Autonomic impairment in REM sleep behavior disorder: a potential biomarker of phenoconversion?

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Since the seminal description in 1986 by Schenck and Mahowald [9], rapid eye movement sleep behavior disorder (RBD) has been well established as one of the earliest and specific prodromal signs of impending α -synucleinopathy-induced neurodegeneration. Idiopathic—or the more accurate contemporary term “isolated”—RBD (iRBD) is a diagnosis implying the absence of other signs or symptoms of clinically manifest α -synucleinopathy [e.g. Parkinson’s disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), or pure autonomic failure (PAF)]. Several longitudinal studies have now demonstrated that patients with iRBD have a very high risk of developing one of these disorders within their lifetime, with an overall phenoconversion rate of close to 90%, or 6–10% per year from the time of the iRBD diagnosis [3, 7, 8]. Like RBD, autonomic impairment is a prodromal manifestation of the α -synucleinopathies, and like RBD can occur decades prior to phenoconversion [2, 10]. Indeed, many patients with RBD have findings consistent with PAF [6] and, conversely, patients with PAF frequently have RBD [4]. The co-segregation of RBD and autonomic dysfunction provides rationale for the evaluation of autonomic impairment as a potential biomarker in patients with iRBD, however few studies on this topic have been reported [1].

In this issue of *Clinical Autonomic Research*, McCarter and colleagues, from Mayo Clinic Minnesota, add to this growing body of literature [5]. The authors report on quantitative measures of autonomic reflex testing in a cohort of patients with iRBD who underwent tests of cardiovagal, adrenergic and sudomotor function, including both quantitative

sudomotor axon reflex and thermoregulatory sweat testing. The authors aimed to determine if the pattern or severity of abnormalities on these tests was predictive of phenoconversion to PD, DLB, MSA, or PAF. The authors performed a retrospective search by RBD diagnosis in the Mayo clinical database, adding CPT codes for video polysomnography (vPSG) and autonomic reflex testing over a 10-year time period. All patients underwent vPSG with confirmation of REM without atonia, following current diagnostic guidelines. This search yielded 378 patients. Patients were excluded if they did not have a diagnosis of iRBD (e.g. if they were already diagnosed with PD, DLB, MSA, PAF, or an autoimmune disorder such as autoimmune autonomic ganglionopathy), if they did not have a diagnosis of RBD at the time of their autonomic testing, if autonomic testing was performed greater than 6 months before or after the diagnosis of iRBD, or if the duration of clinical follow-up after autonomic testing was less than three years. These rigid exclusion criteria left 18 patients for analysis (15 men and 3 women). The average age at RBD diagnosis was 67.1 ± 6.7 years, and the average disease duration was 4.6 ± 3.7 years. Not surprisingly, the authors found a high prevalence of autonomic impairment, with over 80% of patients demonstrating abnormalities across sudomotor, cardiovagal, and cardiovascular adrenergic domains. Twelve out of 18 (67%) patients had sudomotor dysfunction, 5/18 patients (33%) had cardiovagal dysfunction, and 11/18 (61%) had adrenergic dysfunction on autonomic reflex testing. Sudomotor testing demonstrated no differences in central vs. peripheral distributions of abnormalities, supporting a growing body of literature that suggest that peripheral autonomic abnormalities are more common than initially expected in these disorders. The mean duration of patient follow-up was 5–9 years. Twelve out of 18 patients (67%) phenoconverted: 6 developed PD and 6 developed DLB. Patients who developed DLB had a longer duration

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of autonomic symptoms compared to those who developed PD (3.8 ± 3.4 vs. 0.4 ± 0.5 years). The severity of autonomic dysfunction, as measured by composite autonomic severity scale (CASS) scores, did not predict phenoconversion rate; however, when comparing those who developed DLB to those who developed PD, patients with higher total CASS scores and cardiovascular CASS subscores at diagnosis were more likely to develop DLB than PD.

None of the patients in this iRBD cohort were eventually diagnosed with MSA or PAF, as all patients diagnosed with these conditions were given this diagnosis immediately following their autonomic testing, based on interpretation of the results. This highlights the most significant limitation of this study, which is its retrospective design. To truly assess the pattern and severity of autonomic dysfunction as a prognostic biomarker of phenoconversion in iRBD, a prospective longitudinal study is necessary. Other limitations of this study include the small sample size, the male majority of subjects, and the inherent referral bias, in which all patients who underwent autonomic testing were referred for such testing because they were symptomatic, thus capturing patients with greater risk of phenoconversion when compared to iRBD patients in the general population, who may have less severe signs or symptoms of autonomic impairment.

While recognizing the limitations of this small study, the article highlights an important subject worthy of future study, most importantly with longitudinal studies designed to assess the results of autonomic reflex testing as a potential biomarker in patients with iRBD. Such studies, which would assess a host of potential biomarkers in iRBD including not only autonomic function, but cognitive testing, smell testing, functional imaging, and skin biopsy, among other markers, will also be pivotal for future neuroprotective trials. These types of studies are necessary to understand which biomarkers to focus on for clinical outcome measures. We have seen the importance of such natural history studies in the autonomic field [4], and efforts to develop similar studies in the field of RBD are underway (ClinicalTrials.gov: NCT03623672). It has been 34 years since Schenk and Mahowald's first description of iRBD, a parasomnia that we can now use to prognosticate, with near certainty, the development of disease decades ahead. While the strength of such a clinical observation is powerful, the real power will come when we can harness this knowledge to develop treatments in the form of disease-modifying agents, to slow or halt the progression of these disabling disorders.

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Compliance with ethical standards

Conflict of interest None.

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