Neurodegeneration in REM sleep behavior disorder

Stratification keeps improving

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It has now become clear that the neurodegenerative synucleinopathies (Parkinson disease [PD], dementia with Lewy bodies, and multiple system atrophy) have a definable prodromal interval during which subtle symptoms and signs occur but remain below the threshold for disease diagnosis.[1] The strongest clinical prodromal marker, by far, is REM sleep behavior disorder (RBD).[1] Most patients with idiopathic RBD are in fact in the prodromal stages of neurodegeneration.[2] This is of critical importance for the field; there may be no better population to test and eventually use neuroprotective therapy than patients with RBD. For neuroprotective trials to be planned, we need precise estimates of when patients are likely to convert, with markers that are simple and feasible for application across multiple centers. So far, the number of studies assessing predictive markers of neurodegeneration in RBD is limited. Only a few centers have published prospective studies using different markers. Thus, many crucial predictive markers have been assessed only in single studies.

In this issue of *Neurology*®, Li et al.[3] report a comprehensive 4-year prospective follow-up study testing risk markers for neurodegeneration in patients with polysomnographically proven idiopathic RBD. Several findings are notable.

1. Forty percent of patients developed a defined neurodegenerative disease, mostly PD, corresponding to a rate of 10%/y. This risk is similar to estimates from other single-center and multicenter studies (the largest multicenter study estimated a risk of 8.2%/y).[2] Thus, the extremely high risk of neurodegenerative disease in RBD is again confirmed and is generalizable to many contexts.
2. Patients with abnormal dopaminergic imaging (dopamine transporter [DAT]-SPECT) had a 2- to 3-fold increased risk of developing parkinsonism over 4 years. Although this finding is not surprising, it is important for being only the second published prospective study to document that DAT-SPECT can predict PD in any population.[4] Having an abnormal DAT scan identifies a 15% annual neurodegenerative conversion rate. This rate is similar to what can be obtained by documenting abnormal motor testing or decreased olfaction.[5,6] Therefore, DAT scan is a good predictor, although it is not more powerful than other simple measures.
3. Autonomic symptoms are clearly associated with a higher risk of developing neurodegeneration. This was shown only once before, in a multicenter study by the RBD Study Group using the detailed Scales for Outcomes in Parkinson Disease–autonomic (SCOPA-AUT)[2] (a previous single-center study using a brief questionnaire failed to find differences[5]). On breakdown of individual autonomic symptoms, predictive value was observed for gastrointestinal symptoms (seen on the SCOPA-AUT questionnaire only), urinary urge/nocturia, cardiovascular symptoms, and excessive sweating (seen only on the Nonmotor Symptom Questionnaire [NMSQ]).
4. Nonmotor scales used as summary measures (in this case, the NMSQ) can mark an increased risk of developing defined neurodegeneration. In this study, the hazard ratio (HR) of the NMSQ was 3.49 when the top half of scores were compared to the bottom half. Looking in detail, this was driven mainly by autonomic symptoms and daytime somnolence (somnolence increased risk of conversion by HR = 2.7). Note that only one previous study has found that somnolence could stratify risk in idiopathic RBD.[7]
5. Some negative associations were seen. Despite the fact that olfaction may be the best-established predictor of neurodegeneration in RBD[5,6] and of PD in general,[1] no effect of olfaction was found. The authors point out that this may be due to culture-specific issues with the test itself because many odors would be unknown to participants in China. In addition, they found no correlation between higher scores on the RBD screening questionnaire (a proxy of RBD severity) and neurodegenerative risk. This accords with informal clinical observations; sometimes, the intensity of dream-

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enactment behavior reduces as patients convert to defined neurodegeneration.

There are some limitations to point out. The procedures for defining disease diagnoses were somewhat murky, and in particular, only 2 of 18 patients developed dementia as the initial manifestation. This is quite different from the experience in multicenter studies (in which dementia is as common as parkinsonism[2]) and might suggest that screening for cognitive impairment was less intense than for parkinsonism. With only 41 patients (35 with DAT-SPECT), power is limited. Therefore, the negative findings need to be interpreted with caution. For example, on DAT, only the left striatum had a significant predictive value; this apparent difference is most likely a simple combination of chance and limited power because the point estimate of right striatum is similar to that of the left (e.g., right putamen HR = 2.4 vs left putamen HR = 3.7). Several subgroup analyses were included, which should be considered uncertain and preliminary, given the small sample size and absence of clearly compelling a priori hypothesis. Finally, the described estimates of disease risk and predictive value from RBD symptom onset (rather than diagnosis) should be considered unreliable (i.e., the 10.5-year estimated mean survival). The authors were correct to prioritize the outcome from diagnosis because estimating risk from symptom onset would introduce a severe survival-time bias (patients had to be free of parkinsonism or dementia at the baseline examination, so by definition the >5-year interval between symptom onset and baseline is a time of zero disease risk, biasing risk estimates dramatically downward).

Regardless of the limitations, this is an important confirmatory study of the high risk of neurodegeneration in RBD and of the ability to stratify patients with polysomnography-confirmed RBD for clinical trials of neuroprotective agents. Our field is ready to move beyond observational research and to start intervening to prevent disease.

AUTHOR CONTRIBUTIONS

R.B. Postuma: drafted the initial version of the manuscript. C. Trenkwalder: revised the manuscript.

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