ECHOGENIC PATTERNS IN TRANSCRANIAL SONOGRAPHY

Daniel Richter MD[1], Christos Krogias MD[1, 2]

[1] Department of Neurology, St. Josef-Hospital Bochum, Ruhr University Bochum, Germany
[2] Medical Faculty, Ruhr University Bochum, Germany

Abstract

This short review will summarize the major echogenic patterns in transcranial sonography (TCS) for the diagnostic workup of Parkinson's disease (PD). PD is a primary neurodegenerative disorder caused by a loss of dopaminergic cells in the substantia nigra (SN). In addition to the dopamine deficiency, changes in other neurotransmitter systems are present, including alterations in the serotonergic system [1]. The definitive cause of PD is unknown. The disease is characterized by a slowly progressive disease course with bradykinesia as leading motor symptom, but also non-motor symptoms such as depression are common and can precede motor manifestations. The TCS analysis of different brain regions has been proven helpful in the diagnostic workup of PD, including differential diagnostic, non-motor diagnostic, and risk stratification of the healthy elderly population.

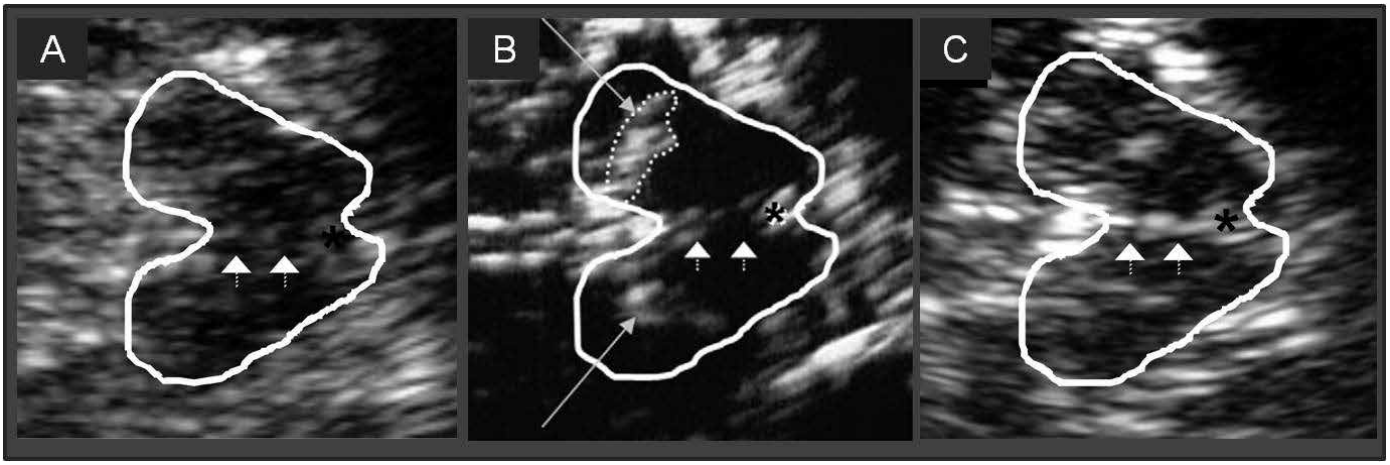
Key words: ultrasound, sonography, substantia nigra, lentiform nucleus

Substania nigra hyperechogenicity

The most prominent echogenic pattern in Parkinson's disease (PD) is a substantia nigra (SN, figure 1) hyperechogenicity that is assessed through the transtemporal bone window. The SN is displayed in the axial mesencephalic examination plane of transcranial sonography (TCS). A hyperechogenicity of the SN is defined by a planimetric measurement that shows an enlarged echogenic signal of the SN [2].

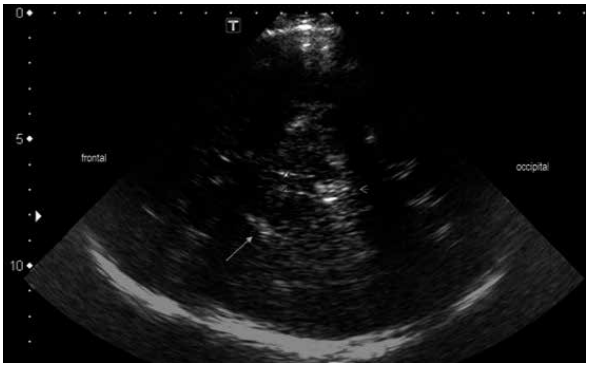
In 1995, Becker et al. published the first study on SN hyperechogenicity in PD [3]. In this first study, 40% of the examined PD patients had a hyperechogenic SN in the TCS examination. In comparison, none of the healthy controls in this study showed an SN hyperechogenicity. In 2001, Berg et al. demonstrated that approximately 90% of the patients with PD have a hyperechogenic SN. Together with an improvement of the TCS image resolution, these

Figure 1. Substantia nigra and brainstem raphe



Legend: The butterfly-shaped midbrain is outlined for better visualization. The asterisk indicates the aqueduct. Arrowheads indicate the brainstem raphe. The long arrows in (B) mark the hyperechogenic enlarged area of Substania nigra. Raphe grading (A-C): (A) Raphe structure not visible, grade 0, pathologic finding. (B) Echogenic line of the raphe is interrupted, grade 1, pathologic finding. (C) Normal echogenicity, grade 2, normal finding.

Figure 2. Nucleus lentiformis hyperechogenicity



Legend: Large arrow displays the hyperechogenicity of the right nucleus lentiformis. Small arrow marks the pineal gland. The distance between the two small crosses defines the third ventricle diameter

results were reproduced by other research groups, proofing the SN hyperechogenicity as a reliable and valid marker for PD and the differential diagnosis of extrapyramidal movement disorders [4, 5, 6, 7]. The enlarged echogenic signal of substantia nigra represents a characteristic hallmark of PD today, with a prevalence in newly diagnosed PD patients of about 80-90% [8, 9]. Therefore, TCS is increasingly applied for the differential diagnosis of PD and essential tremor (ET), where an SN hyperechogenicity is detectable in about 8-16%. The prevalence of an SN hyperechogenicity in the healthy population is even lower [10, 11, 12]. The echogenic area of the SN is routinely evaluated in a single axial mesencephalic examination plane, but it can also be depicted in a coronal examination plane, revealing a good sensitivity of 90.3% and a specificity of 96.9% to distinguish PD from healthy controls and patients with essential tremor, respectively [13].

The extent of the motor symptoms is not correlated with the sonographically measured area size of the SN [14]. Longitudinal studies have demonstrated that the presence of an SN hyperechogenicity in elderly healthy subjects is a factor that increases the risk by approximately 17 times to develop PD within three years [15]. Therefore, the presence of an SN hyperechogenicity has been included in the research criteria for prodromal Parkinson's syndrome [16].

The histopathological correlate of the hyperechogenic SN is still unknown, but it is assumed to indicate an increased amount of iron bound to proteins that differ from ferritin [17]. However, the extent of hyperechogenicity is currently not seen as correlating to progressive neurodegeneration in the SN [9].

Nucleus lentiformis hyperechogenicity

As the SN hyperechogenicity allows a clear distinction between PD, healthy controls, or patients with essential tremor, the discrimination between idiopathic and atypical parkinsonian syndromes (aPS) is insufficient [18]. A meta-analysis by Shafieesabet et al. found a prevalence of SN hyperechogenicity in 84% of PD patients and 28% of aPS patients [19].

Besides the SN, several other structures in the brain have been examined by TCS in extrapyramidal movement disorders [6, 20]. A hyperechogenicity of the nucleus lentiformis (LN, figure 2) was found to appear more frequently in patients with aPS, especially in patients with the parkinsonian phenotype of multiple system atrophy (MSA-P) or in patients with progressive supranuclear palsy (PSP) [21]. Thus, LN hyperechogenicity has been considered as a promising echogenic pattern of aPS. The LN is investigated in TCS using the diencephalic axial examination plane. A meta-analysis examining the frequency of LN hyperechogenicity in PD and aPS demonstrated a prevalence of 76% (95% CI: 0.62-0.88) in aPS compared to 16% (95% CI: 0.10-0.23) in PD [22].

So far, no studies are investigating the cellular and extracellular changes in PD patients with LN hyperechogenicity. However, an increase in the tissue iron level could cause the hyperechogenic alterations of the LN visualized in TCS. Apart from that, Walter et al. conducted a tissue metal analysis in autopsy brains of 11 patients with Wilson's disease (WD), in which the LN hyperechogenicity is a common ultrasound finding [23]. Diagnosis of WD was confirmed for all of these WD cases after an autopsy, and they all showed an LN hyperechogenicity in TCS. The authors found a clear correlation between the LN hyperechogenicity and the putaminal concentration of copper but not iron.

Raphe hypoechogenicity

Besides its value in diagnosing and discriminating Parkinsonian syndromes, TCS is also a valuable tool for investigating non-motor features. Depression and apathy frequently appear in PD patients and can represent early non-motor symptoms [24-26]. Several studies have shown that many PD patients are affected by depression, even in the prodromal state of disease [27].

Brainstem raphe (BR) alterations in TCS have been associated with depression in PD patients, underlining an involvement of the serotonergic system in this non-motor feature of PD [7, 28, 29]. Different from the enlarged echogenic area of the SN, a reduced echogenic signal of the BR is thought to visualize changes in the serotonergic system [7]. The echogenic pattern of BR is assessed by the axial mesencephalic examination plane and classified semi-quantitatively on a three-point scale (figure 1): 0 = raphe structure not visible, 1 = slight and interrupted echogenic ra-

phe structure, 2 = normal echogenicity (echogenicity of raphe structure is not interrupted). Alteration of the BR can also be depicted in the coronal examination plane and have also been associated with apathy in PD [29].

Until now, BR alterations in PD have been investigated in a cross-sectional study approach. Future studies should investigate its structural correlate and the predictive value of BR hypoechogenicity for patients with PD, which might enable the identification of a subgroup of PD patients at higher risk of suffering from or developing depression or apathy.

Conclusion

The assessment of echogenic patterns in PD covers a broad spectrum of diagnostic questions, which the non-invasive TCS technique can quickly assess [30]. Nevertheless, TCS requires a sufficient transtemporal bone window lacking in 5-40% of patients depending on age, sex, and geographic origin [9]. Furthermore, the reliability of the findings depends on a high-quality ultrasound system and the investigator's qualification. Future efforts should further develop this method and achieve its full potential in diagnosing PD and other neurological diseases.

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