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Multimodal imaging in RBD — informing the present and planning for the future

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Abstract

Multimodal imaging in neurodegenerative disorders can provide insights on structural, functional and neurochemical alterations that might not be possible via clinical testing alone. New findings on multimodal imaging in idiopathic REM sleep behaviour disorder (iRBD) have implications for the relationship between iRBD, the clinical phenotype of Parkinson disease, and the underlying substrate of Lewy body disease, particularly for understanding the pathophysiology and designing disease-modifying therapies.

REM sleep behaviour disorder (RBD) is a fascinating parasomnia manifested by dream enactment behaviour associated with abnormal dream mentation and REM sleep without atonia on polysomnography. Although RBD was first considered to be an interesting quirk of nature it is now appreciated to have far more meaningful pathophysiological and prognostic relevance. RBD is commonly associated with the synucleinopathies — particularly with Parkinson disease (PD) and dementia with Lewy bodies (DLB) — and tends to precede the development of PD, DLB and multiple system atrophy by years or decades¹. This long time interval raises the hope that treatment of patients with RBD that is not associated with any other neurological or medical condition (known as idiopathic RBD; iRBD) might delay the onset or prevent the development of PD, DLB and other synucleinopathies².

Investigators are using a variety of clinical, neuropsychological and imaging measures in patients with iRBD to gain an improved understanding of the underlying neuropathologic substrates and to optimize the design of future clinical trials. The Braak staging system of PD, which some investigators have expanded to apply to Lewy body disease more broadly, has provided a useful framework to test a variety of hypotheses³. This staging system involves six stages in which abnormal α -synuclein inclusions develop in neurons in a largely ascending manner over years or decades, beginning in structures in the medulla and olfactory system (stage 1), then pons (stage 2), then midbrain (stage 3), and then limbic and

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neocortical structures (stages 4–6)³. Stages 1–3 are considered to represent the presymptomatic or prodromal phase and stages 4–6 the symptomatic phase with regards to the motor features of PD³. A new study has now investigated sympathetic, parasympathetic, noradrenergic and dopaminergic innervation in patients with iRBD⁴. Knudsen *et al.* assessed neurochemical systems and structures that have been implicated in the prodromal phase of Lewy body disease in the context of the Braak staging system. The team compared findings on multimodal imaging measures between healthy individuals, patients with iRBD and patients with PD. To characterise Braak stage 1, the investigators used ¹¹C-donepezil PET–CT to assess cholinergic (parasympathetic) innervation of the small intestine and the colon and ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy to assess noradrenergic (sympathetic) innervation of the heart, collectively reflecting the integrity of the dorsal motor nucleus of the vagus nerve in the medulla. To characterise Braak stage 2, neuromelanin-sensitive MRI was used to measure the integrity of the locus coeruleus and ¹¹C-methylreboxetine (MeNER) PET was used to assess noradrenergic nerve terminals originating in the locus coeruleus. To characterise Braak stage 3, ¹⁸F-dihydroxyphenylalanine (DOPA) PET was used to assess nigrostriatal dopamine storage capacity of projections originating in the substantia nigra.

Patients with iRBD had decreased colonic uptake of ¹¹C-donepezil, decreased heart:mediastinum ratio of ¹²³I-MIBG, decreased locus coeruleus:pons ratio of neuromelanin-sensitive MRI, and decreased putaminal uptake of ¹⁸F-DOPA compared with healthy individuals. No differences were observed between patients with iRBD and patients with PD regarding the ¹¹C-donepezil, ¹²³I-MIBG, neuromelanin-sensitive MRI, or ¹¹C-MeNER studies. On ¹⁸F-DOPA PET, only ~30% of individuals with iRBD had abnormal findings, in contrast to abnormal findings in 100% of the patients with PD. The authors interpreted their findings as indicating that patients with iRBD had involvement of the peripheral autonomic nervous system (indicative of Braak stage 1) and locus coeruleus and sub-coeruleus (indicative of Braak stage 2) similar to that observed in patients with PD. Furthermore, the team concluded that the majority of the patients with iRBD did not have Braak stage 3 pathology as most of these individuals had normal putaminal dopaminergic storage capacity.

These data are intriguing and timely. Indeed, these results support the tenet that most patients with iRBD have underlying Lewy body disease pathology to a degree of at least Braak stage 2⁵. As neuropathological studies in patients with iRBD are extremely scant, biomarker studies such as these provide important support for the concept of selective vulnerability in the different neurodegenerative proteinopathies — in which some neural systems are affected while others are spared — and also provide inferences on the temporal sequence of neurodegeneration in prodromal Lewy body disease when most clinical measures are insensitive. As with many cross-sectional studies, the degree of overlap between control and affected comparator groups provides additional insights on the meaningfulness of the findings as diagnostic tests. For example, the scatterplots show a high degree of overlap across all three groups on the colonic ¹¹C-donepezil, neuromelanin-sensitive MRI and ¹¹C-MeNER studies, which suggests that any of these measures in isolation might not be diagnostic in individual patients. The authors did not provide multimodal composite data or individual data on each measure for each patient, which

would have offered other investigators additional insights. The striking separation of findings on ^{123}I -MIBG between healthy individuals and patients with iRBD, when considered in the context of the very similar values in these measures between patients with iRBD and patients with PD, suggests that any patient with iRBD who has abnormal findings on ^{123}I -MIBG is likely to have underlying Lewy body disease. In addition, although the frequency of abnormal findings in patients with iRBD on ^{18}F -DOPA PET is relatively low, the presence of low ^{18}F -DOPA uptake would support the presence of underlying Lewy body disease, particularly if the ^{123}I -MIBG ratio is also low. Consequently, these findings substantiate, but do not necessarily extend, previous findings with regards to the potential diagnostic utility of functional dopaminergic imaging scans (^{18}F -DOPA PET and ^{123}I -ioflupane SPECT) and MIBG in the setting of iRBD⁶⁻⁹.

Another consideration is that the presence of abnormal α -synuclein inclusions in any neuron or neuronal network may or may not result in sufficient neuronal dysfunction and neuronal death to cause a clinical or biomarker abnormality. The threshold for the detection of an abnormality on a particular imaging modality depends on the neuronal network being assessed. Knudsen *et al.* attempt to infer which neuronal structures are burdened with abnormal α -synuclein inclusions — a laudable goal. However, a normal finding on an imaging modality cannot infer that no abnormal α -synuclein inclusions are present. Consequently, although many of the patients with iRBD have normal findings on one or more of the imaging modalities, many may still have sufficient abnormal α -synuclein inclusions in key neuronal structures to have at least stage 1, 2 or 3 Lewy body disease.

The success of future trials of disease-modifying therapies for iRBD, presumably of agents that affect α -synuclein pathophysiology, will require the identification of patients with iRBD who have a high likelihood of underlying Lewy body disease and short-term phenoconversion to PD or DLB. The findings from Knudsen *et al.* and other reports⁶⁻⁹, suggest that many of these imaging modalities will be key screening and/or outcome measures in clinical trials. Modalities that show floor effects (such as markedly abnormal MIBG findings) might be useful for screening whereas modalities with variable findings that change over time (such as ^{18}F -DOPA PET and ^{123}I -ioflupane SPECT) might be useful as biomarker outcomes or surrogates. Comprehensive prospective assessments consisting of longitudinal clinical, neuropsychologic, biofluid and neuroimaging studies of a large number of patients with iRBD will also be required to determine the optimal outcome measures, to predict phenoconversion (that is, when and to what major phenotype — PD or DLB) and to estimate sample size^{2, 10}. Although prospective multisite studies that involve patients with iRBD are in progress and others will soon begin, selection of the most informative biomarker measures for natural history studies and clinical trials remains a challenge. The cross-sectional multimodal imaging analyses published within the past few years are laudable, but additional clinical, neuropsychological, biofluid and imaging studies that measure the integrity of nigrostriatal, limbic and neocortical systems longitudinally are needed to plan for the future.

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