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ORIGINAL ARTICLE

Analysis of REM sleep without atonia in 22q11.2 deletion syndrome determined by domiciliary polysomnography: a cross sectional study

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Abstract

Study Objectives: Our aim is to evaluate the presence of REM sleep without atonia (RWA), the objective hallmark of REM sleep Behaviour Disorder (RBD), as prodromal marker of Parkinson's disease (PD), in an adult cohort of 22q11.2 deletion syndrome (22qDS).

Methods: Sleep quality was assessed by means of Pittsburgh quality scale index (PSQI), and RBD symptoms by means of RBD questionnaire-Hong-Kong (RBDQ-HK). Attended domiciliary video-Polysomnography (v-PSG) were performed in 26 adults (18–51 years, 14 females) 22qDS patients. Electromyogram during REM sleep was analyzed by means of SINBAR procedure at 3-second time resolution (miniepochs).

Results: An overall poor sleep quality was observed in the cohort and high RBDQ-HK score in 7 of the 26 patients, two additional patients with positive dream enactment reported by close relatives had low score of RBDQ-HK. Nevertheless, SINBAR RWA scores were lower than cut-off threshold for RWA (mean 5.5%, range 0–12.2%). TST and the percentage of light sleep (N1) were increased, with preserved proportions of N2 and N3. Participants reported poor quality of sleep (mean PSQI > 5), with prolonged sleep latency in the v-PSG. No subjects exhibit evident dream enactment episodes during recording sessions.

Conclusions: RWA was absent in the studied cohort of 22qDS adult volunteers according to validated polysomnographic criteria. High RBDQ-HK scores do not correlate with v-PSG results among 22qDS individuals.

Statement of Significance

The 22q11.2 deletion syndrome, the most prevalent chromosomal deletion disorder, is a genetic risk factor for early-onset Parkinson's disease. As 22q11.2 deletion affects a discrete and well-known segment of the human genome, shedding light on the natural history of 22q11.2 deletion syndrome may help to understand genetic and molecular determinants of Parkinson's Disease. REM sleep behavior disorder is a frequent prodromal condition of Parkinson's disease. We studied the polysomnographic signature of REM sleep behavior disorder, REM sleep without atonia, among 22q11.2 deletion syndrome patients. In contrast to the high prevalence described in questionnaire-based studies, we found no objective evidence of REM sleep behavior disorder in a sample of 22q.11.2 deletion volunteers.

Key words: 22q.11.2 deletion syndrome; early-onset Parkinson's disease; prodromal Parkinson's disease; SINBAR; REM sleep behavior disorder; REM sleep without atonia; domiciliary polysomnography

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Introduction

The 22q11.2 deletion syndrome (22qDS), the most frequent chromosomal deletion disorder affecting 1 in 3 to 6000 births [1], has been recently identified as genetic risk for early-onset Parkinson's Disease (EOPD) [2–5]. The 22qDS is caused by the hemizygous and recurrent (>85% de novo) deletion at the 22q11.2 region and exhibit a heterogeneous presentation including congenital malformations in the palate, cardiovascular system, and disorders of the immune system [1]. The syndrome is considered a natural model to understand the genetic and molecular underpinnings of multiple neurodevelopmental disorders5xx given the frequent occurrence of schizophrenia [6], epilepsy [7], autism [8], and varying degrees of cognitive impairment. In a mouse model of 22qDS it has been recently described the appearance of parkinsonism-like behavior and elevated expression of α-synuclein giving support to the notion that 22q11.2 and Parkinson´s Disease (PD) share fundamental neuropathological substrates [9]. 22qDS carriers exhibit a near 20-times increased risk to develop PD when compared with the general population, with a mean age for onset of motor symptoms close to 40 years [10]. The clinical features of 22qDS-related PD resemble that of idiopathic PD including increased male to female ratio (2:1), gradual progression of motor symptoms, neuropathological features (α-synuclein–positive Lewy bodies and Lewy neurites), and good response to antiparkinsonian medications [4, 10].

Nonmotor prodromal manifestations of typical PD may anticipate parkinsonism in several years, including sensory and autonomic signs [11]. REM sleep Behavior Disorder (RBD) is by far the strongest prodromal marker of α-synucleinopathies [12, 13]. It has been reported a 80% RBD conversion to parkinsonism or dementia within 15 years [14]. Although hyposmia, constipation, and RBD symptoms has been described among 22qDS patients without PD [15], little is known about nonmotor prodromal features of early-onset PD associated to 22qDS [10]. High prevalence of RBD symptoms (28%) has been recently described in a sample of Young 22qDS patients without PD by means of the RBD Questionnaire [15]. Here, we evaluated the presence of REM sleep without atonia (RWA), the objective hallmark of RBD [16], in an adult cohort of 22qDS patients, by means of attended domiciliary video-polysomnography (v-PSG).

Methods

Adults (age 18 years or above) with MLPA (MRC, Holland)-proven 22qDS and living in Chile were invited to participate, as part of an observational study of movement disorders in this condition. They are part of an ongoing longitudinal study of persons with 22q11 in Chile from different ascertainment sources [17]. Exclusion criteria included inability or unwillingness to give informed consent, known diagnosis of Parkinson´s disease, and ongoing pregnancy. The protocol was approved by Comité de Etica Científica, Facultad de Medicina, Clínica Alemana Universidad de Chile and by the Regional Representative of the Ministry of Health (SEREMI). All participants gave written informed consent.

General procedure: history, the Pittsburgh Sleep Quality Index (PSQI) [18], the RBD Questionnaire-Hong Kong (RBD-HK) [19], and instructions (sleep hygiene and sleep log) were administered in a face-to-face interview one week before v-PSG. Close relative's reports on patient's RBD symptoms was documented through the Mayo Clinic Sleep Questionnaire-Informant (MSQ-informant) [20].

Sleep record: attended v-PSG were acquired by means of a portable monitoring system (Alice PDX, Philips Respironics, Murrysville, PA, USA) in patient's habitual sleep environment and remotely monitored by two researchers who remained outside the recording room. Records were scheduled at 23.00 and finished spontaneously in the morning. PSG montage included EEG (F3/M1, C4/M1, O1/M1), electrooculogram and EMG (analog band-pass filtered at 10-100 Hz, chin and bilateral upper limb *Flexor digitorum superficialis*) electrodes, thoracic and abdominal stretch transducers, nasal pressure signal, nose thermistor, and pulse oximetry. Chin and upper limb EMG activity was visually evaluated according to Frauscher et al. (2012) [16]. v-PSG were manually scored according to AASM recommendations [21] on Sleepware G3 version 3.8.0 (Respironics Inc. Murrysville, PA, USA) platform, by at least two researchers. Motor events of REM sleep episodes were evaluated to document, according to published recommendations [22].

Data analysis and Statistics: We performed the Sleep Innsbruck-Barcelona (SINBAR) procedure to diagnose RWA (SINBAR RWA score) based on chin and bilateral Flexor Digitorum Superficialis REM sleep electromyogram (estimated at 3-second miniepochs, cut- off value = 32%) [16, 23]. Demographic factors, or those that may interfere in sleep architecture or predispose to RWA: sex, oral or pharyngeal corrective surgeries, neuropsychiatric comorbidities, current neuropharmacological treatment, and deletion size are summarized in Table 1 and Supplementary Table 2, and were analyzed by means of Mann-Whitney *U* test. Sample PSG parameters were compared by means of signed rank (Wilcoxon's) test to adult normative values for "first night" sleep record (Figure 1 and Table 1) [24]. The number of subjects displaying scores above and below cut-off values for SINBAR score, PSQI and RBD-HK are summarized in Table 1. Relevant PSG parameters were correlated with sleep questionnaires by means of Spearman rank correlations in Figure 2 and Supplementary Figure 1.

Results

Twenty-six 22qDS (12 males and 14 females, age range 18–51 years) participated in the study (Table 1). Females (range: 18–51 years) were slightly older than males (range: 18–39 years). Overweight (BMI > 24.9) was observed in 50% of women and 41% of men (see Table 1). Twenty individuals had palate anomalies, and in 15 cases parents reported corrective surgical treatment including veloplasty, palatoplasty, pharyngoplasty, and laryngoplasty in the remote anamnesis.

Observed neurologic or psychiatric comorbidities were: psychotic episode or schizophrenia (6), affective disorders (3), (2), and epilepsy (2). Ten participants were under current neuropharmacological treatment (drugs: quetiapine, aripripazole, clozapine, olanzapine, sertraline, levetiracetam, and valproic acid). The majority (73.1%) had the common low copy repeat (LCR) A-D of approximately 3Mb deletion and 15.4% exhibit the LCR A-C deletion. The deletion size information of three patients deletion was not available (see Table 1).

Sleep questionnaires. PSQI score reflected poor quality of sleep (Table 1 and Figure 1M), with 14 patients reporting difficulty to fall asleep as major complaint. Twenty subjects reported PSQI

Table 1. Demographic data and genetic background: v-Polysomnography and sleep questionnaires

				Sex				Deletion size			
	Whole sample			Female		Male		AD		AC	
n	26			14		12		19		4	
	Mean (SD)		Norm>/<	Median(IQR)		Median(IQR)		Median (IQR)		Median(IQR)	
Age	26,6	9,2		25,0	12,5	21,0	6.3*	23.0	5.5	31.5	19.5
BMI	25,6	6,5		24,8	8,3	23,7	5,3	23.7	6.0	26.9	6.6
TIB (min)	548,9	33,5		553,7	38,7	557,5	41,9	557,5	48,8	557,5	23,7
TST (min)	459,8	77,7	22/3	486,0	62,8	469,0	40,3	489,5	48,0	482,5	37,0
SE (%)	83,6	12,9	14/8	88,2	11,0	86,4	7,7	87,5	9,2	88,4	1,7
SL (min)	34,6	23,9	20/4	34,0	19,8	27,0	18,9	27,5	21,5	34,5	9,0
WASO (min)	54,7	55,6	7/14	30,7	42,0	51,5	37,6	45,0	33,7	24,5	23,8
N1(%)	10,6	5,6	18/5	8,0	4,3	10,6	7.3*	10,1	4,5	7,4	4,9
N2 (%)	53,5	7,5	14/8	53,5	8,4	53,0	7,3	53,5	9,0	52,2	11,7
N3 (%)	19,3	6,5	10/12	21,0	5,1	19,1	9,5	20,4	7,7	20,5	8,5
REM (%)	16,7	6,7	9/11	17,8	5,4	17,5	12,2	17,8	7,8	22,8	2.4 a
REM L (min)	183,0	108,0	21/3	149,5	96,3	198,5	97,6	155,8	105,4	155,5	72,0
ArI	10,5	7,7	8/12	6,6	5,8	10,9	9.1 a	7,9	7,2	17,4	8.3*
SINBAR	5,5	3,6	0/25	5,4	5,8	5,5	4,1	5,5	5,2	3,1	5,7
AHI	2,6	5,6	3/22	0,8	1,4	1,3	1,2	1,5	1,3	1,1	8,6
PSQI	8,5	3,3	20/6	9,5	5,8	7,5	3,0	9,0	5,5	12,0	6,0
RBDQ-HK	12,7	11,4	7/18	14,0	14,8	8,0	7,0	9,0	16,5	14,0	8,0

Factor deletion size:AD = LCR22A–LCR22D (3 Mb), AC = LCR22A–LCR22C (2 Mb). In three patients, deletion size information was not available. (n = 26, exception made for REM, REM L, SINBAR and RBSQ-HK, where a patient with less than 5 minutes of REM sleep was excluded) Statistics: whole sample in mean and SD; ">Norm" refers to the number of subjects with values higher (>) or lower (<) than 95% confidence interval of normative values (TST, SE, SL, WASO, N1, N2, N3, REM, ArI, AHI)23 or cut-off values for SINBAR (32), PSQI (5) and RBDQ-HK (>17). Factors Sex and Deletion size in median and interquartile range (IQR); within factors comparisons performed with Mann-Whitney U test; *=$p < .05$, a = $p < .1$. TIB: time in bed; TST: Total sleep time; SE: sleep efficiency; SL: sleep latency; WASO: wake after sleep onset; N1, N2, N3 and REM sleep: % of TST, RL: REM sleep latency, ArI: arousal index (events per hour); SINBAR Score (in %); AHI: apnea/hypopnea index (events per hour); PSQI: Pittsburgh sleep quality index; RDBQ-HK: RBD Questionnaire-Hong-Kong.

scores higher than 5 (the cut-off value for poor sleep quality). High RBD risk (RBDQ-HK score > 17, Table 1 and Figure 1N) was reported by seven patients. Two positive records for dream enactment in the MSQ-informant were obtained, both scoring < 17 in the RBDQ-HK, and one of them with apnea/hypopnea index (AHI) = 28.3. Poor quality of sleep was related to low "alertness score" (PSQI vs. MSQ-informant Pearson's correlation: R = –0.364, p = .045, data not shown).

Home v-PSG (see Table 1 and Figure 1). Records started on average at 23:17 and ended spontaneously at 8:29 with a mean time in bed duration of 9.15 hours. The extended time in bed was associated to prolonged total sleep time (TST, Figure 1A). Most parameters of sleep architecture are preserved when compared to normative values, including sleep efficiency, time in WASO, percentages of N2 and N3, and of REM sleep (Figure 1B, D, F, G, and H, respectively). On the other hand, incremented percentages of N1, prolonged sleep latency, and REM sleep latency were observed (Figure 1E, C, and I, respectively). Low levels of arousal and apnea/hypopnea indices are observed (Figure 1K and L). Two patients exhibited increased AHI index, corresponding to mild (9.3) and moderate (28.3) obstructive sleep apnea/hypopnea syndrome (OSA) categories respectively. No significant relationship was obtained between PSQI and polysomnographic results (Supplementary Figure 1, Spearman's correlations, $p > .05$).

Factors such as sex, oral or pharyngeal corrective surgeries, neuropsychiatric comorbidities or current neuropharmacological treatment have little effect on PSG and sleep questionnaires (Figure 1, Table 1 and Supplementary Table 1). Percentage of N1 and arousal index were found slightly higher in males than females (Figure 1E and K). No differences were found for qualitative and PSG parameters between LCR AD and LCR AC deletion size with the exception of higher arousal index and a minor increment in REM sleep percentage among the latter (Table 1).

REM sleep amounts exhibited large variability (range: 24-134 minutes). Of eight patients with amounts lower than normative values for REM sleep time, only one is currently receiving neuropharmacological treatment (Fisher's exact test, p = .078). REM sleep latency longer than 120 minutes was observed in 14 cases (range 37–499 minutes). Mean SINBAR score was far below the cut-off limit for RWA (32%, Figure 1I). None of the sertraline treated or AHI > 5 patients exceeded a SINBAR RWA score of 15%. One female volunteer exhibit a SINBAR RWA score close to the cut-off value (30% and RBDQ-HK = 7, data not shown), that resulted inconclusive as her REM sleep time was minimal (2.5 minutes). No subject exhibit complex motor events compatible with dream enactment (complex/scenic, violent or vocalization) during v-PSG sessions. No relationship was obtained between RBDQ-HK and REM sleep-related parameters (Figure 2, Spearman's correlations, $p > .05$).

Discussion

The analysis of the v-PSG do not support the presence of RWA, the cardinal sign of RBD (Figure 2C). The obtained SINBAR RWA scores are comparable to that of healthy controls as reported elsewhere [25]. Regarding video-recording analysis, although elementary movements were not possible to be confidently evaluated because of technical limitations, no evident dream enactment episode (complex, violent or vocalization) [22] was observed during recording sessions. Signs of RWA or RBD symptoms were absent among patients under sertraline treatment, a

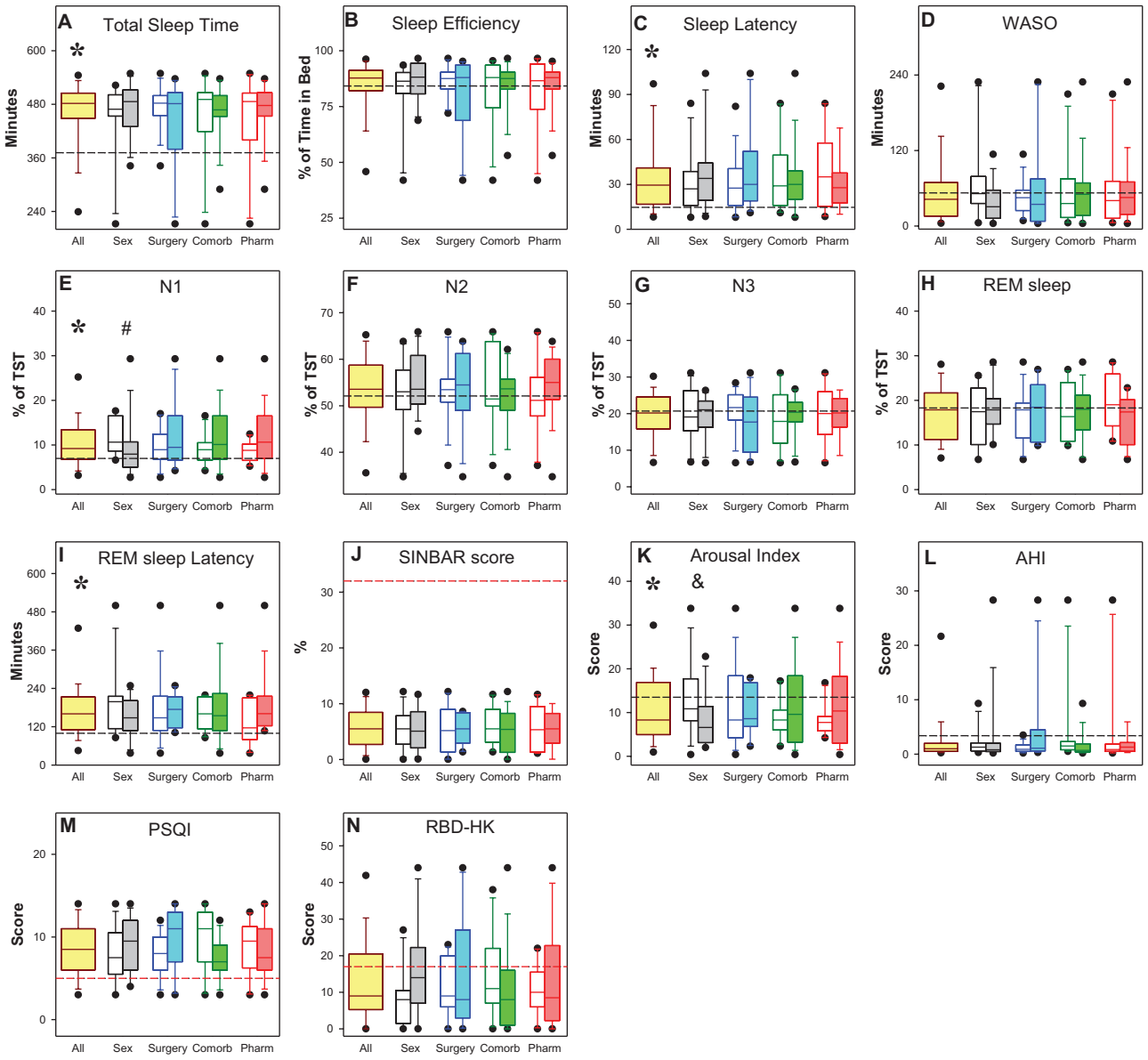

Figure 1. Polysomnographic parameters and quality of sleep among 22q11.2 deletion patients. A–N: Vertical boxplots (median, IQR, 5th and 95th percentiles, outliers are not shown) display the whole- sample (n = 26, yellow boxes) or subsamples obtained by the presence (open boxes) or absence (filled boxes) of the condition specified at the bottom abscissa. A patient with less than 5 minutes of REM sleep was excluded from REM, REM L and SINBAR computations. Factor sex corresponds to men (white box) and women (gray box). The whole sample was compared with normative values (black dashed line) for "first-night" PSG recordings [24] by means of signed rank (Wicoxon's) test. Within factors comparisons performed with Mann-Whitney U test (# = $p < .05$; & = $p < .1$). Cut-off values (red dashed line) of SINBAR score, PSQI and RBD-HK is indicated for reference purpose only.

RWA predisposing condition [26], or high AHI, a condition associated to false positive RBD [27].

Coincident with previous studies reporting elevated prevalence of RBD symptoms among 22qDS patients [15], we found RBDQ-HK scores higher than the cut-off value (>17) in 27% of our sample. On the other hand, the noteworthy 27% rate of RBDQ-HK suggestive of RBD (score > 17, Figure 2A) was not consistent with reports of close relatives in the MSQ- informant. According to Buckley et al [15]. 28% of 50 22qDS individuals (mean age = 36 years) obtained scores compatible with RBD in a validated screening questionnaire (RBD Questionnaire), a proportion similar to our report (27% positive cases according to RBDQ-HK). On the other hand, insufficient screening capacity with high false positive rate has been described for RBD questionnaires in de novo PD [28], or weak diagnostic consistency [29]. The absence of RWA in our sample suggests that the reported prevalence of RBD among 22qDS patients is overestimated when evaluated only by means of currently available sleep questionnaires.

Our protocol was designed to minimize anxiety and discomfort of "first-night" record by performing attended v-PSG in the naturally occurring sleep environment [30]. Our estimated differences respect to normative "first-night" values should be taken cautiously as the supporting meta-analysis include laboratory records only, with mixed (habitual or fixed) sleep schedules, and a wider age span (18–>80 years) [24]. Furthermore, the chosen normative values may overlook the impact of age and gender factors in PSG parameters as our sex-balanced sample

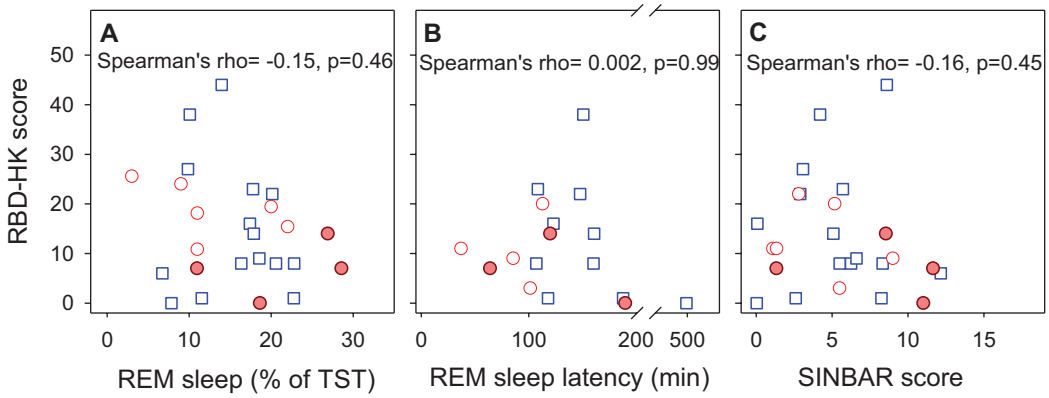

Figure 2. REM sleep-related polysomnographic parameters and RBD Questionnaire-Hong Kong among 22q11.2 deletion patients. A–C: symbols report polysomnographic parameters (abscissa) and RBDQ-HK scores (ordinate) of subjects with (circles, *n* = 10) or without (squares, *n* = 15) pharmacological treatment (see methods for details). Filled (reddish) circles indicate current sertraline treatment (*n* = 4). Spearman's rho and *p* value for the sample's correlation between the corresponding parameter and RBS-HK score is indicated.

present an age span of near 30 years (18-51) with median at 23. Unfortunately, normative values are not available considering both factors simultaneously.

Coincident with previous reports [31],a major complaint found in our sample was difficulty to enter sleep, according to the PSQI. Consistently we obtained a prolonged sleep latency in the v-PSG, with 12 patients exhibiting a median sleep latency longer than 30 minutes. TST was increased with incremented proportions of N1, whereas deep NREM sleep (N3) is not affected for most 22qDS volunteers. REM sleep time was not different to normative values (Figure 2A), with a prolonged REM sleep latency. Two patients (7.7%) of our adult sample (Figure 1I) exhibit AHI scores compatible with adult OSA (AHI > 5), close to the OSA prevalence (10%) reported for 22qDS children [32].

To our knowledge, this is the first study on the presence of RWA performed in 22qDS individuals. RWA was evaluated by means of SINBAR procedure, a method recommended in the International Classification Sleep Disorders-3 [33]. The SINBAR procedure permits a reliable detection of RWA [16, 23, 25] with the minimal combination of EMG channels/muscle [33], an aspect that fits well with our purpose of minimal patient´s discomfort. One relevant limitation in our protocol was that given the restricted number of recording channels in our portable PSG device, the motor activity of *Tibialis anterior* was excluded from our analysis. Our negative report on RBD/RWA should be taken with prudence given the limited size and the youth (median = 26.6) of the sample. 22qDS is a rare disease that limited the recruitment of volunteers to 26 individuals, a fact that precluded a more detailed and robust polysomnographic analysis of gender, and age categories. Nevertheless, the age range of our sample may be adequate to find objective signs of RBD if we consider that (i) the onset for motor symptoms in a sample of 22qDS patients with PD has been estimated close to 39 years [10], (ii) RBD may anticipate the onset of motor symptoms in more than a decade (mean = 14 years) [11–14], and (iii) evidences suggest that RWA may precede RBD [11].

The prolonged anticipation of RBD and RWA with respect to the emergence of full declared α -synucleinopathies has been interpreted in the light of a caudo-rostral progression of peripheral (or enteric) origin of the neurodegeneration [34]. Alternatively, α-synucleinopathies may originate in the central nervous system, where prodromal RWA and RBD conditions are rare or absent as has been proposed for mutation related α-synucleinopathies [35]. The lack of objective evidences of RWA among young 22qDS, a population under genetic risk for early-onset Parkinson's Disease (EOPD) [2–4] is consistent with the latter proposal. Further studies in larger series of 22qDS patients may contribute to confirm that genetic factors may be crucial to the pathogenesis and clinical profile of α-synucleinopathies.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Disclosure Statement

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