

# Transcranial sonography in Parkinson's disease

## Ultrassonografia transcraniana na doença de Parkinson

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### ABSTRACT

Transcranial sonography has become a useful tool in the differential diagnosis of parkinsonian syndromes. This is a non-invasive, low cost procedure. The main finding on transcranial sonography in patients with idiopathic Parkinson's disease is an increased echogenicity of the mesencephalic substantia nigra region. This hyperechogenicity is present in more than 90% of cases, and reflects a dysfunction in the dopaminergic nigrostriatal pathway. This study discussed how the hyperechogenicity of the substantia nigra may facilitate the differential diagnosis of parkinsonian syndromes.

**Keywords:** Parkinson disease/ultrasonography; Ultrasonography, doppler, transcranial; Diagnosis, differential

### RESUMO

A ultrassonografia transcraniana tem se tornado ferramenta útil no diagnóstico diferencial das síndromes parkinsonianas. Trata-se de um método não invasivo e de baixo custo. O principal achado da ultrassonografia transcraniana em pacientes com doença de Parkinson idiopática é o aumento da ecogenicidade, ou hiperecogenicidade, na região da substância negra mesencefálica, presente em mais de 90% dos casos, o que reflete disfunção da via dopaminérgica nigroestriatal. O presente trabalho abordou como a hiperecogenicidade da substância negra pode auxiliar no diagnóstico diferencial das síndromes parkinsonianas.

**Descritores:** Doença de Parkinson/ultrassonografia; Ultrassonografia doppler transcraniana; Diagnóstico diferencial

### INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease, clinically characterized by cog-wheel rigidity,

rest tremor (most common sign), bradykinesia (most important and disabling sign) and postural instability (not associated with primary visual, cerebellar, proprioceptive or vestibular dysfunctions)<sup>(1)</sup>. According to the United Kingdom Parkinson's Disease Society Brain Bank,<sup>(2)</sup> the disease is suspected when bradykinesia is associated with at least one of the clinical signs described above, after the exclusion of several causes of parkinsonism. During the clinical follow-up of these patients at least three of the following criteria should be observed: unilateral onset, rest tremor, progressive disorder, persistent asymmetry affecting side of onset most, a satisfactory response to levodopa, levodopa response for 5 years or more, dyskinesia, and a clinical course of 10 years or more.

The prevalence of PD is estimated to be 150 to 200 cases of the disease per 100,000 inhabitants. It may affect up to 3.3% of individuals older than 65 years. Early symptoms of PD before the sixth decade of life are uncommon<sup>(3)</sup>. In Brazil, a study conducted in the city of Bambuí (MG) revealed that among 1185 participants aged 63 years, 3.3% had PD<sup>(4)</sup>.

Since its first description in 1817, by James Parkinson, the diagnosis of PD remains essentially clinical<sup>(5)</sup>. The confirmation of the diagnosis by histopathological examination is based on the demonstration of a loss of neuromelanin-rich dopaminergic neurons in the substantia nigra (SN) pars compacta, in the midbrain, associated with the occurrence of eosinophilic cytoplasmic inclusions, known as Lewy bodies, in the remnants of the mesencephalic neurons<sup>(2,6)</sup>. According

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to histopathological studies, approximately 25% of individuals with a presumptive diagnosis of PD are misdiagnosed<sup>(5,6)</sup>. When the diagnosis is determined by a neurologist specialized in movement disorders, this number decreases, but remains high (about 10%)<sup>(7,8)</sup>. In most cases, these are not “error” diagnoses, but “uncertain” or “doubtful” diagnoses, especially in the early stages of the disease, when the signs and symptoms are still mild<sup>(9)</sup>. Furthermore, many conditions can mimic idiopathic PD for years, such as atypical or secondary parkinsonian syndromes, essential tremor, and depression associated with motor slowing<sup>(8,10)</sup>. The differentiation of diseases comprising the parkinsonian syndromes presents a challenge in clinical practice, even to those specialized in movement disorders. Characteristic signs of atypical parkinsonian syndromes, such as postural instability, vertical gaze palsy and signs of frontal lobe dysfunction, which are indicative of progressive supranuclear palsy (PSP), and significant autonomic dysfunction, which is suggestive of multiple system atrophy (MSA), commonly occur at later stages. On the other hand, characteristic signs of atypical parkinsonian syndromes, such as postural instability, signs of frontal lobe dysfunction and autonomic dysfunction may also be found in PD<sup>(10)</sup>. In practice, in many cases it is not possible to distinguish the different diagnosis in the early stages considering only the clinical manifestations.

Computed tomography (CT) and magnetic resonance imaging (MRI) have been widely used in the investigation of patients with suspected PD. However, despite modern, these methods are not capable of detecting brain abnormalities that represent the histopathologic substrate of this disease. In clinical practice, these techniques have been indicated to rule out secondary causes of parkinsonism, such as ischemic or hemorrhagic strokes, hydrocephalus, brain tumors, among others. In more advanced stages of atypical parkinsonian syndromes, some MRI findings may help to discriminate between PD and MSA, such as atrophy of cerebellopontine (which may lead to a cross-shaped signal hyperintensity in the pons on the T2 sequence, or hot cross bun sign) and putamen fibers; between PD and PSP, such as frontal or brain stem atrophy; and between PD and corticobasal degeneration, such as predominantly unilateral cortical atrophy<sup>(11)</sup>. Therefore, considering that the correct identification of these conditions is fundamentally important – PD has a better prognosis and responds satisfactorily to levodopa and neurosurgical treatment – the development of methods for demonstrating PD brain changes are needed to reduce diagnostic uncertainty and its socioeconomic impacts.

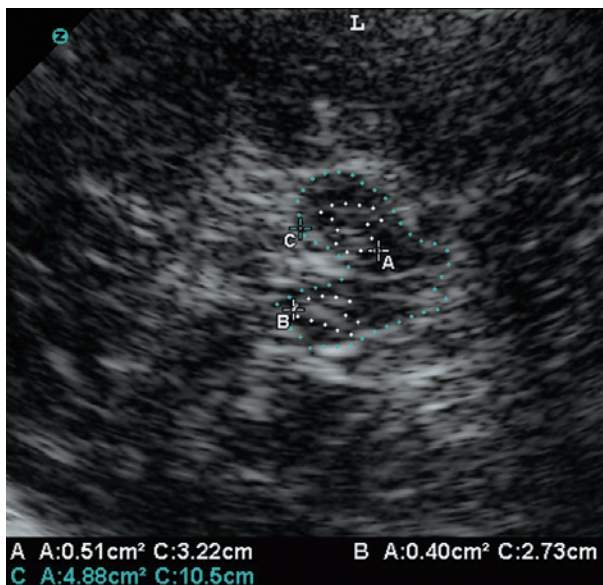
## Transcranial sonography in Parkinson's disease

In the late 1980s, new discoveries in neurosonology allowed the assessment of the echogenicity of deep brain structures, without the need for surgical opening of the skull, using transcranial sonography (TCS). The method was received with skepticism by the scientific community because it was difficult to understand how an “outdated” method based on properties of ultrasonography waves could reveal brain tissue abnormalities not demonstrable by advanced neuroimaging techniques. This is a noninvasive, painless, low cost exam, which is potentially available in developing countries, and which can be performed in patients with involuntary movements of the head, without anesthesia, because the artifacts resulting from the movements can be corrected by the physician during the procedure.

The use of this technique relies on the principle that morphological and functional changes and the chemical composition of the brain structures associated with movement disorders can lead to changes in their echogenicity. This procedure has been considered sensitive and reliable in detecting abnormalities of the basal ganglia of the brain, such as degeneration of the SN in idiopathic PD, lesion of the lentiform nucleus in idiopathic dystonia, and degeneration of the SN and the caudate nucleus in Huntington's disease, among others. The method is also useful in the differential diagnosis of movement disorders and to clarify some of their pathophysiological mechanisms<sup>(12-16)</sup>.

## Clinical significance of the hyperechogenicity of the substantia nigra

Mesencephalic SN hyperechogenicity, defined by most authors as an increased echogenic area in the SN region, was first described in 1995 by Becker et al. in individuals with idiopathic PD<sup>(17)</sup> (Figure 1). This signal occurs in the majority of patients with idiopathic PD (over 90%) and indicates functional impairment of the nigrostriatal dopaminergic system. It is believed to be caused by increased iron content in abnormal protein linkages in the SN region<sup>(18)</sup>. It is not known, however, whether this increased amount of iron in this region is a primary cause of PD, which would cause oxidative stress and injury of dopaminergic neurons, or is a secondary phenomenon in the development of disease. In general, the SN hyperechogenicity is present bilaterally in PD, is more extensive (in terms of echogenic area) on the side contralateral to the more symptomatic side, is stable during the course of the disease, and is clinically associated with rigidity and bradykinesia<sup>(19, 20)</sup>. Despite the controversies, some studies suggest that the larger



**Figure 1.** Transcranial sonography of a patient with Parkinson's disease. Intense hyperechogenicity can be viewed in the region of the substantia nigra of the midbrain bilaterally (A and B). The hypoechoic mesencephalon shows a butterfly shape and is surrounded by the hyperechogenic basal cisterns (C)

the echogenic area of the SN, the earlier the onset of PD and the slower the progression of the disease<sup>(21,22)</sup>. This finding has been considered a biomarker for early diagnosis of PD and not a marker of disease progression<sup>(23)</sup>.

On the other hand, the echogenicity of the SN can be found in about 10% of the healthy population. Studies with positron emission tomography (PET) and single photon emission computerized tomography (SPECT) using, respectively, <sup>18</sup>F-Dopa and <sup>123</sup>I-FP-CIT or [<sup>99m</sup>Tc]-TRODAT-1 as markers of activity of the dopamine transporter molecule (DAT), revealed that, similarly to the SN hyperechogenicity found in PD, this finding is also associated with reduced activity of the nigrostriatal dopaminergic system, which is suggestive of impaired functional reserve of this neural system<sup>(18,24)</sup>. The associations between SN hyperechogenicity and motor retardation in healthy elderly subjects and between SN hyperechogenicity and severity of symptoms associated with neuroleptic-induced parkinsonism have recently been demonstrated<sup>(25)</sup>. Other conditions in which the hyperechogenicity of the SN occurs include: individuals with parkin gene mutation, corticobasal degeneration, dementia with Lewy bodies and spinocerebellar ataxias<sup>(13,26, 27)</sup>.

### Interpretation of the transcranial sonography findings in parkinsonian syndromes

In the management of patients with parkinsonian syndrome, brain ultrasonography findings should only

be considered after receiving medical history and detailed neurological examination of the patients, and never used alone, for they must be analyzed in conjunction with clinical data. Essential tremor, depression, MSA, PSP, and corticobasal degeneration are the major disorders in which parkinsonian signs and symptoms may be present and in which TCS may be useful for differentiating these conditions<sup>(13)</sup>.

### Essential tremor

In the practice of medicine, when the clinical manifestations are not characteristic and/or the patient does not meet the clinical criteria for diagnosis of PD and essential tremor, the presence of SN hyperechogenicity does not rule out essential tremor, but it reinforces the diagnosis of PD. On the other hand, normal echogenicity in SN region favors the possibility of essential tremor. It is noteworthy that the prevalence of SN hyperechogenicity in subjects with essential tremor is two to four times higher than the prevalence of this sign in the healthy population, and patients with essential tremor have three times higher risk of developing PD. Further studies are needed to clarify whether the increased prevalence of SN hyperechogenicity in subjects with essential tremor may explain the higher frequency of conversion of this condition to PD. TCS has a sensitivity of 75-86%, a specificity of 84-93%, and a positive predictive value of 91-95% in differentiating between essential tremor and PD<sup>(13,24,28)</sup>.

### Depression

Approximately 10-45% of patients with PD may have associated depression<sup>(29)</sup>. In addition, individuals with depression may present signs and symptoms that occur frequently in PD, including masking of facial expression, bradykinesia, hypophonia, apathy, motor retardation, cognitive dysfunction, and in some cases, increased muscle tone<sup>(29)</sup>. The echogenicity of the SN can help distinguish between the two conditions: SN hyperechogenicity is generally associated with PD, but not with depression; in patients with depression and hyperechogenicity of the SN, the signs and symptoms of depression may be considered as pre-motor signs and symptoms of PD<sup>(30)</sup>. Patients with depression are at greater risk (two to three times) of developing PD compared to the healthy population and, interestingly, the prevalence of SN hyperechogenicity in patients with depression is about three times higher than in the normal population<sup>(31)</sup>.

The hypoechogenicity of the raphe nuclei of the brainstem is present in 50-70% of cases of unipolar depression, in 40 to 60% of patients with PD and depression, and in about 60% of patients with PD and urinary incontinence. When PD or depression is suspected, normal echogenicity of the SN coupled with hypoechogenicity of the raphe nuclei are indicative of unipolar depression<sup>(32)</sup>.

### Atypical parkinsonian syndromes

According to a prospective blinded study in which patients with diagnostic uncertainty due to mild and initial parkinsonism were followed until the definition of the diagnosis, SN hyperechogenicity was significantly predictive for the diagnosis of PD. In terms of early diagnosis of PD, both the sensitivity and the positive predictive value of SN hyperechogenicity were 94.9%, the specificity and the negative predictive value were both 85.7%, and the initial diagnostic accuracy compared to the final diagnosis was 92.4%. As to the early differential diagnosis between PD and atypical parkinsonian syndromes, the SN hyperechogenicity had a sensitivity of 94.8%, a specificity of 90%, a positive predictive value of 97.4%, a negative predictive value of 81.8%, and a diagnostic accuracy of 93.9%. As to the early differential of atypical parkinsonian syndromes, the finding of hyperechogenicity of the lentiform nucleus had a sensitivity of 66.7%, a specificity of 68.6%, a positive predictive value of 35.3%, a negative predictive value of 88.9%, and a diagnosis accuracy of 68.2%<sup>(33)</sup>.

Studies conducted in patients in advanced stages of disease found that the hyperechogenicity of the SN can discriminate PD from MSA and PSP in more than 90% of cases, because it occurs in most patients with PD and only in a minority of those with MSA and PSP. Furthermore, as the hyperechogenicity of the lenticular nucleus is described in 70-80% of individuals with MSA and PSP, but only in 10-25% of cases of PD, the joint evaluation of the echogenicity of the SN associated with the echogenicity of the lenticular nucleus can discriminate PD from MSA and PSP with a positive predictive value exceeding 90%<sup>(34)</sup>.

Similar to PD, corticobasal degeneration is also associated with increased echogenicity of the SN: about 90% of patients with corticobasal degeneration present SN hyperechogenicity bilaterally. Although this fact limits the use of SN echogenicity to distinguish between the two conditions, it allows discrimination between MSA and corticobasal degeneration. As the enlargement of the third ventricle (distance between the walls >10mm) is common in patients with MSA, the

hyperechogenicity of the SN associated with a distance between the third ventricle walls <10mm can distinguish between corticobasal degeneration and MSA, with a positive predictive value of more than 90%<sup>(34)</sup>.

### Future perspectives

There is strong evidence that SN hyperechogenicity associated with other pre-motor symptoms of PD can predict the risk of developing the disease. In fact, a recent and well conducted study showed that in patients with idiopathic REM sleep behavior disorder, decreased striatal dopamine transporter uptake and SN hyperechogenicity reflect a dysfunction of the nigrostriatal dopaminergic system and may be markers that identify individuals with increased risk of developing PD and dementia with Lewy bodies<sup>(35)</sup>. Future studies should elucidate the value of SN hyperechogenicity in the determination of PD, in its preclinical phase.

### CONCLUSION

Correct diagnosis of parkinsonian syndromes is relevant to the clinical and surgical treatment of patients. TCS plays an important role in this process and can be used in clinical routine.

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