Diagnosis and Atypical Parkinsonian Syndromes

With the help of transcranial ultrasound, it is possible to diagnose idiopathic Parkinson's disease (IPD) and atypical parkinsonian syndromes. This technique is considered easily applicable, low cost, and non-invasive.

**Patients and Methods**

Two centres (University Hospital of Homburg and Würzburg) participated in this study, which included 102 patients with IPD (55 men, 47 women), 34 patients with progressive supranuclear palsy (PSP), and 21 patients with multiple system atrophy (MSA-P). The aim of this study was to differentiate between IPD and atypical parkinsonian syndromes.

**Results**

Low echogenicity of the substantia nigra (SN) was identified in 2% of patients with IPD (n = 2 and 18, respectively), and in 10 patients with PSP (5.5%) but in four patients with MSA-P (12.5%). Increased echogenicity of the SN was found in 10 patients with IPD, 24 patients with PSP, and 20 patients with MSA-P.

**Conclusion**

Transcranial ultrasound can be used as a screening method to differentiate between IPD and atypical parkinsonian syndromes, with low SN echogenicity indicating IPD and increased echogenicity suggesting atypical parkinsonian syndromes.
values revealed that, in a patient with parkinsonian syndrome, the sonographic finding of a distinctly hyperechogenic SN on one or both sides predicted IPD with positive and negative predictive values of 0.83 and 0.78, respectively.

There were no statistically significant correlations between disease severity within the IPD group (Hoehn and Yahr stage) and extent of the hyperechogenic SN signal (Pearson’s and Spearman’s correlation coefficients).

Whereas unilateral or bilateral hyperechogenicity of the lentiform nucleus was found in 13/18 patients with PSP and in 23/32 patients with MSA-P, only 10 patients with IPD showed this echo feature. Differences between these groups were significant (Kruskal–Wallis test p<0.01). Hyperechogenic lentiform nuclei as an indicator for an atypical parkinsonian syndrome had positive and negative predictive values of 0.78 and 0.84, respectively. When both ultrasound variables were combined, the positive predictive value of ultrasound in identifying IPD and atypical parkinsonian syndromes increased significantly (table 1).

**DISCUSSION**

In the present study, in most patients with IPD (88%) a markedly hyperechogenic SN was detected on at least one side corroborating the results of previous studies. In contrast, a hyperechogenic lentiform nucleus was more frequent in the atypical parkinsonian syndromes. Thus, patients with “parkinsonism” who exhibit only a low echogenic SN—particularly when combined with a hyperechogenic lentiform nucleus—are likely to have an atypical parkinsonian syndrome (positive predictive value 0.96), whereas a significantly hyperechogenic SN points towards IPD (positive predictive value 0.91, see table 1). Although this confirms the findings of Walter et al, the present positive and negative predictive values are somewhat lower than those reported in their study.

The ultrasound finding of a hyperechogenic lentiform nucleus corresponds to a decrease in T2 relaxation time on MRL, which is supposed to be related to an increase in the heavy metal concentration in this area.

The underlying reason for the differences in the pattern of SN echogenicity of IPD and atypical PD is unknown. Evidence from animal and post mortem studies points to a relation between SN echogenicity and tissue iron content. However, tissue iron has been found to be elevated not only in IPD but also in MSA-P and PSP. In vitro studies by our group have shown that iron itself does not cause an increase in ultrasound signal intensity (unpublished data). However, it has been hypothesised that binding of increased amounts of iron to iron metabolising proteins or structural alteration of iron binding proteins might lead to differences in the reflection of the ultrasound beam displayed as hyperechogenic signals. This hypothesis was substantiated by a recent study on association of an increase of the iron binding proteins ferritin-H and ferritin-L and SN hyperechogenicity. Moreover, it has been shown that sequence variations in genes encoding for iron metabolising proteins can be linked to IPD and hyperechogenicity of the SN. The kinds of difference between iron metabolism in IPD and in atypical parkinsonian syndromes therefore need to be further elucidated. Additionally, it remains to be investigated what other factors might be involved in the increase of SN echogenicity in IPD.

In the past, use of other imaging tools has been proposed in the differential diagnosis of parkinsonian syndromes. Several positron emission tomography (PET), single photon emission

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**Table 1** Number of patients with two distinct ultrasound findings: one combining a hyperechogenic substantia nigra (SN) on one or both sides predicted IPD with positive and negative predictive values of 0.83 and 0.78, respectively.

<table>
<thead>
<tr>
<th>Echo pattern of the SN and the LN</th>
<th>With Parkinson’s disease</th>
<th>With atypical parkinsonian syndromes</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperechogenic SN combined with regular echogenic LN</td>
<td>58</td>
<td>6</td>
<td>0.91</td>
</tr>
<tr>
<td>Hyperechogenic LN combined with moderate echogenic SN at best</td>
<td>1</td>
<td>28</td>
<td>0.96</td>
</tr>
</tbody>
</table>
computed tomography (SPECT), and MRI variables have been identified as being different in IPD, MSA-P, and PSP.\(^1\) However, most of the findings overlap and provide only moderate accuracy with respect to differential diagnosis of these entities, thus failing to be of significant use for a given patient contact. In addition, these procedures are time consuming, costly, and have limited availability. Recently, MRI volumetry and diffusion-weighted imaging based MRI has been introduced which allows discrimination of atypical PD from IPD with high sensitivity and specificity.\(^1\)\(^2\) Since none of these tools, ultrasound included, visualises a unique pathogenetic feature of any of these disorders, it remains questionable whether these imaging tools can be more than a valuable support to the clinical diagnosis. Each imaging procedure will have to be embedded into the clinical context. Therefore, it is of relevance whether the imaging tool is non-invasive, easily available, and applicable by the clinician. These are the immanent advantages of diagnostic ultrasound imaging, which may outweigh the drawback of investigator dependency in the future.

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