

Chronobiotic Use of Melatonin Improves DaT-Binding in iRBD

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Background: Isolated REM-sleep behavior disorder (iRBD) is recognized as a prodromal state of clinical α -synucleinopathies such as Lewy-body dementia and Parkinson's disease. A pathophysiologic hallmark of α -synucleinopathies is nigrostriatal dopaminergic impairment, with dopamine-transporter (DaT)-SPECT imaging considered the best available prognostic and monitoring marker. DaT binding is reported to decrease with healthy aging by 4-10% per decade, being accelerated to 4-12% per year in patients with iRBD. We have introduced melatonin as a treatment option for iRBD. The aim of the study was to evaluate effects of melatonin on DaT-SPECT imaging in patients with iRBD.

Methods: In a prospective, longitudinal, observational, single-center study until December 2022, we performed at least two DaT-SPECTs in 78 patients with iRBD being treated with melatonin as a chronobiotic (i.e. administration always-at-the-the-same-clock-time; 10-11p.m. - corrected for chronotype); 23 patients were excluded mainly due to change of psychotropic drugs known to influence DaT.

Results: After a mean follow-up of 3.3yrs, only 12 of 55 patients (7female; mean age 70 ± 7 yrs) showed specific binding ratios (SBR) in most affected region (MAR, predominantly right posterior putamen) comparable to usually reported declines with iRBD. In contrast, 7 had declined SBR at a rate comparable to healthy aging, while 36 had actually improved SBR. Improvement after one year (SBR of MAR; $F_{1,25}=20.874$; $p>0.001$) and two years was significant ($F_{1,21}=10.083$; $p=0.005$). After four years more than half of the patients showed a higher SBR than at baseline (20 vs. 16 patients), though this was not significant. 31/55 of our patients at baseline met established criteria for an advanced state. Instead of expected 10-19 patients converting to clinical α -synucleinopathy ($n=31$, FU-mean 3.1yrs), only three patients in our cohort had converted by the end of the observation period.

Conclusions: To the best of our knowledge, present data give first evidence for a consistent increase in DaT-binding ratios in nigrostriatum over time in a cohort of patients with iRBD. In addition, the low conversion rate reported here and a previously reported persisting effect of melatonin on RBD symptoms suggest that melatonin, when used as a chronobiotic, may have a disease-modifying effect in prodromal α -synucleinopathies.