial sonography in addition to clinical characteristics, it is even possible to differentiate two different clinical forms of progressive supranuclear palsy: a "classic" form known as Richardson syndrome and another form known as progressive supranuclear palsy–parkinsonism. In a recent study, we showed that a subgroup of patients with progressive supranuclear palsy–Richardson syndrome had a significantly higher prevalence of lenticular nucleus hyperechogenicity and a significantly wider third ventricle, whereas patients with progressive supranuclear palsy–parkinsonism had a significantly higher prevalence of pathologic substantia nigra hyperechogenicity (73% versus...
Transcranial sonography could also be an important additional diagnostic tool (in addition to the relatively specific clinical manifestations and structural neuroimaging findings in vascular parkinsonism) for differentiating between PD and vascular parkinsonism. Namely, patients with vascular parkinsonism in most cases do not have pathologic hyperechoic signals in the substantia nigra and other basal ganglia structures. On the contrary, they usually have pathologic findings on vascular examinations (Doppler or Duplex sonography of intracranial arteries, particularly the middle cerebral artery), which show increased blood flow velocities and pulsatility indices as typical markers of intracranial vessel stenosis, which is a background for vascular parkinsonism.

On the basis of these promising results, the European Federation of Neurological Societies/Movement Disorder Society European Section recommended application of transcranial sonography, with the highest level of recommendation for diagnosis of PD, differential diagnosis with secondary and atypical parkinsonism, and detection of patients at risk for PD. As a transcranial sonographic examination is highly operator dependent, this recommendation is valid only for adequately trained and very experienced sonographers.

Transcranial Sonography in Other Neurodegenerative Diseases With Movement Disorders

In addition to parkinsonism, transcranial sonography also showed promising results in several other neurodegenerative diseases characterized by movement disorders. Two independent transcranial sonographic studies showed specific echogenic changes in the basal ganglia of patients with WD. Walter et al. investigated 21 consecutive patients with WD (18 with the neurologic form of the disease) and found increased lenticular nucleus echogenicity on at least one side in all who were neurologically symptomatic and in 2 of the 3 patients with the hepatic form of WD. The proposed explanation for lenticular nucleus hyperechogenicity in patients with either the neurologic or hepatic form of WD was increased copper content. Substantia nigra hyperechogenicity was found in almost half of the patients with WD in the same study (10 of 21) without ventricular system dilatation. Interestingly, the transcranial sonographic changes observed were also present in some patients with normal brain MRI findings.

We published results from a larger group of 54 consecutive, clinically stable patients with WD who were classified as having the predominantly neurologic or hepatic form of the disease and were adequately assessable by transcranial sonography from both sides. Transcranial sonography showed a significantly higher prevalence of substantia nigra and lenticular nucleus hyperechogenicity in patients with WD in comparison with healthy controls. Moderate to marked substantia nigra hyperechogenicity was found in 31.5% of our patients with WD (42% of those with the predominantly neurologic form and 7% with the hepatic form of WD). Substantia nigra hyperechogenicity was also found in 8% of healthy controls in our study. Disease severity correlated with the hyperechogenicity of the substantia nigra and with the width of the third ventricle, which was significantly higher in patients with the neurologic form of WD.

Results of both transcranial sonographic studies in patients with WD confirmed the ability of the method for early detection of trace metals in the basal ganglia (probably copper and possibly iron and manganese).

Similar findings were observed in some other neurodegenerative diseases with trace metal accumulation. Our group conducted MRI parallel to transcranial sonography in 5 unrelated patients with pantothenate kinase–associated neurodegeneration, caused by pantothenate kinase–associated neurodegeneration 2 gene mutations. All patients in our study had an eye of the tiger sign on MRI. Hypointense lesions on the T2-weighted MRI images were restricted to the globus pallidus and substantia nigra. Transcranial sonography also revealed bilateral hyperechoic areas restricted to the lenticular nucleus and substantia nigra, with normal values for the third ventricle diameter. Both transcranial sonographic and MRI findings in patients with pantothenate kinase–associated neurodegeneration are in accordance with the pathologic findings that accumulation of iron, even in advanced cases, is restricted to the globus pallidus and substantia nigra, suggesting selective involvement of these brain structures.

In patients with cervical and upper limb dystonia, transcranial sonography displayed hyperechogenicity of the lenticular nucleus (in up to 80% of cases), which is usually more prominent contralateral to the clinically affected side.
Lenticular nucleus hyperechogenicity is probably caused by increased copper and manganese content.6

Two transcranial sonographic studies revealed comparable frequencies of basal ganglia hyperechoic changes as well as a similar pattern of basal ganglia lesions in spinocerebellar ataxia types 2 and 3.27,28 Substantia nigra hyperechogenicity was a frequent finding in both studies (66.7% of those with spinocerebellar ataxia type 2 and 73.3% with spinocerebellar ataxia type 3), indicating a vulnerability of the nigrostriatal dopaminergic system in these patients. Patients with spinocerebellar ataxia type 2 also showed substantial dilatation of the ventricular system, which was represented by increased diameters of the third ventricle on transcranial sonography.27,28 Although evidence of transcranial sonographic alterations in ataxia is limited, with the proposed specific cerebellar examination plane, enlargement of the fourth ventricle and nucleus dentatus hyperechogenicity could be visualized as characteristic findings in patients with spinocerebellar ataxia type 3 as well as spinocerebellar ataxia type 17. Hyperechogenicity of pallidostriatal regions, especially if marked or bilateral, could be a very useful and specific sonographic feature for differentiating between movement disorders with dominant extrapyramidal or ataxic clinical features.27–29

Transcranial Sonography in Psychiatric Diseases

Evidence from clinical, neuroimaging, biochemical, and animal studies implicates basal limbic system and brain stem raphe system involvement in the pathogenesis of mood disorders, particularly depression. This evidence is supported by the typical transcranial sonographic finding of low echogenicity or interruption of the brain stem raphe, which is normally depicted as a highly echogenic continuous line. Raphe hypoechogenicity or lack of visualization on transcranial sonography is observed in 50% to 70% of patients with unipolar depression and could be associated with responsiveness to inhibitors of serotonin reuptake.15,30 These findings support a hypothesis that the brain stem raphe hypoechogenicity that is frequently found in depressive disorders could be a marker of impaired central serotonergic transmission.

Brain stem raphe hypoechogenicity or interruption is even more frequent in patients with depression associated with suicidal ideation. In the only study that investigated the frequency of pathologic transcranial sonographic findings of the brain stem raphe in depression associated with suicidal ideation,31 it was shown that even 86% of these patients had transcranial sonographic abnormalities of the brain stem raphe. This finding was highly significant when compared with the same variable frequency (47%) of patients with major depression without suicidal ideation. Patients with normal echogenic features of the brain stem raphe had less severe symptoms of depression and a lower suicidal ideation risk in this study.31 Reduced brain stem raphe echogenicity in depressed patients was interpreted to be possibly caused by structural alterations (changes of acoustic impedance) of the dorsal raphe nuclei or serotonergic fiber tracts in this region.30

Contrary to the sonographic findings in unipolar depression, transcranial sonography revealed normal or even increased echogenicity (hyperechogenicity) of the brain stem raphe in bipolar disorder, without substantia nigra or other basal ganglia pathologic echogenic signals. It was associated with significant ventricular system dilatation (the third ventricle), irrespective of the existing disease conditions or stages.30 These results suggest that pathologic transcranial sonographic findings of the brain stem raphe (reduced echogenicity, interruption, and lack of visualization) could be specific transcranial sonographic markers of unipolar depression.15,30

The characteristic finding of substantia nigra hyperechogenicity in PD was also frequently found in patients with depression. Those patients who had depression were found to have a strong relationship between motor asymmetry and reduced verbal fluency and observed substantia nigra hyperechogenicity. This relationship was even stronger in younger patients (<50 years) but was independent of age in those who had hypoechogenic, invisible, or interrupted brain stem raphe.32 Increased frequencies of PD-like transcranial sonographic findings in patients with depression require them to be screened for sonographic and clinical signs of early premotor PD.32

One transcranial sonographic study also showed that “the echogenicity of the substantia nigra was significantly larger in children with attention deficit hyperactivity disorder (ADHD) in comparison with healthy controls (F_{1,43} = 9.298; P = .004; effect size = 0.92; specificity was 0.73; and sensitivity, 0.82), without effects of age or sex.”33 Substantia nigra hyperechogenicity in patients with ADHD might be explained by a developmental delay followed by structural changes of basal ganglia structures. This assumption was confirmed by recent neuroimaging studies that have shown structural alterations in the basal ganglia of patients with ADHD. Further studies are needed to differentiate whether substantia nigra hyperechogenicity in ADHD is caused by iron deposition in the substantia nigra or whether the observed basal ganglia hyperechogenicity represents a structural marker of nigrostriatal dopaminergic system dysfunction.33
Further Perspectives on Transcranial Sonography in Neurodegenerative and Psychiatric Diseases

As a supplementary neuroimaging method, transcranial sonography already provides a special look into the brains of patients with certain neurodegenerative and psychiatric diseases. Transcranial sonography is expected to be implemented in the routine everyday diagnostic algorithms of some movement disorders. It is also anticipated that broader application of this method would be important for identifying patients at high risk of developing some neurodegenerative diseases or having disease progression (eg, PD or WD). Further investigations may help us better understand the etiologies and pathophysiologic mechanisms of different neurodegenerative and psychiatric disease as well as develop novel therapeutic and neuroprotective strategies. Intraoperative and postoperative monitoring of the placement of deep brain electrodes in movement disorders is already one promising field for increasing applications of transcranial sonography in the near future.

Conclusions

Transcranial sonography is a valuable, reliable, and very useful neuroimaging method that has an important place in the early and differential diagnosis of psychiatric and neurodegenerative diseases. It is an easily applicable, noninvasive, cost-effective bedside method with a lack of any side effects. Transcranial sonography does not have the limitations described for other neuroimaging modalities, and it could be performed in occasionally tremulous or agitated patients with neurodegenerative or psychiatric diseases. Certain limitations of transcranial sonography are associated with nontransparent acoustic bone windows in a small minority of patients and with operator dependence.

References


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