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Phasic Muscle Activity in Sleep and Clinical Features of Parkinson Disease

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Abstract

Objective—The absence of atonia during rapid eye movement (REM) sleep and dream-enactment behavior (REM sleep behavior disorder [RBD]) are common features of sleep in the alpha-synucleinopathies. This study examined this phenomenon quantitatively, using the phasic electromyographic metric (PEM), in relation to clinical features of idiopathic Parkinson disease (PD). Based on previous studies suggesting that RBD may be prognostic for the development of later parkinsonism, we hypothesized that clinical indicators of disease severity and more rapid progression would be related to PEM.

Methods—A cross-sectional convenience sample of 55 idiopathic PD patients from a movement disorders clinic in a tertiary care medical center underwent overnight polysomnography. PEM, the percentage of 2.5-second intervals containing phasic muscle activity, was quantified separately for REM and non-REM (NREM) sleep from 5 different electrode sites.

Results—Higher PEM rates were seen in patients with symmetric disease, as well as in akinetic-rigid versus tremor-predominant patients. Men had higher PEM relative to women. Results occurred in all muscle groups in both REM and NREM sleep.

Interpretation—Although our data were cross-sectional, phasic muscle activity during sleep suggests disinhibition of descending motor projections in PD broadly reflective of more advanced and/or progressive disease. Elevated PEM during sleep may represent a functional window into brainstem modulation of spinal cord activity and is broadly consistent with the early pathologic involvement of non-nigral brainstem regions in PD, as described by Braak.

Polysomnographic studies across a broad spectrum of alpha-synucleinopathies (including idiopathic Parkinson disease [PD], dementia with Lewy bodies [DLB], and idiopathic rapid eye movement [REM] sleep behavior disorder [RBD]) point to absence of REM sleep atonia as a common feature in these conditions.^{1–5} A key aspect of these observations is that RBD typically precedes the explicit diagnosis of PD or DLB, often by periods of several decades,^{5–7} and may represent an exceptionally early marker of synucleinopathic degeneration. Perhaps less well established is whether signs of RBD may also be prognostic of disease features once a diagnosis of Parkinsonism has been established. Disease

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progression in PD remains an incompletely understood phenomenon, although certain subtypes (eg, tremorous) usually are considered to herald a slower disease course than others (eg, bradykinetic/rigid).^{8,9} Additionally, early stage PD typically manifests asymmetrically, whereas later stage disease typically involves both body sides.^{8,10} In this cross-sectional study, we sought to evaluate whether, within a group of idiopathic PD patients, specific neurophysiological markers derived from overnight polysomnography (PSG) were associated with clinical indices typically associated with more advanced disease or more progressive disease course.

Observations of RBD in parkinsonism have typically, but not exclusively, been derived from clinicians' judgments, based on history and occasionally supplemented by standardized questionnaires. However, measurements of phasic muscle activity recorded from surface electromyographic (EMG) electrodes have indicated large and robust effects in distinguishing the sleep of PD and idiopathic RBD patients who were not yet parkinsonian,^{11–15} with significantly higher rates of phasic discharges noted relative to controls. Very recently, Iranzo et al¹⁶ have shown that elevated muscle activity in sleep becomes worse in idiopathic RBD patients over a mean interval of 5 years in the absence of overt parkinsonism. In this study, we investigated the extent to which such quantified activity may be related to clinical features of PD, including symmetric (SYM) versus predominantly asymmetric (ASYM) involvement, and tremor-predominant versus akinetic-rigid PD phenotype. We hypothesized that (1) patients with bilateral involvement would demonstrate higher rates of phasic muscle activity in sleep and (2) akinetic-rigid patients would exhibit greater motor activation in sleep relative to tremor-predominant patients.

Patients and Methods

Patients

Idiopathic PD patients (mean age, 63.4 years; standard deviation [SD], 10.7; 44 men; 11 women) from the Movement Disorders Clinic in the Department of Neurology at Emory University School of Medicine participated in this study. The study was approved by the Emory institutional review board. Patients had been diagnosed with PD for 9.6 years (SD, 6.8). Fifteen patients had bilateral motor system involvement, whereas the remaining 40 showed unilateral impairment (16 left-sided; 24 right-sided). All patients were right-handed, with the exception of 3 who were left-handed and demonstrated unilateral impairment (2 right-sided, 1 left-sided).

Additional descriptive information (Table) indicated that relative to patients with unilateral involvement, patients with bilateral motor signs were slightly older, but did not differ in gender composition, disease duration, or history of dream enactment behaviors, as reported globally by the clinician, who was blind to the PSG results. A standardized questionnaire was not used to determine dream enactment history. Most patients received L-dopa/carbidopa. The proportions of patients in each group receiving selegiline, antidepressants (either serotonin reuptake inhibitors or tricyclic antidepressants), or various dopamine agonists were not significantly different (see Table for frequencies). A subgroup of 28 patients (mean age, 61.3 years; 21 men; 7 women; mean years with PD, 10.9) underwent additional blind evaluation using the motor component of the Unified Parkinson Disease Rating Scale (UPDRS).¹⁷

PSG

All patients underwent a single night of PSG, including surface EMG channels for recording from the mentalis, bilateral anterior tibialis (AT), and bilateral brachioradialis (BR). As previously described, we used a modified stage scoring system to identify only REM and

indeterminate non-REM (NREM) sleep in these patients.¹⁸ Phasic muscle activity was quantified using a modification¹¹ of the system originally described by Lapierre and Montplaisir¹⁹ (also used by Iranzo et al¹⁶) to generate a phasic electromyogram metric (PEM) for each stage (REM and NREM) and recording site (5: mentalis, left and right AT, left and right BR). In the Lapierre and Montplaisir system, a distinction is made between phasic muscle activity and sustained tonic activity. In our modification,¹¹ we quantify only the former. Our rationale for this approach is derived from studies of the electrophysiology of muscle activity²⁰ that have indicated that the relative presence or absence of tone for a given muscle group will depend on the passive stretch and tension properties of that muscle. Because sustained tonic activity of a muscle represents an amalgam of motor units firing at different rates, phasic muscle events, when distinguishable from background activity in the context of low-impedance surface recordings, is the most elemental feature of the firing of the motor unit. In this study, we defined phasic muscle activity on a particular channel as a potential at least 4× the amplitude of the background activity on that channel, with duration of at least 100 milliseconds and a detectable return to baseline within a 2.5-second interval. PEM data were presented as a ratio, that is, the percentage of 2.5-second intervals with phasic muscle activity relative to the total number of 2.5-second intervals in REM or NREM sleep.¹¹ Because we defined PEM on the basis of intervals containing activity (rather than by the number of definable phasic muscle bursts per se), it was possible that a given 2.5-second unit may have contained >1 detectable phasic burst; however, in such situations, the score for that activity was still noted as 1. All 2.5-second units of sleep not containing phasic activity were thereby considered 0, unless artifact caused by gross body movement was so great as to preclude a baseline level. (See visual templates in Bliwise et al¹¹ for examples.) Other than our analyses being limited to only phasic activity in sleep (rather than including sustained tonic muscle activity), this approach to quantification of elevated muscle activity strongly resembles those used by Lapierre and Montplaisir¹⁹ and Consens et al,¹⁴ who used 2.0- and 3.0-second units, respectively.

Data were scored by a single scorer for whom inter-rater reliability had been established previously at 0.77,¹¹ and who was blind to the patient's clinical condition. Tremor, although rare during sleep, was included in such scoring. We also scored more traditionally defined periodic leg movements in sleep (PLMS) following conventional scoring rules.²¹ PLMS were adjusted per hour of sleep, to yield a PLMS index (PLMSI). All EMG signals were derived from bipolar derivations (to minimize pulse artifact) with filter settings of 10 to 100 Hz recorded on Grass Model 78 polysomnographs. Start-of-night impedances generally were below 5,000 Ω .

Statistical Analyses

To test our primary hypotheses (asymmetric versus symmetric disease, tremorous versus akinetic/rigid subtypes), we relied on 2-group *t* tests using 10 (2 stages by 5 sites) PEM measures as dependent variables and adopted family-wide, conservative Bonferroni adjustments for multiple comparisons with a significance level set at 0.005. We employed 2-tailed probabilities for all comparisons. Exploratory analyses (eg, associations with dream-enactment behavior by history, body side comparisons within ASYM patients, gender comparisons, medication effects) employed unadjusted *t* tests, also with 2-tailed probabilities. For categorical variables, we calculated 2-by-2 contingency tables and employed Fisher exact test, to allow for small expected cell sizes.

Results

For all 55 patients considered as a group, there were no associations between any measure of PEM and age or reported disease duration. Patients with RBD by history (*n* = 18) were no more likely to have higher PEM rates. Consistent with previous data suggesting that

quantification of PEM activity may partially, but not completely, reflect PLMS,¹¹ NREM PEM rates from both left and right AT were associated modestly with PLMS ($r = 0.32$, $p < 0.02$ and $r = .30$, $p < 0.03$, respectively).

Conventional polysomnographic measures suggested somewhat poorer quality (lower sleep efficiency) and shorter sleep (total sleep time) among SYM patients, but without differences in PLMSI, respiratory disturbance index, or REM% (see Table). The Figure shows comparisons of PEM rates across all recording sites in both REM and NREM sleep. Statistically significant differences occurred with higher PEM rates in SYM patients observed in 7 of 8 limb recordings (including REM and NREM values) at the 0.05 level, and 2 comparisons (left BR NREM, left AT NREM) remained significant even after Bonferroni adjustment (ie, $p < 0.005$). Mentalis PEM activity did not differentiate SYM versus ASYM patients, and excluding the 3 left-handed cases did not affect any of the foregoing results. Among the ASYM patients, we compared PEM values from left versus right limbs in REM and NREM sleep for patients with predominant left- versus right-sided involvement. None of the PEM measures significantly differentiated affected versus unaffected body sides.

Nearly all patients were on L-dopa therapy. To examine possible effects of other medication use, we compared patients who were also receiving or not receiving dopamine agonists, selegiline, and antidepressant medications. Individuals receiving agonists were younger (59.5 ± 10.6 years vs 68.1 ± 8.9 years, $t = 3.24$, $p = 0.002$) and on average had been diagnosed twice as long (12.1 ± 6.0 years vs 6.8 ± 6.5 years, $t = 3.07$, $p = 0.003$) as those not taking such medications. Patients receiving selegiline or antidepressant medication also had longer disease duration (12.2 ± 7.0 years vs 7.9 ± 6.2 years, $t = 2.42$, $p = 0.019$ for selegiline; 12.6 ± 7.1 vs 7.5 ± 5.9 , $t = 2.90$, $p = 0.006$ for antidepressant medication), but without differences in age. Relative to PEM, all comparisons of individuals taking versus not taking these medications were nonsignificant, with the exception of the right BR PEM activity during REM in patients receiving antidepressant medication, which was higher in the medication group ($p = 0.046$), but did not reach significance after Bonferroni adjustment. Among those 50 patients receiving L-dopa, daily dose was unrelated to any PEM measure for those patients receiving this drug, nor did any differences in PEM rates occur when those 5 patients not receiving L-dopa were combined with the 5 patients whose final daily L-dopa dose occurred prior to 4 PM, when compared to the remaining 45 patients.

There were no differences in any PEM measure between the 28 patients with UPDRS versus the 27 patients for whom standardized UPDRS ratings were unavailable. For those patients with UPDRS, we derived a measure of relative predominance of tremor versus rigidity by calculating the maximal 5-site UPDRS tremor rating (bilateral upper/lower extremities plus lips/jaw) (range, 0–4) minus the maximal 5-site rigidity rating (bilateral upper/lower extremities plus lips/jaw) (range, 0–4). Overall tremor versus rigidity predominance thus could range from –20 to +20, and results indicated that rigidity predominated in this subsample (mean UPDRS sum difference = –3.5; range, –18 to +20). Five patients were considered predominantly tremorous and tended to demonstrate less PEM activity than rigid patients for the following: chin NREM ($p = 0.006$), left BR NREM ($p = 0.097$), right BR REM ($p = 0.027$), right BR NREM ($p = 0.072$). Chin REM and all AT values trended in a similar direction; however, all of these comparisons fell short of significance following Bonferroni adjustment.

Men and women did not differ in age (64.5 ± 9.8 years vs 60.0 ± 13.6 years, $t = 1.25$, $p = 0.22$), disease duration (9.3 ± 7.1 years vs 10.9 ± 5.8 years, $t = 0.70$, $p = 0.49$), or reported history of dream-enactment behavior (32% vs 36%, Fisher exact test $p = 1.00$); however, men demonstrated significantly higher rates of PEM activity on 7 of 10 site/stage measures, including mentalis NREM ($p = 0.001$), left BR REM ($p = 0.003$), right BR REM ($p =$

0.002), right BR NREM ($p = 0.047$), left AT REM ($p = 0.0006$), left AT NREM ($p = 0.024$), and right AT REM ($p = 0.0002$), with rates approximately double those of women for all these variables.

Discussion

These data indicate that PEM represents a highly relevant, polysomnographically derived measurement of sleep in PD patients that has both some hypothesized (eg, SYM versus ASYM), but also some unexpected (eg, sex differences), clinical correlates. Although fewer patients were available for subtype analysis, we also found that tremor-predominant patients exhibited less motor activity during sleep than did akinetic/rigid patients. We interpret this effect as suggestive of the predominance of inhibitory pallidal influences on descending mesopontine circuits that are more likely to occur in rigidity, in contrast to dysfunction of corticothalamic loops thought to subserve tremor. Recent data suggesting that tremor-predominant patients may be less likely to show qualitatively characterized RBD are consistent with this observation.^{22,23} Additionally, data suggest that tremor-predominant patients have a more benign course when compared to akinetic/rigid patients.^{24,25} This relative sparing of systems responsible for PEM could reflect different pathologies or different temporal and/or spatial course of disease progression.

Our data did not show associations between clinical characterization of RBD and PEM measures. This may reflect the fact that such RBD characterization was performed globally as a clinician's judgment, rather than as a continuous measure. Future studies examining correlations between PEM and questionnaires that measure the tendency to RBD as a continuous trait²⁶ would allow a better understanding of whether the neurophysiologic marker described here can also reflect severity of dream enactment behavior.

The basis for the excess levels of phasic muscle activity detected in the sleep of PD patients remains poorly understood. Deficiencies in dopaminergic systems may not account entirely for the phenomenon.²⁷ During REM sleep, elevations in unit firing within the substantia nigra reticulata²⁸ have been reported, and these could represent a substrate for the high rates of PEM. The specific basis for such descending influences, which must override the descending inhibition characteristic of REM sleep, are uncertain,²⁹ but those effects probably operate via both direct and monosynaptic pathways through more caudal areas, such as the mesopontine region (especially the pedunculopontine nucleus and midbrain extrapyramidal area), sub-lateral dorsal nucleus, and/or magnocellular reticular formation.³

Although a plausible explanation for the observed associations with PEM rates during REM sleep, these state-dependent considerations do not explain why PEM elevations were also seen in NREM sleep, during which reticulata firing rates are no higher than during waking.²⁸ One possible explanation may be that other regions with high firing rates in NREM sleep, including the ventral globus pallidus,³⁰ and even more caudal sites, such as non-respiratory-associated neurons within the solitary tract nucleus,³¹ may also be disinhibited. Alternatively, lesions of the rostral ventral mesopontine junction have been shown in cats to cause transient increases in aperiodic phasic activity during NREM sleep,³² which is not dissimilar from the prolonged phasic activity seen in REM sleep with more caudal lesions. Thus, direct involvement of this more rostral area by the parkinsonian disease process might explain PEM during NREM. Our study is not the first to note high rates of muscle activity in NREM sleep in synucleinopathic conditions. Abundant aperiodic leg muscle activity during NREM sleep was seen in an early series of idiopathic RBD patients.³³

Because sleep per se is associated with a general decrease in tone across many muscle groups in humans,³⁴ the skeletal musculature represents a convenient window to monitor such widespread descending influences. These effects may be obscured during active wakefulness when the musculature of the body is otherwise activated by the demands of active locomotion, maintenance of upright posture, and other adaptive activities. Tonic activation may be particularly relevant in a condition like PD, in which elements of dystonia and hypertonicity can be prominent during wakefulness. EMG studies during wakefulness have suggested abnormally fast flexion bursts³⁵ or higher variability in the duration of such bursts.³⁶ A more general disinhibition influencing both REM and NREM sleep would also fit our observations that, even in predominantly asymmetric patients, PEM activity did not lateralize, and this is consistent with widespread bilaterality of fiber tracts descending from the brainstem (estimated at 70–90%).³⁷ Additionally, in asymmetric PD, dopamine receptor transporter within the striatum is lost on both ipsi- and contralateral sides,³⁸ which is consistent with nonlateralization of PEM activity in relation to affected body side.

The vast majority of patients in this study were receiving L-dopa therapy for their condition. Although we noted no obvious associations between L-dopa dose or the timing of final dose and PEM activity, we cannot be certain that such dopaminergic treatment had no impact on such activity, as predrug/postdrug polysomnographic data were not available. Because between 35% and 53% of our patients, however, additionally used dopamine agonists, selegiline, or antidepressants, we were able to provide some preliminary evaluation of possible drug effects by comparing individuals using versus not using such medications. Our data, again limited by absence of within-subjects design, cannot be considered definitive, but they imply that these classes of medication were not associated with either lower or higher rates of PEM. Future interventional studies would be required to demonstrate more definitively that these medication classes had no effect on PEM activity. By contrast, it is widely known that other classes of medications, most notably selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and tricyclic antidepressants, are associated with clinically defined RBD and, in some cases, with elevated phasic muscle activity as well.³⁹

Certainly the labor-intensive task of visually quantifying EMG activity is amenable to different automated approaches, as others have shown.¹³ It remains to be seen whether the distinction of phasic and sustained tonic muscle activity may have relevance to the PD subtypes and/or PD severity that we have investigated here. Certainly, it would be necessary to show reliable discrimination between these types of muscle activity as a first step in such analyses. We also would stress that quantification of the entire night of PSG from all electrode sites and all sleep stages may not be necessary to appreciate this putative marker of disease course. For example, we have recently shown that quantification of PEM activity from a single REM period provided very strong differentiation of normal versus presumptively pathologic levels of such activity, the latter derived from nonparkinsonian patients who demonstrated a history of dream-enactment behavior.¹² There may be considerable diagnostic yield in quantifying muscle activity during sleep in patients with known or suspected synucleinopathy, especially in anticipation of the development of medications that alter disease course as distinct from those targeting symptomatic relief.

Gender differences in rates of phasic muscle activity were conspicuous and unanticipated in this study. There was no indication that men in our study had worse disease than women, at least when indexed by years with diagnosis, daily L-dopa dose, or bilateral versus unilateral involvement. Estradiol is protective of glutamate-induced toxicity in mesencephalic dopamine neurons in vitro,⁴⁰ and has been associated with higher dopamine levels in vivo in mice made parkinsonian by systemic N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine injection⁴¹ or 6-hydroxydopamine infusion.⁴² Interestingly, despite such steroidal influences

on the dopamine system, human studies have not found a difference in estradiol or other sex hormone levels in men with and without RBD,⁴³ nor a relationship between plasma testosterone levels and qualitative descriptions of dream enactment behaviors in PD.⁴⁴ This finding is of interest, given some,⁴⁵ but not unequivocal,⁴⁶ evidence of beneficial effects of exogenous testosterone administration in men with PD. RBD case series have typically been more likely to be male,^{1,47} a finding that has sometimes been interpreted as reflecting the greater likelihood of men, relative to women, being referred clinically for evaluation of potentially aggressive and dangerous behavior. Apart from such potential referral bias, our data suggest that men with PD showed a clearly demonstrable and robust neurophysiologic substrate (ie, PEM) for overt behavioral abnormalities. Such differences may warrant further investigation.

At the broadest level, our data are compatible with the neuropathologic findings arguing for the spatial and temporal course of brainstem neurodegeneration in PD.⁴⁸ Assessments of sleep, not limited to measurements of muscle activity, but also involving daytime alertness,⁴⁹ have become increasingly recognized as clinically relevant features of parkinsonism that predate development of the waking motor manifestations and ones that often require intervention.⁵⁰ Specific measurements derived from overnight polysomnography, such as PEM, may represent an important tool to refine diagnosis, prognosis, and, possibly, outcomes in PD.

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FIGURE.

Comparison of phasic electromyogram metric (PEM) rates in both rapid eye movement (REM) and non-REM (NREM) sleep in Parkinson disease (PD) patients with predominantly asymmetric (black) and symmetric (light crosshatch) involvement. Data from age-matched controls (dark crosshatch) derived from Bliwise et al¹¹ are shown for further comparison. Asterisks refer to non-Bonferroni adjusted statistically significant comparisons between asymmetric and symmetric groups at $p < 0.05$. Statistical significance after adjustment ($p < 0.005$) was maintained for left (L) brachioradialis (Brach) NREM and left anterior tibialis (Ant Tib) NREM comparisons. PD patients (both subgroups) demonstrated significantly higher PEM rates relative to elderly normal controls at the $p < 0.005$ level with Bonferroni correction for all 10 comparisons (see Table 2 in Bliwise et al¹¹). Ment = mentalis; R = right.

TABLEComparisons of Patients with SYM versus Predominantly ASYM Features^a

Variable	SYM Features, n = 15	ASYM Patients, n = 40	<i>p</i>
Mean age, yr (SD)	68.1 (7.4)	61.9 (11.3)	0.06
% male	93.3	75.0	0.25
Mean disease duration (SD)	9.2 (7.8)	9.8 (6.5)	0.82
Dream enactment history, % (n)	20.0 (3)	37.5 (15)	0.34
Using L-dopa, %	86.7	92.5	0.50
Mean L-dopa dose, mg (SD) [n = 50]	680 (666)	777 (508)	0.59
Using dopamine agonists, %	53.3	52.5	1.00
Using antidepressants, %	53.3	37.5	0.36
Using selegiline, %	46.7	37.5	0.55
Mean total sleep time, min (SD)	249.7 (91.8)	301.4 (92.7)	0.07
Mean sleep efficiency, % (SD)	58.2 (20.1)	69.0 (17.3)	0.05
Mean REM, % (SD)	16.9 (11.1)	14.0 (10.5)	0.37
Mean respiratory disturbance index, events/h (SD)	8.0 (9.6)	6.0 (8.4)	0.44
Mean periodic leg movement index, events/h (SD)	13.1 (14.4)	16.1 (20.2)	0.61

SYM = symmetric; ASYM = asymmetric; SD = standard deviation; REM rapid eye movement sleep.

^aComparisons performed either with *t* tests or Fisher exact test.