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Letter to the Editor

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Expanding the framework on multimodal biomarkers in isolated REM sleep behavior disorder: Response to Carpi et al.

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Dear Editor,

We sincerely appreciate the Letter by Carpi et al. (2025)[1] addressing our recent review on fluid- and tissue-based biomarkers for predicting phenoconversion in isolated REM sleep behavior disorder (iRBD).[2] Their contribution introduces critical elements from recent studies that extend the framework we previously outlined. We welcome the opportunity to further contextualize the ongoing discussion on biomarker development in prodromal α-synucleinopathies.

The primary aim of our review was to provide an updated and comprehensive overview of fluid- and tissue-based biomarkers in iRBD, emphasizing the promise of integrated, multimodal approaches for early detection and risk stratification. The increasing focus on accessible biofluids and peripheral tissues reflects a broader shift toward noninvasive approaches suitable for population-level screening and targeted interventions. Accordingly, biomarkers measurable in blood, urine, stool, skin, and mucosal samples are emerging as reliable early diagnostic tools, improving accessibility for clinical applications. Building on this perspective, the recent works by Carpi, Fernandes, and Liguori provide original evidence that strengthens the rationale for such approaches. In more detail, the points raised by Carpi et al. shed light on three key aspects: (i) the importance of two blood-based biomarkers (neurofilament light chain [NfL] and glial fibrillary acidic protein [GFAP]), which are attracting increasing attention in neurology; (ii) the dynamic evolution of biomarker profiles, introducing a temporal dimension to the interpretation of specific markers; and (iii) the potential role of circadian biomarkers, expanding the framework toward physiological processes directly linked to sleep regulation.

Regarding blood-based biomarkers, emerging consensus states NfL as a robust indicator of early neuronal injury across neurodegenerative disorders, including iRBD.[3] Coherently, Liguori and colleagues confirmed significantly higher plasma NfL levels in iRBD patients compared to controls.[4]

The role of GFAP, however, remains less clear. As the literature on GFAP in RBD is still scarce, the recent findings from the authors are significantly relevant to our understanding of related inflammatory processes in prodromal α-synucleinopathies. While some studies specifically link elevated plasma GFAP to amyloid pathology within the α-synucleinopathy spectrum, Liguori et al. found significantly higher GFAP plasma levels in iRBD patients compared to controls.[4] These seemingly divergent results may reflect the dynamic temporal profile of GFAP changes. Notably, GFAP reflects an early astrocytic response to Aβ aggregates and related inflammatory processes,[5] which could explain its elevation in iRBD patients. Given the observation that Alzheimer's disease patients exhibit higher NfL and GFAP plasma levels compared to iRBD patients and controls,[4] we fully agree with the authors' hypothesis of a likely ongoing neurodegenerative process

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in the early iRBD stage, with NfL and GFAP reflecting complementary aspects of neuronal injury and glial activation. Further longitudinal studies will be essential to clarify the specific roles and temporal dynamics of these markers in iRBD.

Carpi et al. also significantly advance the discussion by suggesting the incorporation of circadian biomarkers, particularly melatonin secretion, into multimodal panels—an aspect not addressed in our original review. They report significant preliminary evidence of reduced evening salivary melatonin and circadian dysregulation in iRBD compared to elderly controls, consistent with reports of reduced 24-h melatonin secretion in Parkinson's disease (PD).[6,7] While promising, the prognostic value and clinical utility of circadian markers remain to be validated in larger cohorts and longitudinal studies. Nevertheless, combining such physiological markers with fluid- and tissue-based biomarkers could ultimately provide valuable insight into the sleep-related pathophysiology of neurodegeneration.

In conclusion, we welcome the contribution of Carpi et al. to this evolving discussion. Their findings highlight both the complexity of prodromal α-synucleinopathies and the necessity of longitudinal validation. Advancing iRBD biomarker research requires multimodal integration, combining biofluid and tissue sampling, neuroimaging, and physiological measures to develop predictive panels that capture heterogeneous phenoconversion trajectories. Clinical translation will require standardized protocols, comprehensive longitudinal datasets, and cross-domain biomarker integration to achieve precise and early identification of individuals at highest risk of clinical progression.

Author contributions

Giulia Bruschi and Elisa Bortolin authors contributed equally to this work.

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