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Review Article

Neuroimaging of rapid eye movement sleep behavior disorder: transcranial ultrasound, single-photon emission computed tomography, and positron emission tomography scan data

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ABSTRACT

Idiopathic rapid eye movement sleep behavior disorder (iRBD), which typically develops in middle-aged individuals or later and progresses chronically, is a common clinical manifestation of Lewy body–related syndrome. It is important that combinations of neuroimaging markers in iRBD are considered for the purpose of diagnosing neurodegenerative diseases such as Parkinson disease (PD), dementia with Lewy body disease (DLB), or multiple system atrophy (MSA) at an early stage. Important advances have been made in the diagnosis of PD or DLB using imaging methods such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans or transcranial B-mode ultrasonography (TCS). These methods are important in clinical research, in which the identification of biomarkers for iRBD offers diagnostic opportunities and points the way to new therapeutic strategies. This review focuses on neuroimaging studies of rapid eye movement sleep behavior disorder (RBD) patients using techniques such as TCS, SPECT, and PET scans.

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a heterogeneous disease entity consisting of a variety of manifestations [1–8]. Idiopathic RBD (iRBD), which typically develops in middle-aged individuals or later and progresses chronically, is a common clinical manifestation of Lewy body–related syndrome. Schenck et al. [9] reported longitudinal data on a group of 29 men ages 50 years or older who were initially diagnosed with iRBD after extensive polysomnographic and neurologic evaluations; however, 38% (11/29) were eventually diagnosed with a parkinsonian disorder (presumably Parkinson disease [PD]) 3.7 ± 1.4 years after the initial diagnosis of RBD and 12.7 ± 7.3 years after its onset [9]. A 16-year update [10] of the Schenck et al. series published in 1996 found an 81% conversion rate from iRBD to parkinsonism or dementia disorders, such as PD, dementia with Lewy bodies (DLB), multiple system atrophy (MSA), unspecified dementia, and clinically diagnosed Alzheimer disease with autopsy-confirmed combined Alzheimer disease plus Lewy body disease pathology [10]. IRBD often is accompanied by subtle motor signs, decreased striatal dopaminergic innervation, and reduced presynaptic striatal dopamine transporter binding on single-photon emission computed tomography (SPECT) or positron emission tomography (PET) scans. Furthermore, despite the limited number of pathologic reports on iRBD, its characteristics have been shown to have a close relationship with Lewy body pathology [11,12]. Therefore, additional neuroimaging features that could distinguish iRBD with Lewy body–related α synucleinopathies due to other causes would be helpful in clinical practice.

Transcranial B-mode ultrasonography (TCS) is a noninvasive imaging technique that was initially developed for evaluating cerebrovascular disorders, particularly arterial stenosis and occlusion. Since the mid 1990s, however, TCS has evolved to enable visualization of brain parenchymal structures and has been more recently applied to PD and other movement disorders [13]. Becker et al. [14] first observed hyperechogenicity of the substantia nigra (SN) in PD using TCS.

PD patients consistently have reduced numbers of presynaptic dopamine transporters and normal postsynaptic D2 receptor binding [15]. Dopamine transporter SPECT (DAT-SPECT) is widely used for improving PD diagnosis. These techniques examine the uptake or reuptake of ligands into the dopaminergic nerve terminals in the striatum, enabling the functional visualization of the nigrostriatal

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dopamine system. ^{123}iodine-labeled (S)-2-hydroxy-6methoxy-*N*-([1-ethyl-2-pyrrolidinyl]methyl) benzamide (^{123}I-IBZM) is a highly specific dopamine D2 receptor ligand suitable for measuring striatal receptor activity by SPECT. This agent demonstrates specific binding to dopamine D2 receptors. The dopamine D2 receptor binding potential in the striatum is presumed to be normal or slightly elevated in PD. Seiybl et al. [16] investigated the use of ^{123}iodine-β-carbomethoxy-3β-(4-iodophenyftropane) (CIT) as a probe of dopamine transporters in PD patients using SPECT and demonstrated reduced [^{123}I]-β-CIT uptake compared with the age- and gender-matched controls [16].

Such neuroimaging studies might considerably help shorten the diagnostic process of RBD. Neuroprotective and disease-modifying drug research is intensifying and results mostly rely on accurate early diagnosis. These methods also are important in clinical research, in which the identification of biomarkers for iRBD offers diagnostic opportunities and points the way to new therapeutic strategies. This review focuses on neuroimaging studies of RBD patients using techniques such as TCS, SPECT, and PET scans.

2. Correlation of TCS, SPECT, and PET findings in iRBD

Enlarged SN hyperechogenicity (SN+), as assessed by TCS, is present in approximately 90% of PD patients, independent of age and disease stage. Midbrain hyperechogenicity also is observed in approximately 10% of healthy controls and has been proposed as a potential risk marker for PD in these subjects. This finding led to a large cross-sectional assessment of more than 400 healthy subjects, 9% of whom had SN hyperechogenicity. Additionally, many of these individuals showed reduced fluorodopa uptake on PET [17], raising the possibility that some normal individuals with SN hyperechogenicity might already have a functional deficit of the nigrostriatal system and might be destined to develop PD [17,18]. Subsequent studies continued to suggest that TCS might be useful as a diagnostic tool for clinical and for preclinical PD. Using age-corrected data, the motor signs of PD were shown to begin when the decrease in the percentage of [^{123}I] FP-CIT binding ratios in the putamen was 46% to 64% [19]. There was a significant correlation between the extension of the echogenic SN area and striatal β-CIT binding [20]. ^{18}Fluorodihydroxyphenylalanine (DOPA) uptake was lowest in patients with PD, followed by individuals with SN+, and finally in healthy controls without SN+[21].

Conversely a lack of correlation between SN echogenicity and striatal FP-CIT uptake also was found [22,23]. The authors hypothesized that the pathogenic substrate of SN+ is different from that associated with the degeneration of dopaminergic SN projection neurons. Furthermore, in asymptomatic and symptomatic *parkin* mutation carriers, echogenic SN areas were found to be enlarged [24]. Brain parenchyma sonography demonstrated SN+ in concordance with abnormal nigrostriatal ^{18}F-DOPA PET in all symptomatic and three asymptomatic *parkin* mutation carriers. Thus, SN+ was suggested as an early marker for the detection of preclinical parkinsonism. Moreover, SN+ is a stable marker because the area of echogenicity is not related to the disease stage and was found not to change during the course of disease progression over a 5-year follow-up period [25]. Thus, SN+ may reflect a pathogenic process that initiates the degeneration of dopaminergic neurons but does not reflect its morphologic substrate. The clinical interest and utility of the findings of our study (Fig. 1) are that hyperechogenic alterations in the SN may be suggestive of the existence of preclinical dopaminergic dysfunction and of an underlying neurodegenerative disorder associated with nigrostriatal dysfunction in patients with iRBD. SN+ subjects have an approximate 2-fold increased probability for the combined occurrence of the risk markers for impaired motor performance and hyposmia vs those with SN−, and SN+ is more regularly observed in subjects with higher Unified Parkinson Disease Rating Scale (UPDRS) motor scores, in particular in subjects with UPDRS scores >3 [26]. This observation indicates that the ultrasound feature may serve as a marker for nigrostriatal vulnerability in affected healthy individuals or in those in the premotor phase of PD.

To examine the sensitivity and specificity of TCS findings to discriminate between iRBD patients and normal subjects, we undertook a pooled analysis of three studies, all of which defined SN+ as an area $\geqslant$0.20 cm^2 at the side of greater SN echogenicity. Unger et al. [27] reported five iRBD patients who underwent TCS; SN+ was detected in two of these iRBD patients. Stockner et al. [28] reported that 19 (37.3%) of 51 patients with iRBD and 16 (10.7%) of 149 control subjects were found to have SN+, while Iwanami et al. [29] reported that 14 (41.2%) of 34 patients with iRBD and 2 (9.5%) of 21 control subjects were found to have SN+. The sensitivity and specificity of the TCS finding to discriminate between iRBD patients and normal subjects were reported as 0.373 and 0.893, respectively, in the report by Stockner et al. [28], and 0.412 and 0.903, respectively, in the report by Iwanami et al. [29]. The pooled analysis of these three studies [27–29], which included 260 subjects who were adequately assessable on TCS of whom 90 had defined iRBD and 170 were normal subjects, revealed a combined sensitivity and specificity of the TCS finding to discriminate between iRBD patients and normal subjects of 0.389 and 0.894, respectively.

In a recent comparison of olfactory identification and SN hyperechogenicity in iRBD, PD, and normal controls, the concomitant abnormality of olfactory identification and increased SN echogenicity

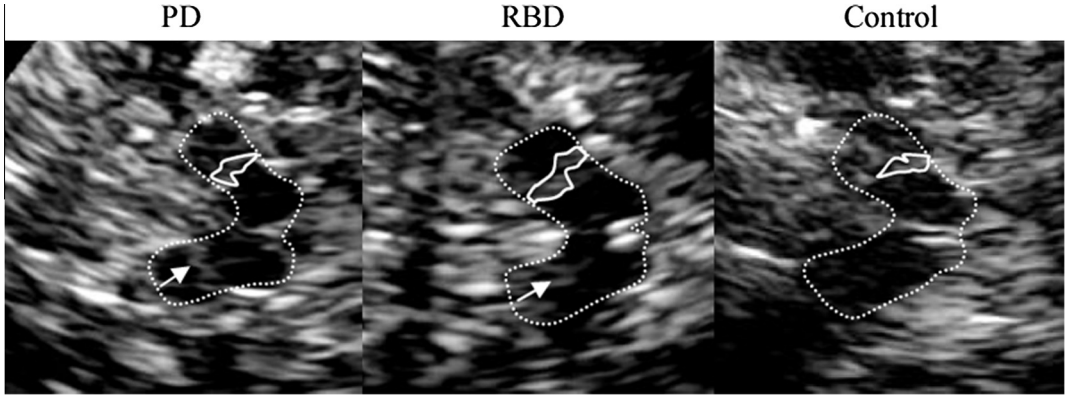

Fig. 1. Typical examples of transcranial ultrasound images of the midbrain, encircled by dotted lines, in PD and iRBD patients and control subjects. The area of enlarged hyperechogenic substantia nigra signal is encircled (solid lines) on the ipsilateral side for planimetric measurement. The arrows indicate areas of hyperechogenicity. *Abbreviations:* PD, Parkinson disease; iRBD, idiopathic rapid eye movement sleep behavior disorder (from Iwanami et al. Sleep Med 2010:361–5 [29]).