Parkinson risk in idiopathic REM sleep behavior disorder

Preparing for neuroprotective trials

Ronald B. Postuma, MD
Jean-Francois Gagnon,
PhD
Josie-Anne Bertrand, PhD
Daphné Génier
Marchand, BSc
Jacques Y. Montplaisir,
MD

Correspondence to
Dr. Montplaisir:
jy.montplaisir@umontreal.ca

ABSTRACT

Objective: To precisely delineate clinical risk factors for conversion from idiopathic REM sleep behavior disorder (RBD) to Parkinson disease, dementia with Lewy bodies, and multiple system atrophy, in order to enable practical planning and stratification of neuroprotective trials against neurodegenerative synucleinopathy.

Methods: In a 10-year prospective cohort, we tested prodromal Parkinson disease markers in 89 patients with idiopathic RBD. With Kaplan-Meier analysis, we calculated risk of neurodegenerative synucleinopathy, and using Cox proportional hazards, tested the ability of prodromal markers to identify patients at higher disease risk. By combining predictive markers, we then designed stratification strategies to optimally select patients for definitive neuroprotective trials.

Results: The risk of defined neurodegenerative synucleinopathy was high: 30% developed disease at 3 years, rising to 66% at 7.5 years. Advanced age (hazard ratio [HR] = 1.07), olfactory loss (HR = 2.8), abnormal color vision (HR = 3.1), subtle motor dysfunction (HR = 3.9), and nonuse of antidepressants (HR = 3.5) identified higher risk of disease conversion. However, mild cognitive impairment (HR = 1.8), depression (HR = 0.63), Parkinson personality, treatment with clonazepam (HR = 1.3) or melatonin (HR = 0.55), autonomic markers, and sex (HR = 1.37) did not clearly predict clinical neurodegeneration. Stratification with prodromal markers increased risk of neurodegenerative disease conversion by 200%, and combining markers allowed sample size reduction in neuroprotective trials by >40%. With a moderately effective agent (HR = 0.5), trials with fewer than 80 subjects per group can demonstrate definitive reductions in neurodegenerative disease.

Conclusions: Using stratification with simply assessed markers, it is now not only possible, but practical to include patients with RBD in neuroprotective trials against Parkinson disease, multiple system atrophy, and dementia with Lewy bodies. *Neurology*® 2015;84:1104-1113

GLOSSARY

DLB = dementia with Lewy bodies; **HR** = hazard ratio; **ICSD-II** = *International Classification of Sleep Disorders-Second Edition*; **MCI** = mild cognitive impairment; **MSA** = multiple system atrophy; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder.

REM sleep behavior disorder (RBD) is characterized by loss of REM sleep paralysis, allowing patients to “act out” dreams.¹ Idiopathic RBD is an extremely powerful predictor (or, prodromal marker) of neurodegenerative synucleinopathies, including Parkinson disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), and >80% eventually develop neurodegenerative disease.^{2,3}

This has extreme importance for development of neuroprotective therapy against synucleinopathy; no prodromal marker of disease has near RBD’s predictive value.⁴ Patients with idiopathic RBD are ideal candidates for neuroprotective trials against synucleinopathy; one can intervene earlier, before neuronal loss progresses past rescue, and before symptomatic therapies confound assessments.⁵

However, barriers remain to including patients with idiopathic RBD in neuroprotective trials, namely, (1) disease risk is not yet fully defined; (2) a proportion may be at lower disease risk, therefore their inclusion reduces power; and (3) even at current estimates, conversion rates

Supplemental data
at Neurology.org

From the Department of Neurology (R.B.P.), McGill University, Montreal General Hospital; Centre d’Études Avancées en Médecine du Sommeil (R.B.P., J.-F.G., J.-A.B., D.G.M., J.Y.M.), Hôpital du Sacré-Cœur de Montréal; Department of Psychology (J.-F.G.), Université du Québec à Montréal; and Department of Psychiatry (J.Y.M.), Université de Montréal, Canada.

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may still be too low for practical trial design, particularly if duration is limited (e.g., patent-protected agents).

Ten years ago, we commenced a prospective cohort study of patients with idiopathic RBD. We assessed a broad array of potential predictive markers of neurodegenerative synucleinopathy, and repeated assessment annually (several individual markers have been published^{6–13}). We now report the comprehensive 10-year follow-up evaluation, addressing the following questions: (1) What is the true risk of neurodegenerative synucleinopathy? (2) What is the precise predictive value of prodromal neurodegenerative markers in RBD? and (3) Can markers be combined to select high-risk groups for neuroprotective trials?

METHODS **Standard protocol approvals, registrations, and patient consents.** This trial was approved by the local research ethics board, and all patients provided informed written consent to participate.

Patients and evaluations. Patient selection and evaluation procedures were described in detail elsewhere.¹⁴ All patients had idiopathic RBD defined with standard *ICSD-II* criteria. All had baseline neurologic examination excluding defined neurodegenerative disease. Each annual evaluation included a complete evaluation for parkinsonism (UK Brain Bank criteria) and dementia (Movement Disorder Society dementia criteria¹⁵). Follow-up occurred annually until development of neurodegeneration, including home evaluation if patients were unable to come in person; any patients lost to follow-up were analyzed as censored at last visit.

We then evaluated a broad panel of potential prodromal synucleinopathy markers. Annually assessed markers included the following:

1. Olfactory dysfunction—Cross-Cultural 12-item test¹⁶
2. Color vision testing—Farnsworth-Munsell 100-hue test¹⁷
3. Quantitative motor testing⁶:
 - a. Alternate tap—hand motor speed
 - b. Purdue Pegboard—hand dexterity/speed, finger-eye coordination
 - c. Timed Up and Go—gait/transfer speed
 - d. Unified Parkinson's Disease Rating Scale, Part III
4. Autonomic—orthostatic, urinary, erectile, bowel symptoms from the MSA rating scale¹⁸ orthostatic hypotension tested using manual measurement, supine and after 1 minute standing
5. Cognitive testing—annual neuropsychological examination (outlined elsewhere¹⁹) evaluating dementia/mild cognitive impairment (MCI),¹⁹ Montreal Cognitive Assessment²⁰ since 2006

Baseline markers (not repeated annually) included the following:

1. Beck Depression Inventory²¹
2. Beck Anxiety Inventory
3. Tridimensional Personality Questionnaire²²
4. Percentage tonic REM on polysomnogram⁹
5. Percentage REM sleep with phasic activity
6. Antidepressants and symptomatic RBD therapy (clonazepam, melatonin)

Analysis. Disease risk was estimated with Kaplan-Meier analysis. For testing prodromal markers, Cox proportional hazards was performed, adjusting for baseline age and sex. For stratification, all predictive markers were classified binarily (normal/abnormal). Olfaction was classified abnormal if <80% of age/sex-adjusted normal, and color vision if errors >125% normal.¹⁰ Individual motor tests were defined abnormal using cutoffs for ideal sensitivity/specificity defined in our study of parkinsonism in RBD (alternate tap <175 taps, Purdue <11 pegs, Timed Up and Go >7.5 seconds, Unified Parkinson's Disease Rating Scale score >3 excluding action tremor).¹¹ Autonomic symptoms were classified present/abnormal if >0 on the MSA rating scale, and systolic orthostatic blood pressure decrease ≥ 10 mm Hg was classified abnormal (also based on sensitivity/specificity cutoffs).

For combining markers, we performed Kaplan-Meier analysis, stratified to presence of marker combinations. We calculated percentage disease conversion at defined intervals (3/5 years), and estimated the proportion eligible in each stratification strategy. Finally, we estimated sample size requirements for a theoretical neuroprotective trial. This assumed a categorical definitive endpoint (disease conversion), 2 groups (placebo single-dose treatment), $\alpha < 0.05$, and 80% power. We used a time-to-event analysis (http://hedwig.mgh.harvard.edu/sample_size/time_to_event/para_time.html, trial accrual = 2 years, follow-up = 2 years [i.e., median follow-up = 3 years], median time to failure). We tested 3 effectiveness assumptions for the neuroprotective agent: moderately effective (hazard ratio [HR] = 0.5), modestly effective (HR = 0.7), and dramatically effective (HR = 0.2). On secondary analysis, we also estimated sample size using binomial probability (2 proportions, <http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html>), delineating a 2-year follow-up (total calendar time = 4 years, assuming 2-year accrual), and 50% reduction in total proportion developing disease at study end.

RESULTS **Neurodegenerative outcomes.** Ninety-five patients were seen at baseline between June 2004 and 2012. Eighty-nine (94%) had ≥ 1 follow-up examination and were eligible for analysis. Of the 6 without follow-up, 2 died before follow-up, and 4 were lost to follow-up. After completing at least one follow-up, an additional 2 patients who were still disease-free died, and 3 were lost to follow-up. Average follow-up to December 2013 was 5.4 ± 2.9 years (disease-free follow-up duration, disease as terminal event = 3.8 ± 2.4 years). Among the 89 patients, a total of 375 annual examinations were performed (86% of perfect attendance). Baseline age was 66.9 ± 9.3 years, and 65 (73%) were male. RBD symptom duration before baseline was 9.2 ± 9.2 years.

Over follow-up to December 2013, 41 patients developed neurodegenerative disease. Twenty-one were diagnosed with primary dementia and 20 with parkinsonism (PD = 17, MSA = 3). Seven were diagnosed at the second annual visit, 6 at year 3, 12 at year 4, 4 at year 5, 5 at year 6, 2 at year 7, 2 at year 8, 1 at year 9, and 2 at year 10. Of the 21 with dementia, 18 had ≥ 1 cardinal parkinsonism manifestation (11 met full UK Brain Bank criteria for parkinsonism²³), and the remaining 3 had abnormal quantitative motor testing; therefore, most, if not all, had DLB.^{11,16,24} Of 17

patients with PD, 8 had MCI at diagnosis. Therefore, we observed considerable overlap between parkinsonian and cognitive signs.

On Kaplan-Meier analysis (figure 1), we found very high rates of defined neurodegenerative disease: 30% developed neurodegeneration at 3 years, 47% at 5 years, and 66% at 7.5 years.

Outcome according to baseline markers. Patients who eventually developed disease were older than those who remained disease-free (69.6 vs 64.6). Males and females had similar disease risk. All subsequent analyses were adjusted for age and sex (table 1, figure 2).

Tonic REM% was associated with higher risk on unadjusted, but not adjusted, analysis. Thirty-five patients were taking clonazepam alone, 7 melatonin alone, 6 both, and 41 neither. Symptomatic treatment with either melatonin (HR = 0.55) or clonazepam (HR = 1.30) did not affect neurodegenerative outcome.

As anticipated, motor abnormalities were very strong predictors of neurodegenerative disease. Defining a motor examination as abnormal (2/4 quantitative motor test abnormalities¹¹) increased HR to 3.9 (95% confidence interval = 1.9–8.0). Of note, this was even stronger for dementia diagnosis (HR = 9.8 [2.6–37.4]) than for primary parkinsonism (HR = 2.5 [0.9–7.4]), perhaps consistent with the slower pace of parkinsonism evolution in DLB.¹¹

Abnormal olfaction was associated with an HR for neurodegenerative disease of 2.3 (1.12–4.5). Excluding patients with MSA (olfaction is normal in MSA) produced an HR of 2.8 (1.3–6.0).

Similarly, those with abnormal color vision were at higher conversion risk (HR = 3.1 [1.5–6.3]). This effect was much stronger for primary dementia than parkinsonism (HR = 10.3 [2.8–38.6] vs 1.5 [0.49–4.6]).

We found no clear evidence that baseline MCI could predict clinical PD (HR = 1.1 [0.39–3.0]). However, baseline MCI predicted conversion to primary dementia (HR = 8.0 [1.4–44.2]).

Depressive or anxiety symptoms did not predict who developed disease. A possible antidepressant trigger, however, was associated with lower risk, as recently described.¹³ Because of numerous reports of a “Parkinson personality,” we assessed personality variables in a subset of patients (n = 46). Although these variables differed compared with controls,¹⁴ no personality variable predicted neurodegenerative conversion. No autonomic variables predicted disease risk.

When patients developing Lewy body disease were divided into presentation with “parkinsonism first” vs “dementia first,” there were relatively few differences between groups (table e-1 on the *Neurology*® Web site at Neurology.org). However, patients presenting dementia first were more likely to have baseline MCI, color vision impairment, and olfactory impairment.

Stratifying risk for clinical trials. We then tested potential selection strategies to increase likelihood of conversion to clinical neurodegenerative disease (table e-2). Using single markers, stratification could increase likelihood of conversion to disease, sometimes with only minimal loss in screening. Simple measures such as removing possible antidepressant-caused RBD or patients younger than 55 years increased conversion rates modestly. Other clinical signs were more powerful stratifiers, albeit with more recruitment cost. Selecting patients with olfactory loss would allow 52% cohort eligibility and increased 3-year conversion from 30% to 40% and 5-year conversion from 47% to 63%. Selecting those with motor impairment (2/4 quantitative motor tests) increased conversion more dramatically, to 56% at 3 years and 74% at 5 years (45% eligible).

We then explored whether combining markers could further stratify disease risk (table e-3, figure 3). We found numerous potential strategies for increasing conversion rates. For example, removing age younger than 55 years and possible antidepressant-caused RBD, combined with any one of abnormal olfaction, color vision, or motor impairment, increased disease risk to 44% at 3 years and 61% at 5 years, while retaining 66% eligibility. Stricter eligibility requirements could

Figure 1 Development of defined neurodegeneration in idiopathic RBD

Shown is the Kaplan-Meier plot of disease-free survival of patients with idiopathic REM sleep behavior disorder (RBD). Ticks indicate censoring events.

Table 1 Potential predictors of disease at baseline in idiopathic RBD

	Total cohort (n = 89)	Developed disease (n = 41)	Still disease-free (n = 48)	HR (95% CI, adjusted)	p (adjusted)
Age, y	66.9 ± 9.3	69.6 ± 8.6	64.6 ± 9.3	1.07 (1.02-1.12)	0.003 ^a
Sex, % male	73	66	79	1.39 (0.72-2.67)	0.35
Duration RBD before baseline, y	9.2 ± 9.3	7.8 ± 8.1	10.4 ± 10.1	0.97 (0.92-1.02)	0.24
Antidepressant use, %	29	15	42	0.29 (0.12-0.68)	0.005 ^a
Use of clonazepam, %	46	54	40	1.30 (0.69-2.45)	0.41
Use of melatonin, %	15	7	21	0.55 (0.17-1.83)	0.37
Beck Depression Inventory	10.2 ± 7.0	8.5 ± 6.1	11.8 ± 7.5	0.97 (0.92-1.03)	0.29
Beck Anxiety Inventory	9.6 ± 8.3	8.3 ± 8.9	10.6 ± 7.8	0.96 (0.91-1.01)	0.12
Depression or anxiety ever diagnosed, %	41	35	46	0.63 (0.32-1.25)	0.19
TPQ-Novely Seeking (n = 46)	92.3 ± 12.6	90.1 ± 12.5	95.2 ± 12.4	0.99 (0.96-1.03)	0.72
TPQ-Harm Avoidance (n = 46)	95.9 ± 17.9	96.6 ± 18.2	95.0 ± 17.8	1.01 (0.99-1.04)	0.31
TPQ-Reward Dependence (n = 46)	95.7 ± 12.8	94.7 ± 12.8	97.1 ± 13.0	0.98 (0.95-1.01)	0.25
TPQ-Perseverance (n = 46)	121.9 ± 17.2	123.0 ± 14.0	120.6 ± 21.0	0.99 (0.97-1.01)	0.35
Mild cognitive impairment, %	59	70	50	1.80 (0.88-3.6)	0.10
UPSIT, % normal					
Excluding MSA	74.0 ± 27.6	61.4 ± 24.9	84.7 ± 25.8	0.15 (0.04-0.53)	0.003 ^a
Including MSA	75.2 ± 27.8	64.4 ± 24.5	84.7 ± 25.8	0.21 (0.06-0.68)	0.023 ^a
Abnormal olfaction, %					
Excluding MSA	55	76	38	2.8 (1.3-6.0)	0.002 ^a
Including MSA	53	71	38	2.3 (1.12-4.5)	0.010 ^a
Farnsworth-Munsell, % normal	129 ± 56	140 ± 69	119 ± 40	2.6 (1.6-4.4)	0.002 ^a
Abnormal color vision, %	47	59	38	3.1 (1.5-6.3)	0.002 ^a
Tonic REM% (HR per 10%)	48.2 ± 30.2	56.6 ± 28.3	40.8 ± 30.2	1.10 (1.00-1.21)	0.065
% Phasic REM (HR per 10%)	31.6 ± 16.8	31.1 ± 14.6	32.1 ± 18.7	1.00 (0.79-1.22)	0.94
Systolic BP decrease (HR per 10 mm Hg)	13.3 ± 14.9	18.2 ± 16.9	9.1 ± 11.6	1.13 (0.92-1.32)	0.22
Orthostatic symptoms	0.26 ± 0.47	0.30 ± 0.51	0.22 ± 0.44	1.32 (0.69-2.5)	0.37
Urinary dysfunction	0.36 ± 0.57	0.48 ± 0.27	0.27 ± 0.44	1.49 (0.83-2.7)	0.18
Erectile dysfunction	1.7 ± 1.4	2.0 ± 1.2	1.5 ± 1.5	0.97 (0.67-1.40)	0.89
Constipation	0.70 ± 0.92	0.91 ± 1.0	0.52 ± 0.81	1.13 (0.81-1.58)	0.47
Abnormal autonomic (2/4 measures), %	44	58	33	1.32 (0.70-2.5)	0.37
Timed Up and Go, s	6.8 ± 1.6	7.4 ± 1.8	6.1 ± 1.1	1.34 (1.09-1.66)	0.007 ^a
Alternate tap test (HR per 10 taps)	177 ± 33	164 ± 30	190 ± 31	0.84 (0.74-0.95)	0.004 ^a
Purdue Pegboard (no. pegs)	11.0 ± 1.8	10.6 ± 2.0	11.4 ± 1.5	0.75 (0.59-0.96)	0.026 ^a
UPDRS, Part III	4.1 ± 4.1	6.0 ± 4.9	2.5 ± 2.3	1.18 (1.10-1.28)	<0.001 ^a
Abnormal motor testing (2/4 measures), %	44	68	24	3.9 (1.9-8.0)	<0.001 ^a

Abbreviations: BP = blood pressure; CI = confidence interval; HR = hazard ratio; MSA = multiple system atrophy; RBD = REM sleep behavior disorder; TPQ = Tridimensional Personality Questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test.

The *p* values performed using Cox proportional hazards analysis, adjusted for age and sex.

^a Significant values.

dramatically increase conversion; motor impairment and age/antidepressant exclusion obtained a 65% 3-year rate (36% eligible). Requiring 2/3 abnormalities increased 3-year conversion to 60% and 5-year conversion to 80% (31% eligible), and 3/3 abnormalities identified near-certain conversion (92% at 5 years).

Sample size requirements for clinical trials. Using unselected patients with RBD, the sample size required for a moderately effective agent was 134 participants per group. This reduced considerably for dramatically effective agents (29 participants) and increased for modestly effective agents (423 participants). Stratification could

Figure 2 Predictive markers of neurodegeneration in idiopathic RBD

Shown is the Kaplan-Meier plot of disease-free survival of patients with idiopathic REM sleep behavior disorder (RBD), stratified according to presence of baseline markers: (A) olfaction, (B) color vision, (C) mild motor dysfunction, (D) autonomic dysfunction, (E) depression/anxiety, and (F) REM atonia loss. To mimic a clinical trial recruitment strategy, results are presented according to baseline assessment only (i.e., patients who develop a de novo marker abnormality over the course of the follow-up remain in the "marker-free" group). Solid line indicates patients with normal values, dashed line abnormal values. The 50% REM atonia (F) is for percentage tonic REM. Hazard ratios (HRs) are with Cox proportional hazards, adjusting for age and sex.

further reduce sample size requirements (table 2). For example, age/antidepressant exclusion with olfactory, motor, or color vision loss reduced sample size estimates by >25% (98, 33, 311 patients). Age/antidepressant exclusion with motor impairment reduced requirements by >40% (72, 23, 234 patients).

DISCUSSION The current study has 3 major findings:

1. When comprehensively examined with annual in-person evaluation, risk of PD and related synucleinopathy is very high in RBD, higher than many earlier reports.^{7,25,26}
2. This risk is predictable by assessing other markers. We expand on our previous findings that advanced age, olfaction, color vision, quantitative motor function, and nonantidepressant use mark a higher risk of defined neurodegenerative synucleinopathy.

Moreover, we assessed new variables: borderline increased risk is associated with MCI, but depression, anxiety, personality, and symptomatic RBD medications do not predict conversion.

3. By stratifying RBD cohorts with predictive markers, subpopulations can be identified with up to 65% risk in 3 years. Therefore, clinical trials for neuroprotective therapy in synucleinopathy are feasible, even over short time frames.

Our first major finding was the very high conversion rate to clinical disease. This is consistent with 2 key recent follow-up studies indicating 76% and 81% conversion.^{2,3} Of note, our current rate estimate was higher than our earlier reports.⁷ This difference may be attributable to:

1. Follow-up frequency: Our previous reports relied on a combination of annual in-person examination (after 2004) and ad hoc in-person examination/self-report

Figure 3 Combining predictive markers of neurodegeneration in idiopathic RBD

Shown is the Kaplan-Meier plot of disease-free survival of patients with idiopathic REM sleep behavior disorder (RBD), stratified according to combinations of baseline markers: (A) removing antidepressant-triggered RBD and age 55 years and older; (B) addition of olfaction and motor combined; (C) addition of olfaction and color vision combined; and (D) addition of motor and color vision combined. Solid line indicates patients with normal values, dashed lines mean that 1 of 2 measures is abnormal, dotted lines mean both measures are abnormal.

Table 2 Sample size estimates for a neuroprotective clinical trial

	3-y conversion, %	Sample size (per group) moderate effect (HR = 0.5)	Dramatic effect (HR = 0.2)	Small effect (HR = 0.7)	Binomial probability estimate (50% reduction in proportion)
Baseline (no stratification)	30	134	47	423	199
Age >55 y, no antidepressant trigger, and abnormal:	35	118	41	374	166
Olfaction	44	98	33	311	125
Color vision	49	90	30	286	108
Motor (2/4)	65	72	23	234	73
Olfaction and color vision	60	77	25	248	82
Olfaction or color vision	40	106	36	335	141
Olfaction and motor	63	74	24	239	76
Olfaction or motor	44	98	33	311	125
Color vision and motor	63	74	24	239	76
Color vision or motor	55	82	27	263	92
1/3 abnormalities	44	98	33	311	125
2/3 abnormalities	60	77	25	248	82
3/3 abnormal	64	73	24	237	74

Abbreviation: HR = hazard ratio.

For the first 3 calculations, the assumption is for a 2-year clinical trial plus a 2-year accrual period (i.e., median follow-up = 3 years) with disease conversion as a binary variable (converted vs disease-free), with $\alpha < 0.05$, and β (power) = 0.80. Sample size numbers are for each group (i.e., total trial size = $2 \times$ the number). Results are based on time-to-event analysis. A moderate-effective agent is defined as providing an HR of 0.5, a small effect as 0.7, and a dramatic effect at 0.2. The first 3 estimates use time-to-event (see methods). The last estimate is an alternate calculation that uses simple binomial probability (i.e., 2-year follow-up study [plus accrual time], calculating proportion affected after 2 years of follow-up).

(before 2004). Here, all diagnoses were made on systematic annual in-person examination, often before patients reported substantial symptoms, suggesting that self-reports were insensitive.

2. Diagnostic sensitivity: Since 2004, all patients were examined for parkinsonism by a movement disorders specialist (R.P.), and neuropsychological examination became standard; this likely allowed earlier disease diagnosis. Also, the current Movement Disorder Society criteria¹⁵ allow earlier dementia diagnosis.
3. Lower loss to follow-up: Our intensive follow-up resulted in very low attrition. We noted that patients who were difficult to locate or refused to attend (requiring home visits) often had dementia or parkinsonism; therefore, loss to follow-up might bias toward lower disease estimates.
4. RBD diagnosis: Recently, quantification of REM atonia has become more standardized; we now applied a specific REM atonia cutoff.²⁷ Presumably, misdiagnosed patients would have lower disease risk.

Therefore, neurodegenerative disease risk in idiopathic RBD is extremely high; in fact, it appears that only a small minority of patients do not have an underlying neurodegenerative process.

Our second major focus was an examination of potential predictive clinical markers of PD/DLB, using patients with RBD as a test model. We confirmed and expanded on our previous findings for

many variables. Olfactory testing predicts disease, but it is not perfect; 2/39 patients with PD/DLB had normal olfaction at diagnosis, and patients with MSA had normal olfaction. Color vision was clearly associated with increased risk, although it may better predict dementia (all patients with dementia had abnormal test at diagnosis, but 8 without dementia tested normally). As we recently published,¹¹ motor dysfunction strongly predicted disease, regardless of parkinsonism/dementia primary diagnosis. Finally, we were again unable to establish autonomic dysfunction as disease predictor in idiopathic RBD.¹² An obvious potential explanation is unreliability of these simple autonomic estimates, but we observed similar findings with cardiac autonomic dysfunction on ECG.²⁸ Another explanation could be that autonomic dysfunction is the earliest prodromal marker, and therefore nearly all have loss at RBD onset.

We also assessed novel predictive markers. There has been considerable interest in a putative “Parkinson personality,”²⁹ and we previously found personality differences in patients with RBD compared with controls.¹⁴ However, on prospective follow-up, baseline personality variables did not predict conversion risk. Although this could be construed as evidence against the Parkinson personality, it could also suggest that PD personality is lifelong, present equally in idiopathic RBD and established PD.

Although the presence of MCI at baseline predicted dementia, it notably did not predict primary diagnosis of PD, considering the considerable overlap between DLB and PD.¹⁶ Note that unlike some cohort studies,^{3,30} MCI was not delineated a disease outcome in this study (we consider it a marker of cognitive loss that indicates likely transition to dementia,³¹ analogous to mild parkinsonian signs as predictors of full parkinsonism¹¹). We are currently preparing a full analysis of neuropsychological variables predicting evolution from normal cognition to MCI/dementia in this cohort. Also, although we delineated primary dementia vs parkinsonism, we consider PD and DLB emerging from idiopathic RBD to be pathophysiologically similar, consistent with a recent PD definition statement proposing that they should not be considered mutually exclusive diagnoses.³²

We found no evidence that symptomatic treatment for RBD affected neurodegenerative outcome. One might have speculated that RBD itself could accelerate neurodegeneration, perhaps via failure of normal REM sleep maintenance; if so, risk might be lower in those receiving therapy. We found no clear evidence for this possibility.

Whereas depression and anxiety predict PD in population-based studies,⁴ we found no effect on conversion risk in RBD. This was not simply lack of power; both indices were slightly lower in those who developed disease. One explanation could be confounding by antidepressants, which are associated with lower risk (perhaps because they trigger earlier presentation of RBD¹³); note, however, that HRs did not change when antidepressants were added to the model (Beck anxiety HR = 0.96/0.96, Beck depression HR = 0.97/0.99).

Our third major finding is that disease risk can be stratified effectively in idiopathic RBD. Moreover, these stratification procedures need not be complex—every marker in this study can be tested in <15 minutes. With some marker combinations identifying >80% 5-year conversion rates, the additive value of more invasive/expensive tests for identifying neuroprotective trial candidates is unclear.

The high conversion rate attainable with stratification has very important implications for the future of neuroprotective therapy. A major reason for the failure to develop neuroprotective synucleinopathy therapy may be that the disease has been present many years before clinical parkinsonism or dementia; it is simply too late to intervene. With idiopathic RBD, one can treat disease in prodromal stages, potentially before irreversible damage, and before symptomatic PD therapy confounds assessment. Two major issues have limited using patients with RBD for clinical trials, which may now no longer apply. First, based on previously

published conversion rates, sample size estimates would exceed 300 to 500 participants, even in long-duration trials. Now, stratification using predictive markers enables trials with fewer than 150 participants. Second, patients with RBD were thought to be few and confined to subspecialty sleep clinics. However, as awareness has expanded, diagnosis is more frequent. To illustrate, the RBD study group quickly recruited 347 patients for an epidemiologic study,³³ well within sample size calculations (multiple centers would still be required for most trials).

There may be a tradeoff between conversion risk and lead time; selecting for advanced prodromal signs limits the lead time gained by using RBD. Therefore, if a neuroprotective agent might work specifically in very early synucleinopathy, stratification strategies may differ (e.g., exclude subtle motor impairment, at the cost of increased duration/size). Of course, we do not suggest that once neuroprotective therapy is available, only those RBD patients with specific risk factors are candidates; this remains an individual clinical decision (if >80% ultimately develop synucleinopathy,² one might suggest that all are neuroprotective treatment candidates). Rather, stratification enables selection for trials in settings when financial resources and/or maximal study duration are limited (most settings). There is little doubt that disease conversions will increase further over time, also among those with initially normal prodromal markers. It should also be recognized that patients with PD/DLB who have RBD represent a subgroup of PD³⁴; therefore, results from RBD trials may not completely generalize to other populations. Our primary analysis was for all neurodegenerative disease outcomes; since patients with RBD develop both dementia and parkinsonism, they are perhaps better trial candidates for agents that target synucleinopathy in general.

Our study has some limitations. To maximize generalizability and eventual scalability, we focused on markers assessable in all patients. Many other variables could be assessed (and have been assessed in subcohorts) including MRI,³⁵ SPECT/PET,^{36,37} transcranial ultrasound,³⁷ MIBG scintigraphy,³⁸ ECG,³⁹ EEG,⁴⁰ etc. Diagnosis of neurodegenerative disease remains clinical, and the time of “crossed threshold” is difficult to define; other clinicians may have diagnosed disease earlier or later than we did. Although the sample size was large, with a 10-year study duration, there is nonetheless imprecision in all estimates; future neuroprotective trials should choose sample sizes slightly beyond our projections. However, our study has some notable strengths, particularly the annual standardized evaluation up to 10 years, systematic diagnostic protocols, comprehensive evaluation of broadly applicable markers, and limited loss to follow-up.

Therefore, our findings suggest that it is now not only possible, but also practical to include patients with RBD in neuroprotective trials against PD and DLB.

AUTHOR CONTRIBUTIONS

R.B.P. was responsible for study concept, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. J.-F.G. was responsible for study concept, acquisition of data, interpretation of data, and revision of the manuscript. J.-A.B. and D.G.M. were responsible for acquisition of data and revision of the manuscript. J.Y.M. was responsible for study concept, obtaining funding, interpretation of data, and revision of the manuscript.

STUDY FUNDING

This study was supported by the Fonds de la Recherche du Québec—Santé, the Canadian Institutes of Health Research, and the W. Garfield Weston Foundation.

DISCLOSURE

R. Postuma received personal compensation for travel and speaker fees from Novartis Canada, Allergan Canada, and Teva Neurosciences, and is funded by grants from the Fonds de la Recherche du Québec—Santé, the Parkinson Society of Canada, the Webster Foundation, the W. Garfield Weston Foundation, and by the Canadian Institutes of Health Research. J. Gagnon is funded by grants from the Fonds de la Recherche du Québec—Santé, the W. Garfield Weston Foundation, and the Canadian Institutes of Health Research. D. Génier Marchand and J. Bertrand report no disclosures relevant to the manuscript. J. Montplaisir received personal compensation as consultant (Impax Pharma, Servier, Jazz Pharma, Merck, Valeant), speaker (Valeant), and received financial support for research activities from Merck, GlaxoSmithKline, is funded by grants from the Fonds de la Recherche du Québec—Santé, the W. Garfield Weston Foundation, and by the Canadian Institutes of Health Research. Go to Neurology.org for full disclosures.

Received March 17, 2014. Accepted in final form November 19, 2014.

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This Week's *Neurology*® Podcast

Age of first exposure to football and later-life cognitive impairment in former NFL players (see p. 1114)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the March 17, 2015, issue of *Neurology*. In the second segment, Dr. Howard Goodkin talks with Dr. Robert Stern about his paper on the age of first exposure to football and the effect of later-life cognitive impairment on former NFL players. Dr. James Addington then reads the e-Pearl of the week about REM behavior disorder. In the next part of the podcast, Dr. Michelle Johansen focuses her interview with Dr. Kevin Barrett on the topic of stroke in the setting of endocrine disorders.

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