ORIGINAL ARTICLE

Objective rest–activity cycle analysis by actigraphy identifies isolated rapid eye movement sleep behavior disorder

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Background and purpose: Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is characterized by abnormal behaviours during REM sleep. Several studies showed that iRBD is a prodromal stage of synucleinopathies. Therefore, identifying iRBD in the general population is of utmost importance. In this study, we explore whether the assessment of rest–activity rhythm features can distinguish patients with iRBD from patients with disorders characterized by other pathological motor activity during sleep and healthy controls.
Methods: Nineteen patients with video-polysomnographic diagnosis of iRBD, 39 patients with other disorders with motor activity during sleep [19 with restless leg syndrome (RLS) and 20 with untreated sleep apnea syndrome (SAS)] and 16 healthy controls underwent 2-week actigraphy and video-polysomnography, and completed REM sleep behavior disorder screening questionnaires. Non-parametric analyses were applied to assess the rest–activity rhythm features.
Results: Patients with iRBD showed lower sleep efficiency, increased estimated wake after sleep onset and increased frequency of prolonged activity bouts compared to those with RLS and controls, while no difference emerged compared with SAS patients. Moreover, patients with iRBD presented increased occurrence of estimated nap in comparison to those with RLS, those with SAS and controls. The I < O, a 24-h measure that expresses the relationship between nocturnal and diurnal motor activity intensity, distinguished patients with iRBD from those with RLS, those with SAS and controls, with an area under the curve greater than that of REM sleep behavior disorder screening questionnaires. An I < O of 98.32 shows the best balance between sensitivity (63.2%) and specificity (89.1%).
Discussion: The I < O index distinguished iRBD patients from those with other pathological motor activity during sleep and controls, confirming its use as an objective measure suitable to screen large at-risk populations.

Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia, first described 30 years ago [1], characterized by abnormal behaviours and excessive muscle activity during REM sleep [2].

Rapid eye movement sleep behaviour disorder has been categorized into isolated RBD (iRBD) and secondary RBD [3], when associated with other neurological/neurodegenerative disorders [4-6], autoimmune diseases [7], or brainstem lesions [8]. Results from long-term follow-up studies [9], investigations in patients with long-standing iRBD [10], and studies evaluating biomarkers of synuclein-related neurodegeneration (including α-synuclein accumulation

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outside the central nervous system) [11,12], provided consistent evidence that iRBD is an early-phase α-synucleinopathy, eventually evolving into Parkinson's disease, dementia with Lewy bodies or multiple system atrophy [13].

According to the current International Classification of Sleep Disorders (ICSD-3) for a definitive diagnosis, the presence of REM sleep without atonia documented by video-polysomnography (v-PSG) is mandatory [2]. Nevertheless, v-PSG is time- and resource-demanding and therefore not suitable for large-scale RBD screening.

To overcome this issue, screening tools (mainly questionnaires) have been proposed to identify people at risk of RBD [3]; however, apart from the limitations intrinsic to this approach, criticism has been raised regarding their external validity [14-16].

Some studies have evaluated the utility of actigraphy in assessing the presence and severity of RBD in patients with Parkinson's disease, and more recently in patients with iRBD, as a possible screening tool [17,18]. Along with providing sleep estimates, actigraphy can be used to measure rest–activity rhythm, a well-defined behavioural marker of circadian rhythms [19].

Although circadian rhythm abnormalities are common in the elderly [20], increasing evidence indicates that in neurodegenerative diseases there is a higher degree of circadian rhythm disruption and this may occur long before the onset of clinical symptoms [21,22].

Several studies have successfully used actigraphy to identify manifestations of circadian rhythm disruption in neurodegenerative diseases, whereas only one study has assessed circadian rhythms (serum melatonin concentration) in iRBD [23,24].

The present study aims to characterize, for the first time, the rest–activity rhythm of patients with iRBD and to compare it to that of patients with other disorders with motor activity during sleep [i.e. restless leg syndrome (RLS) and untreated sleep apnea syndrome (SAS)] and to that of healthy controls. As a secondary aim we assessed daytime napping behaviour in patients with iRBD and its relationship with subjective sleepiness.

Methods

Participants

We analysed actigraphic recordings of patients evaluated for sleep disorder complaints at the Sleep Disorders Unit of the Medical University of Innsbruck. The patients underwent a diagnostic protocol encompassing clinical evaluation performed by a sleep medicine specialist, actigraphy (14 days) and v-PSG. In addition, they completed the Epworth Sleepiness Scale (ESS) [25], the RBD screening questionnaire (RBDSQ) and the Hong-Kong RBD questionnaire (RBDQ-HK) [26,27].

Permission to use the RBDSQ was obtained from the Mapi research trust. The final sample comprised three clinical groups: patients with iRBD ($n = 19$), patients with RLS ($n = 20$) and patients with untreated SAS ($n = 19$). Three out of 19 patients with iRBD and five out of 20 patients with RLS were receiving symptomatic treatment at the time of actigraphy and v-PSG. Sixteen adults ($n = 16$) referred to the sleep laboratory for suspicion of sleep disorders, objectively excluded by the aforementioned assessment, served as healthy controls. This series of patients and controls partially overlaps with that of a previously published study [18]. The study was approved by the ethics committee of the Medical University of Innsbruck and all participants provided written informed consent.

Actigraphy

Micro Motionlogger Watch actigraphs were used in this study. The device consists of a triaxial accelerometer, a photodiode, a case temperature sensor and an 'event-marker' button. Actigraphs were initialized in zero-crossing mode; changes in acceleration exceeding $0.01g$ are integrated across the three axes and expressed in activity counts (arbitrary units, AU). Epoch length was set at 30 s. Participants wore the device continuously across the 24-h period and were asked to retain their usual sleep–wake schedule during the assessment. They were instructed to press the event marker when turning off the lights in the evening and again when they got out of bed in the morning. Periods of device removal, evident from the persistent decrease of case temperature, were excluded from the analysis.

Sleep and circadian rest–activity rhythm measures

Actigraphic recordings were divided into nocturnal and diurnal periods based on individual bedtime and wake-up time, indicated via the event marker and verified through the ambient light sensor. Mean diurnal and nocturnal parameters were computed across the 2 weeks of recording. The Cole-Kripke algorithm was applied to obtain estimated sleep measures [28].

Epochs with sudden increase of light exposure and motor activity >100 counts were excluded from the analysis of nocturnal period. Moreover, given the impossibility of inferring whether sleep interruptions are awakenings or pathological motor activity manifestations in patients with iRBD, we labeled the awakenings identified by the algorithm as 'activity bouts'.

For the nocturnal period we considered bedtime, wake-up time, midpoint of sleep, estimated wake after sleep onset (eWASO), estimated sleep efficiency (eSE), activity bouts and prolonged activity bouts (i.e. those lasting >5 min.).

For the diurnal period we considered daytime motor activity, estimated diurnal sleep episodes (eNap) frequency (with a nap being defined as a period of at least 10 min and up to 3 h identified as sleep by the scoring algorithm, preceded and followed by a period of at least 30 min identified as wake), and mean estimated nap minutes.

The non-parametric circadian variables computed were: interdaily stability, which reflects the day-to-day consistency of motor activity, intradaily variability, which reflects the frequency of transitions between rest and active periods, relative amplitude of the rest–activity rhythm [29], and the I < O index, which expresses the relationship between nocturnal and diurnal motor activity intensity and is computed as the percentage of motor activity counts measured when the participant is in bed which is lower than the median of motor activity counts when the participant is out of bed [30].

Statistical analysis

Data for each group were explored using descriptive statistics (mean ± SD). Differences in gender distribution, age, body mass index (BMI) and questionnaire scores were analysed by means of chi-squared and one-way ANOVA. Differences in actigraphic sleep and non-parametric circadian measures were analysed through ANOVA, followed by Bonferroni's *post hoc* test; the Benjamini–Hochberg false discovery rate procedure was applied to correct for multiple comparisons [31]. The potential diagnostic value of non-parametric measures was assessed through receiver-operating characteristic curves.

Finally, the relationship between age, diurnal sleepiness and actigraphic measures was analysed, separately for each group, through Pearson correlation. Statistics were analysed with SPSS 19.0, and P/q values < 0.05 were considered statistically significant. Additional analyses taking into account the effects of age are reported in Appendix S1.

Results

Demographic, clinical data and questionnaire scores are reported in Table 1.

Chi-squared tests showed significant differences in gender distribution ($\chi^2_{(3)} = 12.94$, $P < 0.005$). One-way ANOVA showed significant differences in age ($F_{(3,70)} = 18.68$, $P < 0.0001$), with patients with iRBD

Table 1 Demographic, clinical data and questionnaire scores

	iRBD (n = 19)		SAS (n = 19)		RLS (n = 20)		HC (n = 16)	
Men/Women, n	16/3		18/1		10/10		9/7	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
Age, years	71.68 ± 7.85	55–84	50.53 ± 11.29	30–69	47.50 ± 14.19	24–70	43.63 ± 15.66	22–69
BMI, kg/m^2	26.67 ± 3.59	18.47–32.80	30.30 ± 4.93	24.90–43.25	23.95 ± 2.42	19.50–27.55	25.73 ± 4.24	17.78–35.19
ESS	5.79 ± 3.95	1–15	5.11 ± 3.70	1–14	6.35 ± 4.40	0–18	7.00 ± 5.30	0–21
RBDSQ score	6.47 ± 2.52	3–11	2.37 ± 1.12	1–4	5.60 ± 2.76	1–11	2.63 ± 2.58	0–7
RBDQ-HK score	24.44 ± 15.24	0–54	5.05 ± 4.90	0–17	13.40 ± 15.15	0–66	11.19 ± 10.51	0–30
AHI	4.83 ± 4.88	0–14	38.73 ± 23.62	17–94	1.52 ± 1.36	0–5	2.39 ± 1.58	0–5
PLMS index	42.06 ± 43.47	5–154	23.22 ± 23.43	0–67	28.98 ± 46.34	2–218	8.57 ± 9.23	0–35

AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; iRBD, isolated rapid eye movement sleep behavior disorder; PLMS, periodic limb movements; RBDQ-HK, Hong-Kong rapid eye movement sleep behavior disorder questionnaire; RBDSQ, rapid eye movement sleep behavior disorder screening questionnaire; RLS, restless leg syndrome; SAS, untreated sleep apnea syndrome.

being older than patients with SAS, patients with RLSand control subjects (all $P < 0.0001$). Differences also emerged in BMI ($F_{(3,70)} = 9.16$, $P < 0.0001$), with patients with SAS presenting higher BMI values than the other groups (all $P < 0.05$). No differences were observed in ESS scores ($F_{(3,70)} = 0.61$, P = non-significant), while significant differences were observed for RBDSQ ($F_{(3,70)} = 14.62$, $P < 0.0001$) and RBDQ-HK scores ($F_{(3,70)} = 7.70$, $P < 0.0005$), with patients with iRBD having significantly higher scores than patients with SAS and controls (all $P < 0.05$), but there was no difference between patients with iRBD and those with RLS.

Actigraphic nocturnal/diurnal sleep measures and non-parametric circadian variables are reported in Table 2. Statistically significant differences, after correcting for multiple comparisons with Benjamini–Hochberg's false discovery rate procedure, were found for eSE ($F_{(3,70)} = 4.83$, $q < 0.05$), eWASO ($F_{(3,70)}$=6.41, $q < 0.005$), prolonged activity bouts ($F_{(3,70)} = 4.38$, $q < 0.05$), eNap ($F_{(3,70)} = 5.99$, $q < 0.005$) and I < O ($F_{(3,70)} = 10.05$, $q < 0.0001$). *Post hoc* tests showed that patients with iRBD had lower eSE and higher eWASO compared to patients with RLS and controls but not compared to patients with SAS.

Patients with iRBD also had a higher occurrence of prolonged activity bouts compared to those with RLS, those with SAS and controls. Moreover, patients with iRBD had a higher eNap frequency than those with RLS, those with SAS and controls. Finally, patients with iRBD had lower I < O values than those with RLS, those with SAS and controls.

Receiver-operating characteristic curves for I < O and for RBDSQ and RBDQ-HK questionnaire scores are shown in Fig. 1.

The I < O index had an area under the curve (AUC) of 0.82, higher than that observed for RBDSQ (0.78) and RBDQ-HK questionnaire scores (0.80). An I < O value of 98.32 displays the best balance between sensitivity (63.2%) and specificity (89.1%; positive predictive value = 66.7%, negative predictive value = 87.5%, accuracy = 82.4%).

Analysis showed a positive relationship between ESS and eNap for patients with SAS ($r = 0.52$, $P < 0.05$) and those with RLS ($r = 0.55$, $P < 0.05$), while no significant correlation was found in patients with iRBD ($r = 0.32$, P = non-significant) or controls ($r = 0.03$, P = non-significant). Age and I < O were found to be negatively correlated in the iRBD group ($r = -0.54$, $P = <0.05$), and age and eNap frequency were found to be positively correlated in healthy controls ($r = 0.68$, $P < 0.005$).

Discussion

In the present study we showed, for the first time, that non-parametric actigraphic analysis is a promising approach to identifying patients with iRBD.

A previous study showed that quantitative actigraphic sleep parameters can distinguish patients with iRBD from healthy controls but failed to distinguish them from patients with conditions that might mimic the features of RBD, while visual analysis of nocturnal activity profile performed by sleep experts is able to identify patients with iRBD and also distinguish them from patients with different motor manifestations during sleep [18].

In line with these findings, we considered different and more commonly reported actigraphic measures and found that none of them successfully distinguished patients with iRBD from the other clinical groups. By contrast, the dichotomy index I < O, a non-parametric 24-h measure that expresses the percentage of activity counts during the nocturnal period that is lower than the median of activity counts during the diurnal period [30], is able to distinguish patients with iRBD not only from controls but also from patients with different types of motor activities during sleep.

Our results indicate that actigraphic assessment may have a relevant role in the diagnostic evaluation of iRBD. Actigraphy analysis, alone or in combination with screening questionnaires, could represent an effective, easy-to-use and objective screening tool. However, its possible application in epidemiological settings needs to be evaluated in further studies.

Actigrams of four representative participants, together with a graphic representation of the I < O index computation, is shown in Fig. 2.

Analysis of the diagnostic accuracy of the I < O index revealed a large AUC, comparable to those observed for two widely used questionnaires for RBD screening, with the key advantage of being an objective measure. Apart from the AUC, there are some intrinsic limitations of questionnaires that actigraphy can overcome: (1) questionnaires provide false-negative results in patients with RBD who are not aware of their symptoms and who sleep alone for other reasons (e.g. snoring) and (2) actigraphy provides objective measures which are therefore more reliable [15]. The I < O index, originally proposed as a measure to assess circadian motor activity features, has received scant attention in the field of sleep medicine and circadian rhythm research, while it has been widely used in cancer research [32,33].

Table 2 Actigraphic nocturnal/diurnal measures, nonparametric variables and *post hoc* results for patients with isolated rapid eye movement sleep behavior disorder, patients with untreated sleep apnea syndrome, patients with restless leg syndrome and healthy controls

	iRBD (n = 19) Mean ± SD	SAS (n = 19) Mean ± SD	RLS (n = 20) Mean ± SD	HC (n = 16) Mean ± SD	FDR q-value	iRBD vs. SAS	iRBD vs. RLS	iRBD vs. HC	SAS vs. RLS	SAS vs. HC	RLS vs. HC
Sleep timing											
Bedtime	22:30 ± 0:56	22:49 ± 0:45	23:04 ± 0:31	23:10 ± 0:37	ns						
Wake time	6:56 ± 0:52	6:36 ± 1:05	7:10 ± 1:14	7:38 ± 1:18	ns						
Midpoint	2:44 ± 0:52	2:43 ± 0:52	3:08 ± 1:07	3:26 ± 0:56	ns						
Nocturnal measure											
eSE	78.62 ± 13.39	84.24 ± 13.45	88.50 ± 10.08	91.87 ± 2.30	<0.05	ns	<0.05	<0.005	ns	ns	ns
eWASO	83.79 ± 53.40	56.97 ± 55.40	36.34 ± 29.46	27.20 ± 12.24	<0.005	ns	<0.005	<0.005	ns	ns	ns
Activity bouts	14.89 ± 5.19	13.12 ± 7.73	11.88 ± 6.54	11.01 ± 5.34	ns						
Prolonged activity bouts	7.82 ± 3.87	6.03 ± 4.24	4.94 ± 2.54	4.03 ± 1.75	<0.05	ns	<0.05	<0.01	ns	ns	ns
Diurnal measures											
DMA	107.67 ± 17.67	107.76 ± 9.98	111.70 ± 12.87	114.56 ± 11.01	ns						
eNap	6.53 ± 5.56	3.24 ± 2.45	3.37 ± 2.72	1.18 ± 1.42	<0.005	<0.05	<0.05	<0.001	ns	ns	ns
eNapD	24.92 ± 16.53	18.57 ± 12.19	19.65 ± 20.19	13.03 ± 9.62	ns						
Non-parametric variables											
IS	0.77 ± 0.08	0.78 ± 0.09	0.76 ± 0.13	0.78 ± 0.09	ns						
IV	0.49 ± 0.16	0.42 ± 0.12	0.40 ± 0.16	0.35 ± 0.11	ns						
RA	0.81 ± 0.08	0.84 ± 0.10	0.87 ± 0.11	0.90 ± 0.03	ns						
I < O	97.62 ± 1.69	98.83 ± 0.90	99.19 ± 0.46	99.20 ± 0.41	<0.0005	<0.005	<0.0001	<0.0001	ns	ns	ns

DMA, daytime motor activity; eNap, estimated diurnal sleep episodes; eNapD, mean estimated nap minutes; eSE, estimated sleep efficiency; eWASO, estimated wake after sleep onset; FDR, false discovery rate; I < O, dichotomy index; iRBD, isolated rapid eye movement sleep behavior disorder; IS, interdaily stability; IV, intradaily variability; RA, relative amplitude; RLS, restless leg syndrome; SAS, sleep apnea syndrome.

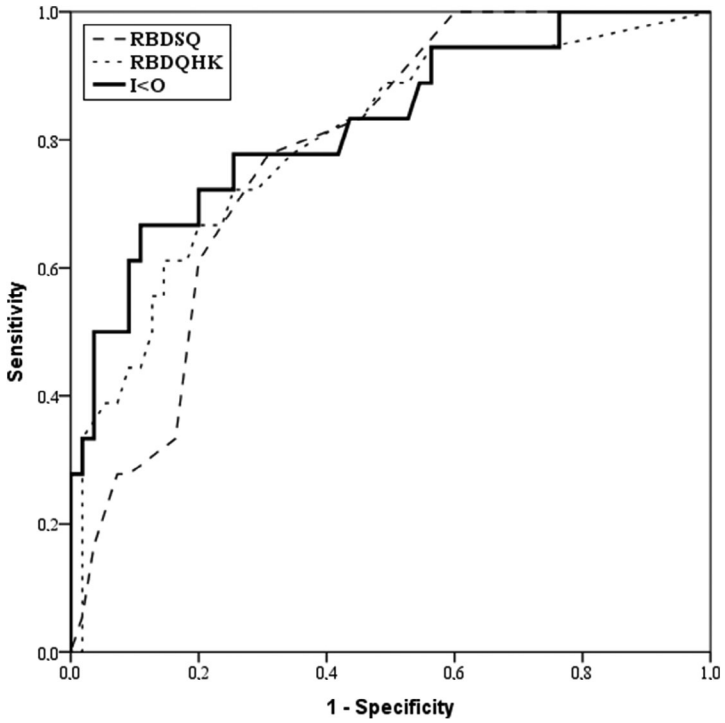

Figure 1 Receiver-operating characteristic curve for I < O index, rapid eye movement sleep behavior disorder screening questionnaire (RBDSQ) score and the Hong-Kong rapid eye movement sleep behavior disorder questionnaire (RBDQ-HK) score.

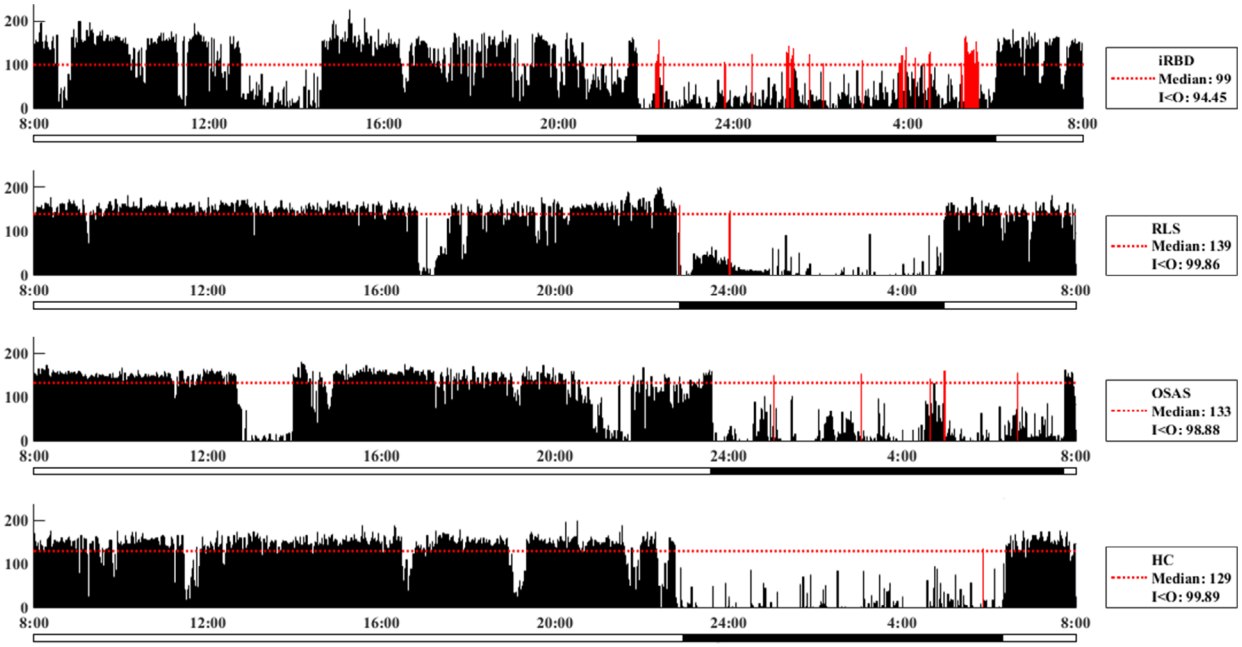

Figure 2 Activity data of four representative participants. Red bars indicate epochs with motor activity higher than the median of diurnal motor activity. HC, healthy controls; iRBD, isolated rapid eye movement sleep behavior disorder; RLS, restless leg syndrome; SAS, sleep apnea syndrome.

The other non-parametric measures commonly used to describe the features of circadian rest–activity rhythm did not differ between patients with iRBD and the other groups, indicating that the mechanism that couples the rest–activity rhythm with the zeitgebers is not impaired. Conversely, by analysing the daytime behavior, we have shown, for the first time, that patients with iRBD present an overrepresentation of daytime prolonged inactivity periods compared to healthy controls, patients with SAS and patients with RLS. Notably, while correlation analysis disclosed a positive relationship between ESS score and eNap number in patients with SAS and those with RLS, such a relationship was not observed in patients with iRBD. This finding may either indicate that patients with iRBD overlook this aspect, or that the ESS may not be suitable to assess sleepiness in a clinical population which is mostly composed of elderly people.

Some limitations of the present study should be acknowledged. First, groups were not matched for age, with patients with iRBD being significantly older than controls and patients with SAS and RLS, and further studies with a paired case–control design are required to confirm our findings. Second, the study has a relatively small sample size which may not be entirely representative of the iRBD disease spectrum. Third, the control group comprised people referred to the sleep laboratory for suspicion of sleep disorder that was ruled out by v-PSG study. Even if this did not influence our objective actigraphic parameter results, we cannot exclude the possibility that it might have influenced questionnaire answers. Future studies are required to evaluate the utility of the I < O index in distinguishing iRBD from mimics (non-REM parasomnias, sleep-related hypermotor epilepsy) and to assess its value in patients with RBD secondary to neurological disease (Parkinson's disease, Lewy body dementia and multiple system atrophy).

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Disclosure of conflict of interest

Ambra Stefani reports support for research from Axovant, outside the submitted work. Giuseppe Plazzi participated in advisory boards for UCB, Jazz pharmaceuticals, Bioprojet and Idorsia, outside the submitted work. Birgit Högl reports personal fees from Otsuka, Mundipharma, UCB, Janssen Cilag, Lündbeck, AbbVie, Lilly, Axovant, Benevolent, Roche and Takeda, outside the submitted work. The other authors have no potential conflicts to disclose.

Data availability statement

Data are available from the corresponding authors on reasonable request.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary data analysis.

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