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SHORT COMMUNICATION

Biomarkers of neurodegeneration in isolated and antidepressant-related rapid eye movement sleep behavior disorder

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Abstract

Background and purpose: This study compared the features of isolated rapid eye movement (REM) sleep behavior disorder (iRBD) and antidepressant-related REM sleep behaviour disorder (RBD) with the aim of highlighting markers that might distinguish the two entities.

Methods: The observational cohort study included RBD patients with and without antidepressant use (antiD+ and antiD− patients, respectively), without cognitive impairment and parkinsonism. Clinical features of RBD, subtle motor and non-motor symptoms of parkinsonism, sleep architecture, REM atonia index, dopamine transporter-single photon emission computed tomography (DAT-SPECT) and skin biopsies for the intraneuronal alpha-synuclein (α-syn), were evaluated in the baseline work-up.

Results: Thirty-nine patients, 10 antiD+ and 29 antiD−, were included. AntiD+ patients (more frequently female) reported more psychiatric symptoms, less violent dream enactment, and less frequent hyposmia. Dermal α-syn was detected in 93.1% of antiD− versus 30% of antiD+ patients ($p = 0.00024$). No differences appeared in other motor and non-motor symptoms, Movement Disorder Society–Unified Parkinson's Disease Rating Scale part III score, DAT-SPECT, or polysomnographic features.

Conclusions: Patients with antidepressant-related RBD have clinical and neuropathological features suggesting a lower risk of evolution than those with iRBD.

KEYWORDS
alpha-synuclein, antidepressant-related REM sleep behavior disorder, skin biopsy

INTRODUCTION

Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is considered a prodromal stage of neurodegenerative disease with underlying synucleinopathy, and may present biomarkers of neurodegeneration, predicting phenoconversion [1].

In some cases, RBD and its neurophysiological fingerprint REM sleep without atonia (RSWA) appear to be triggered by medications, especially antidepressants [2]. It remains unclear whether antidepressants may cause iatrogenic RBD unrelated to neurodegeneration or reveal a subclinical degenerative iRBD earlier than would otherwise have occurred within the natural evolution of synucleinopathy [3].

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Besides the temporal link between antidepressant initiation and RBD onset, there are no clear characteristics differentiating patients with iRBD from pharmacologically induced RBD (pRBD). The aim of this study was to evaluate the clinical, neurophysiological and neuropathological differential features of antidepressant-related RBD compared to iRBD.

METHODS

Participants

This observational cohort study, conducted at the Sleep Center of the Clinica Neurologica Unit at *IRCCS Istituto delle Scienze Neurologiche di Bologna*, enrolled consecutive patients diagnosed with RBD [4], and with neither cognitive impairment (defined by the adjusted Montreal Cognitive Assessment score < 26) [5] nor parkinsonism (defined by the Movement Disorder Society–Unified Parkinson's Disease Rating Scale part III [MDS-UPDRS-III] score > 5) [1]. We excluded patients with brain lesions accountable for secondary RBD and with features suggestive of narcolepsy.

Data collection

Data, collected from the baseline diagnostic work-up, included the characteristics of RBD, the symptoms of prodromal parkinsonism (i.e., subjective complaint of motor slowing or tremor, cognitive complaints, psychiatric symptoms, hyposmia, constipation, sexual and urinary dysfunction, symptoms of orthostatic hypotension) assessed with a semi-structured interview, orthostatic hypotension measured with bedside standing test, and MDS-UPDRS-III score.

From the diagnostic video polysomnography we included the sleep architecture and RSWA, automatically quantified as REM atonia index on chin electromyogram [6].

Immunohistochemistry was performed for the detection of intraneuronal phosphorylated alpha-synuclein (α-syn) on skin biopsies from the cervical C7 paravertebral area and distal legs, according to a published protocol [7]. Cerebral dopamine transporter (DAT) single photon emission computed tomography (SPECT) was performed within 3 months from diagnosis.

Statistical analysis

Data are presented as frequencies, means and standard deviations. Univariate comparisons were conducted between patients receiving antidepressants since before the onset of RBD (antiD+) and those who had never taken antidepressants (antiD−) and between those with positive or negative skin biopsy result for α-syn (SYN+ and SYN−). The Fisher test was used to compare frequencies of nominal variables.

Continuous variables were checked using multivariate analyses for the simultaneous effect of age, antidepressant treatment and α-syn on the skin biopsy (predictors) on clinical and polysomnography features (dependent variables), applying the General Regression Module of STATISTICA version 6 (StatSoft Inc., Tulsa, OK, USA). For each dependent variable, the univariate effect of the predictors was obtained by taking into consideration the effect of the other predictors. The size of the effect on each variable was assessed by means of Cohen's *d*: effect size was considered small for *d* values <0.2, medium for $0.2<d>0.5$, large for $0.5<d>0.8$, very large for $0.8<d>1.2$, and huge for $d>2$. A *p* value <0.05 was taken to indicate statistical significance.

RESULTS

Thirty-nine patients were enrolled, 10 in the antiD+ and 29 in the antiD− group. Among the antiD+ patients, six were taking serotonin re-uptake inhibitors (SSRIs), two were on serotonin-norepinephrine re-uptake inhibitors (SNRIs), one was on vortioxetine (serotonin modulator and stimulator) and one was on bupropion (norepinephrine and dopamine reuptake inhibitor). Three antiD+ patients and one antiD− patient were receiving beta-blockers, all prescribed after the reported clinical onset of RBD, and thus not considered relevant.

Comparison between antiD+ and antiD− groups

AntiD+ patients were more frequently female, more frequently reported psychiatric symptoms, had less frequently violent dream-enacting behavior (DEB), and less frequently had hyposmia. Skin biopsy was positive for α-syn in 93.1% of antiD− versus 30% of antiD+ patients ($p=0.00024$). No differences were detected in subjective motor impairment, constipation, symptoms of sexual and urinary dysfunction, orthostatic hypotension, cognitive complaints, frequency of DEB, or DAT-SPECT results (altered in 7/27 antiD− vs. 0/8 antiD+ patients; Table 1).

Besides the obvious highly significant effect of age on age at onset and at diagnosis of RBD ($p<0.000001$), we found a significant effect of treatment with antidepressants on age at diagnosis of RBD, with antiD+ patients being on average 6.6 years younger than antiD− patients, with a large effect size. A longer REM sleep latency was found in the same antiD+ group, without statistical significance but with a large effect size (Table 2).

Comparison between SYN+ and SYN− groups

Thirty patients (76.9%) tested positive for α-syn in the skin biopsy. Compared to SYN− patients, SYN+ patients reported significantly higher rates of violent DEB, falls from bed, and hyposmia, lower frequencies of psychiatric symptoms, and antidepressant assumption.

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TABLE 1 Comparisons of frequencies between patients taking or not taking antidepressants (antiD+ and antiD−, respectively) and between patients with skin biopsy positive or not for α-synuclein (SYN+ and SYN−, respectively).

	Antidepressant use					Skin biopsy α-synuclein detection				
	AntiD− (*n* = 29)		AntiD+ (*n* = 10)		Fisher test	SYN− (*n* = 9)		SYN+ (*n* = 30)		Fisher test
	n	%	*n*	%	*p* value	*n*	%	*n*	%	*p* value
Female	4	13.8	5	50	**0.032**	3	33.3	6	20	0.406
RBD frequency					0.163					0.084
Daily	1	3.4	1	10		1	11.1	1	3.3	
Daily < weekly	14	48.3	3	30		2	22.2	15	50	
Weekly < monthly	12	41.4	4	40		4	44.4	12	40	
Monthly < annual	2	6.9	1	10		1	11.1	2	6.7	
<Annual	0	0	1	10		1	11.1	0	0	
Violent DEB	25	86.2	4	40	**0.009**	3	33.3	26	86.7	**0.004**
Falls from bed	14	73.7	3	33.3	0.095	2	25	15	75	**0.03**
Hyposmia	16	55.2	1	10	**0.024**	0	0	17	56.7	**0.002**
Constipation	15	51.7	2	20	0.14	1	11.1	16	53.3	0.052
Genito-urinary symptoms	11	37.9	1	10	0.131	3	33.3	9	30	1.000
Orthostatic hypotension	5	17.2	1	10	1.000	1	11.1	5	16.7	1.000
Psychiatric symptoms	4	13.8	10	100	**<0.00001**	7	77.8	7	23.3	**0.005**
Cognitive complaint	8	27.6	1	10	0.4	1	11.1	8	26.7	0.654
Motor complaint	4	13.8	0	0	0.556	0	0	4	13.3	0.556
Skin biopsy a-syn	27	93.1	3	30	**0.00024**	-	-	-	-	-
Antidepressants	-	-	-	-	-	7	77.8	3	10	**<0.00001**
DEB PSG-recorderd	26	89.7	7	70	0.163	6	66.7	27	90	0.123
DAT-SPECT	7	25.9	0	0	0.166	0	0	7	25	0.301

Note: Bold indicates *p* values <0.05.

Abbreviations: DAT-SPECT, dopamine transporter single photon emission computed tomography; DEB, dream enactment behavior; PSG, polysomnography; RBD, rapid eye movement sleep behavior disorder.

No other clinical or instrumental findings differed between groups (Table 1).

While the univariate analysis did not disclose any significant effect of α-syn detection, an effect size that is large for MDS-UPDRS-III score, which was higher in the SYN+ group, was apparent. An almost large effect size was associated with a higher percentage of sleep stage N1 and a reduced REM atonia index, indicating a trend towards a more pronounced RSWA in SYN+ patients (Table 2).

DISCUSSION

This study investigated the baseline characteristics of antidepressant-related RBD and of iRBD, aiming to mismatch these two groups of patients, with the support of skin biopsy for α-syn detection.

AntiD+ patients were younger than antiD− patients, and had lower rates of hyposmia, a known prodromal feature of Lewy body diseases including iRBD [8].

Violent DEB was found to be more typical of antiD− patients, similar to the findings of a previous study by Lam et al. [9].

Skin biopsy was less frequently positive for α-syn in patients on antidepressant medications than in those who were antidepressant-free. The presence of α-syn in the skin appears to discriminate iRBD from controls with excellent specificity (100%) and variable sensitivity (58%–87%) [8], while its significance as a progression biomarker is currently under evaluation in longitudinal studies [8]. The different rates of skin biopsy positivity between antiD+ and antiD− detected in our cohort contrast with a study reporting positive α-syn in skin biopsy (performed using a similar immunohistochemistry method) in 16 out of 25 RBD subjects with no correlation with antidepressant use [10]. However, our results are supported by higher rates of antidepressant use found among 21 iRBD patients with negative real-time quaking-induced conversion (RT-QuIC) assay for α-syn in the skin and the cerebrospinal fluid, compared with 70 iRBD patients with α-syn detection [11].

Considering participants grouped by skin biopsy results, SYN+ patients were more likely to present an association with clinical biomarkers of degeneration, such as hyposmia and constipation [1] (the latter without significance). Analogous differences were detected between SYN+ and SYN− iRBD based on RT-QuIC [11]. Thriving DEB, more frequent violent episodes of RBD with more frequent falls from the bed, were more common in SYN+ patients, similarly to

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TABLE 2 Comparisons between patients taking or not antidepressants (antiD+ and antiD−, respectively) and between patients with skin biopsy positive or not for α-synuclein (SYN+ and SYN−, respectively).

	Antidepressant							Skin biopsy α-synuclein						
	AntiD− (*n* = 29)		AntiD+ (*n* = 10)		GRM		Effect size	SYN− (*n* = 9)		SYN+ (*n* = 30)		GRM		Effect size
	Mean	SD	Mean	SD	*F*	*p*	Cohen's *d*	Mean	SD	Mean	SD	*F*	*p*	Cohen's *d*
RBD onset, years	59.4	8.73	55.6	12.18	0.009	0.925	0.36	58.3	13.98	58.7	8.49	0.552	0.463	−0.03
RBD diagnosis, years	68.1	7.19	61.5	8.37	7.927	**0.008**	0.85	63.3	9.63	67.3	7.31	1.491	0.231	−0.48
MDS-UPDRS part III	2.2	2.17	1.1	1.91	0.368	0.548	0.56	0.4	1.33	2.4	2.14	3.515	0.070	−1.10
Sleep latency, min	20.3	26.63	18.6	15.62	0.101	0.753	0.08	23.9	21.57	18.6	25.02	0.709	0.406	0.23
REM latency, min	99.9	69.38	159.8	95.82	0.611	0.440	−0.72	149.4	107.15	105.0	69.13	0.102	0.752	0.49
Sleep efficiency, %	70.2	17.26	71.0	9.25	0.057	0.813	−0.05	72.3	9.70	69.9	16.94	0.035	0.853	0.17
Total sleep time, min	313.7	84.90	314.6	43.79	0.266	0.609	−0.01	316.6	44.26	313.1	83.74	0.253	0.618	0.05
Stage N1, %	14.8	11.35	9.9	4.91	0.000	0.983	0.56	8.9	4.65	15.0	11.10	0.665	0.421	−0.71
Stage N2, %	41.7	10.06	46.8	9.54	0.673	0.418	−0.52	44.8	8.43	42.5	10.57	0.122	0.729	0.24
Stage N3, %	27.0	13.32	25.7	13.44	0.637	0.430	0.10	28.5	12.34	26.2	13.59	0.343	0.562	0.18
Stage R, %	16.0	7.00	17.5	7.96	0.101	0.752	−0.20	17.9	7.62	16.0	7.11	0.455	0.505	0.26
PLMS index	22.0	26.06	18.0	19.11	0.004	0.948	0.18	14.9	19.96	22.8	25.46	0.517	0.477	−0.35
Apnea/hypopnea index	3.3	5.00	2.0	2.63	0.452	0.506	0.33	2.4	2.61	3.1	4.98	0.002	0.968	−0.18
REM atonia index	0.481	0.166	0.594	0.235	0.055	0.815	−0.56	0.617	0.228	0.478	0.168	0.870	0.358	0.69

Note: Bold indicates *p* values <0.05.

Abbreviations: MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; PLMS, periodic leg movements during sleep; RBD, rapid eye movement sleep behavior disorder; REM, rapid eye movement; SD, standard deviation.

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the antiD− group. These findings, together with the trend towards higher MDS-UPDRS-III scores and increased RSWA, suggest the presence of a constellation of subthreshold signs of neurodegeneration in SYN+ patients. Similarly to RSWA, which is reported to worsen with the progression from iRBD to synucleinopathies [12], more violent DEBs might also suggest a progression. Altered DAT-SPECT was documented only in patients with SYN+ and antiD−, although this did not reach significance, possibly due to the small sample size.

Overall, our cohort of antiD+ RBD patients, partly overlapping with SYN− RBD patients, showed a milder sleep disorder phenotype and fewer features of covert neurodegeneration than antiD− iRBD. pRBD could thus include, in addition to early subtypes of iRBD unveiled by antidepressant use [3], purely iatrogenic, non-degenerative forms of RBD. These hypotheses need to be tested in longitudinal studies also including antidepressant withdrawal. pRBD can be considered with a lower risk of future phenoconversion, especially when accompanied by lack of hyposmia and constipation, and mild DEB, and in the absence of in vivo synuclein detection. Furthermore, skin biopsy is a minimally invasive procedure with minor side effects, and, in the clinical context of a patient with RBD taking antidepressants, α-syn detection strongly supports its neurodegenerative etiology, without the need to carry out a problematic withdrawal of the medication to confirm the diagnosis of iRBD. For this purpose, it is necessary to standardize the protocol for skin biopsy, as different procedures (e.g., a single biopsy) can influence accuracy in detecting synucleinopathies [13, 14].

The alternative hypothesis of pRBD being a more advanced synucleinopathy than iRBD, with the additional neurodegenerative risk factor of depression, is not supported by our findings [3].

We acknowledge some study limitations. We did not include healthy controls, but focused on patients with possible etiological relevance. Clinical follow-ups and smell tests were available only for some of the participants and were not included in the present study. Hyposmia was reported based on clinical interview. Moreover, our analysis was underpowered, preventing us from analyzing the effect of different classes of antidepressants and our results are related essentially to SSRI and SNRI use. Indeed, SSRIs and SNRIs impair RSWA and periodic limb movements during sleep more than other antidepressants, also in children and adolescents (i.e., without significant degenerative risk) [15]. Finally, the small number of female patients did not allow us to analyze a gender effect in our multivariate analysis.

In conclusion, these findings represent preliminary confirmation of our hypothesis and indicate the possibility that pathophysiological differences might underlie iRBD and pRBD; among patients with pRBD, at least some might have iatrogenic non-degenerative forms. However, prospective studies are necessary to fully elucidate the role of antidepressants on the natural history of RBD.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest relevant to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Zenodo.org at http://doi.org/10.5281/zenodo.10102898.

ETHICS STATEMENT

The study was approved by the local ethics committee (*Comitato Etico Interaziendale Bologna-Imola*, CE-BI, protocol number 16098) and conducted according to the Declaration of Helsinki; all participants provided written informed consent.

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