

Letter to the Editor

Risk of Neurodegeneration in Patients with Rapid Eye Movement Sleep Behavior Disorder

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Accepted 26 March 2022

Pre-press 19 April 2022

Abstract. I discussed the risk of phenoconversions from idiopathic/isolated REM sleep behavior disorder (iRBD). Comorbidity with iRBD, such as obstructive sleep apnea, may accelerate the risk of α -synuclein-related neurodegenerative diseases. Further studies are needed to specify the risk factors of phenoconversion from iRBD.

Keywords: α -synuclein-related neurodegenerative diseases, rapid eye movement sleep behavior disorder, risk factors

I read with great interest the report by Zolfaghari et al. [1], demonstrating no significant association between cardiovascular risk factors and subsequent phenoconversions from idiopathic/isolated REM sleep behavior disorder (iRBD) to parkinsonism or dementia, which was categorized into α -synucleinopathies. I have some comments about their study.

First, Zhang et al. [2] reported the predictive factors for α -synuclein-related neurodegenerative diseases in patients with iRBD with a mean follow-up duration of 5.8 years. They are members of the study group by Zolfaghari et al. [1], and the adjusted hazard ratio (aHR) (95% confidence intervals [CIs]) of age and nitrate derivative use for phenoconversion were 1.05 (1.02-1.08) and 2.18 (1.06-4.47), respectively. In addition, HR (95% CI) of rural living, lipid-lowering medication use, respiratory medication, and inhaled

β -agonist use for phenoconversion were 0.53 (0.35-0.81), 0.59 (0.38-0.92), 0.36 (0.14-0.91), and 0.34 (0.12-0.95), respectively. Prior pesticide exposure was also a protective factor for phenoconversion. Among protective factors, lipid-lowering medication use presented 41% risk reduction of phenoconversion, which may be partly related to the marginal risk of dementia with Lewy bodies in patients with hypercholesterolemia in the report by Zolfaghari et al. [1].

Second, Jo et al. [3] investigated the association between sleep disturbances and phenoconversion to neurodegenerative diseases in 226 patients with RBD, including 111 patients with periodic limb movements during sleep and 110 patients with obstructive sleep apnea (OSA). Among 186 patients with iRBD, 18 developed neurodegenerative diseases with a mean follow-up duration of 2.5 years. In contrast, Zhang et al. [2] reported that the overall phenoconversion rate was 24.2% after 3 years, and the difference in incidence of phenoconversion may be related to age, comorbidities, and the severity of

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RBD in each study. As there is a risk of phenoconversion in OSA patients, the combination of RBD and OSA may present additive or synergistic effect for phenoconversion.

Finally, patients with iRBD represents an early manifestation of α -synucleinopathies, such as Parkinson's disease and dementia with Lewy bodies, and there is a need to prescribe neuroprotective drugs for parkinsonism and mild cognitive impairment [4]. As patients with iRBD have an increased risk of abnormal α -synuclein deposition during the neurodegenerative process, development of useful biomarkers that can predict phenoconversion is indispensable in α -synucleinopathy patients with iRBD [5].

REFERENCES

- [1] Zolfaghari S, Lewandowski N, Pelletier A, Naeimi SA, Gagnon JF, Brillon-Corbeil M, Montplaisir JY, Postuma RB (2022) Cardiovascular risk factors and phenoconversion to neurodegenerative synucleinopathies in idiopathic REM sleep behavior disorder. *J Parkinsons Dis*, doi: 10.3233/JPD-212984.
- [2] Zhang H, Iranzo A, Högl B, Arnulf I, Ferini-Strambi L, Manni R, Miyamoto T, Oertel WH, Dauvilliers Y, Ju YE, Puligheddu M, Sonka K, Pelletier A, Montplaisir JY, Stefani A, Ibrahim A, Frauscher B, Leu-Semenescu S, Zucconi M, Terzaghi M, Miyamoto M, Janzen A, Figorilli M, Fantini ML, Postuma RB (2022) Risk factors for phenoconversion in rapid eye movement sleep behavior disorder. *Ann Neurol* **91**, 404-416.
- [3] Jo H, Kim D, Song J, Choi S, Joo E (2021) Sleep disturbances and phenoconversion in patients with REM sleep behavior disorder. *J Clin Med* **10**, 4709.
- [4] Iranzo A, Ramos LA, Novo S (2021) The isolated form of rapid eye movement sleep behavior disorder: The upcoming challenges. *Sleep Med Clin* **16**, 335-348.
- [5] Miglis MG, Adler CH, Antelmi E, Arnaldi D, Baldelli L, Boeve BF, Cesari M, Dall'Antonia I, Diederich NJ, Doppler K, Dušek P, Ferri R, Gagnon JF, Gan-Or Z, Hermann W, Högl B, Hu MT, Iranzo A, Janzen A, Kuzkina A, Lee JY, Leenders KL, Lewis SJG, Liguori C, Liu J, Lo C, Ehgoetz Martens KA, Nepozitek J, Plazzi G, Provini F, Puligheddu M, Rolinski M, Rusz J, Stefani A, Summers RLS, Yoo D, Zitser J, Oertel WH (2021) Biomarkers of conversion to α -synucleinopathy in isolated rapid-eye-movement sleep behaviour disorder. *Lancet Neurol* **20**, 671-684.