Early View

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International Parkinson and Movement Disorder Society

Neurodegeneration in Idiopathic REM Sleep Behavior Disorder: Nailing Down the Numbers

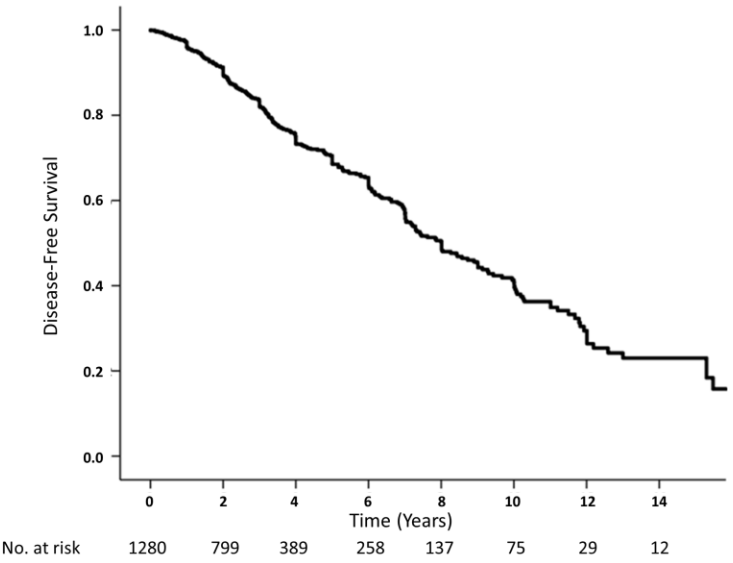
– Ron Postuma, MD, MSc, McGill University Health Centre, Montreal General Hospital, Montreal, QC, Canada

For over twenty years we have known that patients with idiopathic REM sleep behavior disorder (RBD) are at high risk of developing neurodegenerative synucleinopathies (PD, DLB, and MSA). Those single centers with the longest follow-up have found that over 80% of their cohort eventually phenoconverts to fully defined neurodegenerative disease. This has huge implications for the field, especially for the possibility that neuroprotective therapies could be applied at these beginning stages, early enough to have lasting impacts. There remain some important residual questions, especially: 1) is this a universal phenomenon in all sleep centers? 2) what is exactly the risk of phenoconversion? (we need precise numbers to plan interventions accurately), 3) are there simple and reliable ways to identify those who will convert sooner? and 4) what sample sizes are needed for definitive neuroprotective trials?

Now a 24-center, 1280 patient study from the International REM Sleep Behavior Disorder Study Group has helped answer these questions[1]. Its main findings:

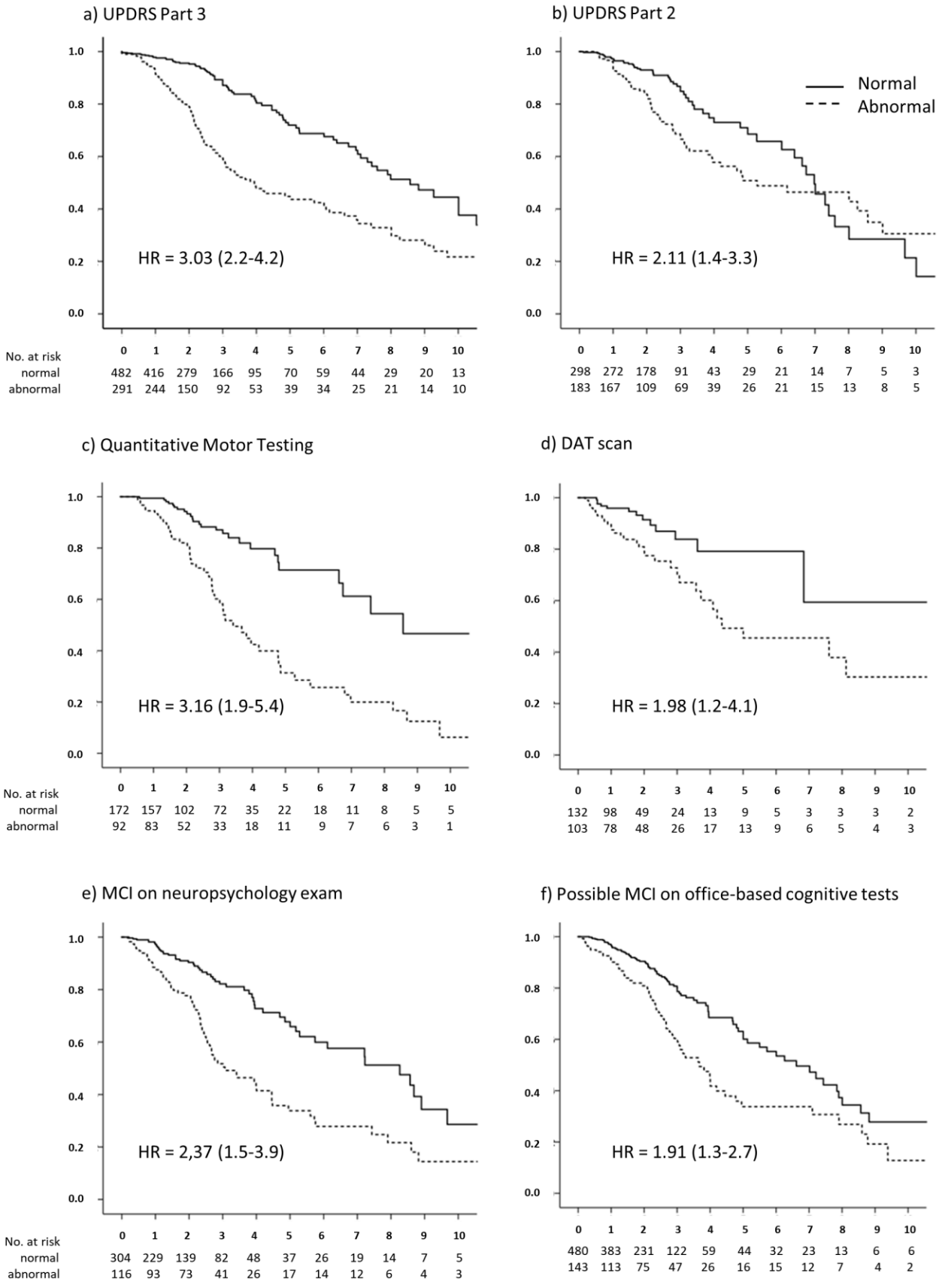
1) The spectacularly high neurodegenerative risk is not a local phenomenon – these rates are seen across the world, with all centers documenting substantial phenoconversion risks
2) Conversion rates averaged 6-7% per patient per year, so 50% will develop dementia or parkinsonism by 8 years of follow-up.
3) Many markers predicted faster phenoconversion. Unsurprisingly, motor variables were among the strongest predictors; abnormal motor tests were associated with 3-fold increased phenoconversion rates. What was surprising was that simple quantitative motor tests were as predictive in this population as were more sophisticated neuroimaging procedures such as DAT scan. Also notable, motor variables predicted 'dementia-first conversion' and 'parkinsonism-first' conversions equally (in fact, subtle motor findings are seen even longer before diagnosis of DLB than in PD without dementia). The similarity of the pre-dementia/parkinsonism states was not just a motor phenomenon; except for cognitive variables, all measures predicted dementia and parkinsonism equally. Olfactory tests were the next strongest predictors, with hazard ratios of just under 3 (higher if you exclude MSA). Color vision (generally a test of visuospatial cortical function) specifically predicted dementia. Constipation and erectile dysfunction marked a 1.7-fold increased risk. Variables that did not predict phenoconversion included sex, mood disorders, other sleep conditions, and substantia nigra ultrasound (although negative findings need to be interpreted cautiously given possible floor effects in very long-duration markers, confounding by antidepressant-triggered RBD, etc.).
4) Sample size calculations are encouraging. For an unselected RBD population in a 2-year trial, using an agent that reduces rate of phenoconversion by 50%, it would require 366 patients per arm to demonstrate prevention of parkinsonism/dementia. Selecting patients on factors such as motor testing or olfactory loss could reduce sample sizes to as low as 150 patients per arm. Given that the study included 1280 patients, it seems that a trial-ready population for neuroprotection already exists in the centers of the RBD study group.

Figure 1 - Overall Outcome (Kaplan-Meier Survival Curve)



So, the ground work has been prepared. With numerous exciting potential neuroprotective agents in preclinical or early clinical testing, we now eagerly await the first neuroprotective trial in prodromal PD.

Figure 2 – Motor and Cognitive Predictors of Outcome



References

1. Postuma RB, Iranzo A, Hu M, et al. Risk and Predictors of dementia and parkinsonism in idiopathic REM sleep behavior disorder: A Multicenter Study. Brain 2019;142.