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Journal of the Chinese Medical Association 76 (2013) 25–30

www.jcma-online.com

Original Article

Sleep disruption in spinocerebellar ataxia type 3: A genetic and polysomnographic study

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Received December 14, 2011; accepted June 6, 2012

Abstract

Background: Sleep structure disruption and rapid eye movement (REM) sleep behavior disorders (RBD) have been previously reported in patients with neurodegenerative diseases. However, similar studies have rarely been quantitatively conducted in type 3 spinocerebellar ataxia (SCA3).

Methods: Fifteen patients with SCA3 and 16 healthy controls were recruited and evaluated by clinical history, International Cooperative Ataxia Rating Scale (ICARS), Epworth sleepiness scale (ESS), and polysomnography.

Results: Patients with SCA3 had reductions in sleep efficiency and percentage of REM sleep, which were negatively correlated with the severity of ataxia as evaluated by ICARS. REM sleep reduction occurred regardless of the presence of RBD, and severe reduction of REM sleep may significantly disturb the assessment of RBD.

Conclusion: Poor sleep efficiency and REM sleep aberrations are the characteristics of sleep structure disruption in SCA3 as the disease progresses. The incidence of respiratory disturbance during sleep or excessive daytime sleepiness was not significantly higher in SCA3 patients than controls.

Keywords: polysomnography; REM sleep behavior disorder; spinocerebellar ataxia

1. Introduction

Cerebellar ataxias comprise many neurodegenerative diseases, in which the autosomal dominant spinocerebellar ataxias (SCA) usually have symptoms beginning at since early- to mid-adulthood. Currently, there is still no remedy of SCA. The most common SCA is type 3 (SCA3), followed by types 1, 2, and 6. Each type of SCA is rare in general population.[1] SCA3 is also known as Machado-Joseph disease; it is caused by an abnormal expansion of CAG trinucleotide repeat in *ATXN3* gene on chromosome 14q32.[1,2] The CAG repeat length is inversely correlated with the age at disease onset. Clinically, SCA3 is characterized by progressive cerebellar ataxia, ophthalmoplegia, pyramidal and extrapyramidal dysfunctions and peripheral neuropathy. Neuropathologic studies revealed a widespread neuronal degeneration, including the dentate nucleus, spinocerebellar tract, superior and middle cerebellar peduncles, medial longitudinal fasciculus, vestibular and pontine nuclei, locus coeruleus, red nuclei, globus pallidus, substantia nigra, subthalamic nuclei, Clarke column, and spinal anterior horn cells, with relatively preserved cerebellar Purkinje cells and inferior olives.[1,3–6]

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1726-4901/$ - see front matter
http://dx.doi.org/10.1016/j.jcma.2012.09.006

Sleep disturbances have been noticed in various types of SCA, including types 1, 2, 3, and 6.[7] It is important to diagnose and treat sleep disturbances in patients with SCA in order to improve the quality of life. In SCA3, many types of sleep disturbances haven been reported, including periodic limb movements during sleep (PLMS),[8,9] rapid eye movement (REM) sleep behavior disorder (RBD),[8−12] restless leg syndrome (RLS),[8,10,13,14] excessive daytime sleepiness (EDS),[12] and obstructive sleep apnea (OSA).[15] However, the risk factors of these sleep disturbances in SCA3 are not yet known. We proposed a hypothesis that the severity of ataxia may predict the presence of sleep disturbances in SCA3. Thus, 15 patients with SCA3 and 16 healthy controls were recruited and evaluated with ICARS, overnight audiovisual polysomnography (PSG) and questionnaires of daytime sleepiness to quantitatively correlate ataxia with the features of sleep disruption.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. After the written informed consent was obtained, 15 consecutive patients with SCA3, regardless of sleep complaints, including five women and 10 men, age: 45.2 ± 10.6 (mean ± standard deviation) years, range: 26−61 years, CAG repeat length in the expanded alleles: 60−81, age at disease onset: 35.1 ± 11.4 years, range: 16−53 years, duration of illness: 10.1 ± 4.9 years, range: 5−20 years (Table 1), and 16 healthy controls, including nine women and seven men, age 43.4 ± 11.4 years, range, 24−57 years, were recruited into this study. Eight of the 15 patients with SCA3 had the habit of regular hypnotics use. Three of them quit using hypnotics three nights before the PSG examination but the other five (patients 6, 7, 11, 12, 13) could not sleep at all without taking hypnotics (Table 1). By contrast, none of the controls had sleep complaints, chronic pulmonary, neurologic, psychiatric or cardiovascular disease, history of drug abuse, or taking hypnotics. The severity of ataxia was rated by the International cerebellar ataxia rating scales (ICARS), which is a semiquantitative 100-point scale "compartmentalized" into posture/stance, limb ataxia, dysarthria, and oculomotor disability. It has been validated as a useful clinical tool.[16]

2.2. Polysomnography recording

All participants underwent all-night PSG with continuous audiovisual recordings, including electroencephalography (EEG: C3-A2, C4-A1, O1-A2), electro-oculography (EOG), submental surface electromyography (EMG), nasal and oral air flow, thoracic and abdominal respiratory movements, finger oximetry, and electrocardiography. Sleep was staged according to the standard criteria.[17] Sleep onset latency was defined as the time from lights off to the start of stage 1 sleep for continual 3 epochs or other stages for 1 epoch. REM sleep latency referred to the time from sleep onset to REM sleep onset. Sleep efficiency was defined as the ratio of total sleep time to time in bed. Arousals were scored following the Atlas and Scoring Rules by the Atlas Task Force of the American Sleep Disorders Association (1992). Respiratory events referred to apnea and hypopnea. Apnea was defined as cessation of breathing (decreased nasal or oral air flow to less than 20% of baseline) for 10 seconds or longer, whereas hypopnea denoted a decrease of nasal or oral air flow to 20%−50% of baseline with ≥4% in oxyhemoglobin saturation. Respiratory disturbance index (RDI) was defined as the respiratory disturbance per hour of sleep. RDI ≥ 5 was defined as having respiratory disturbance during sleep according to the criteria proposed by American Academy of Sleep Medicine.[18]

On the day of PSG, ICARS was assessed and sleep history regarding abnormal behaviors during sleep was obtained from the patients, their bed partners or caregivers. The Epworth

Table 1
Patient demographics.

Patient number/sex	CAG repeat	Age at onset of ataxia (yrs)	Disease duration (yrs)	ICARS	BMI	ESS	Age at onset of clinical RBD (yrs)	Prior Medications
1/F	70	50	11	39	24.1	8	No RBD	—
2/F	77	35	10	41	12.6	13	No RBD	—
3/M	78	36	6	32	25.9	4	36	—
4/M	75	42	8	43	21.8	2	50	—
5/M	76	30	17	81	17.5	7	No RBD	—
6/M	69	55	3	16	27.9	3	58	CZ/ZC/PT
7/M	60	47	12	57	N/A	N/A	55	ZC/BP
8/M	71	37	17	6	25.3	1	50	—
9/M	81	20	6	33	18.9	5	25	—
10/M	77	28	6	22	21.8	3	No RBD	—
11/M	74	35	8	69	21.5	4	No RBD	CZ/ZD
12/F	64	32	20	53	23.4	9	No RBD	RP/ST
13/F	79	30	11	56	18	5	36	ZD
14/F	80	22	10	29	22.9	11	No RBD	—
15/M	78	25	9	66	21.6	4	28	—

BMI = body mass index; BP = bupropion; CZ = clonazepam; ESS = Epworth sleepiness scale; ICARS = International Cooperative Ataxia Rating Scale; N/A = not applicable; PT = paroxetine; RBD = REM sleep behavior disorder; RP = risperidone; ST = sertraline; ZC = zopiclone; ZD = zolpidem.

Sleepiness Scale (ESS) was used to evaluate excessive daytime sleepiness. Excessive daytime sleepiness (EDS) was defined as ESS $\geq$ 10.[19]

RBD was suspected on the basis of a long-standing history of violent sleep behaviors and unpleasant dreams. PSG evidence of intermittent increase of tonic and phasic EMG activities during REM sleep was required to make the diagnosis definitive.[20,21] PSG features of REM sleep without atonia (RSWA) was defined according to the proposed criteria of Lapierre and Montplasir.[22]

2.3. Statistical analysis

PSG features were compared using the Wilcoxon rank sum (Mann-Whitney) test. The clinical severity of ataxia, rated in ICARS, was correlated with sleep efficiency, REM sleep percentage, ESS, sleep onset latencies, sleep stage shifts, RDI, REM sleep with phasic chin density, and RSWA period by Spearman's rank correlation. The proportions of participants who had excessive daytime sleepiness (ESS $\geq$ 10) and respiratory disturbance during sleep (RDI $\geq$ 5) were compared between patients and controls by Fisher's exact test. A p value of less than 0.05 in the two-tailed tests was considered significant. Multiple linear regression was not used to control factors affecting sleep, such as age, sex, or disease duration, because of the limited sample size and the use of nonparametric statistical methods.

3. Results

By clinical history, RBD was reported in eight patients (Table 1) but not in any of the controls by the time of PSG was performed. Clinical RBD subsequently developed in three more patients (one man and two women: patient 1, 2, 5) during the 3-year follow-up after PSG. The mean age at onset of clinical RBD was 42.3 $\pm$ 12.6 years (range, 25−58 years), which occurred 5.75 $\pm$ 4.0 years after the onset of ataxia. Only four patients with RBD reported occasional unpleasant dreams, including fighting with people or falling off cliffs. While dreaming, seven patients with RBD fell off the bed. In all the patients with RBD, the bed partners had witnessed abnormal behaviors during sleep, such as hitting, kicking, talking, or shouting. The PSG features of the patients with SCA3 are summarized in Table 2. Although eight patients had clinical RBD, neither vigorous movements on the EMG nor sounds on microphone recording that mimicked speech was observed in these patients during the single-night PSG recording.

EDS (ESS $\geq$ 10) was observed in only two of the 15 patients (Table 1). Neither the average ESS nor the prevalence of EDS was significantly different between the patients and controls (Table 3). ESS did not correlate with ICARS, disease duration or the expanded length of trinucleotide repeat.

Five of the 15 patients had respiratory disturbance during sleep (RDI $\geq$ 5; Table 2). However, neither the average RDI nor the prevalence of respiratory disturbance differed between the patients and controls (Table 3).

Compared with healthy controls, patients with SCA3 had a decrease in sleep efficiency and an increase in arousal index, more sleep stage shifts, longer wake time after sleep onset and stage I sleep, shorter stage II sleep, less REM sleep, longer REM sleep onset latencies, as well as more RSWA and REM sleep with phasic chin densities (Table 3). The sleep efficiency, REM sleep percentage, REM sleep onset latency, and percentage of RSWA and REM sleep with phasic chin densities were not statistically different between the patients with RBD and those without (Table 4). REM sleep percentage was either very short in some patients (only 2.1%, 2.3%, and 1.2% of total sleep time in patients 3, 9 and 13, respectively; all of them had RBD) or totally absent in others (patient 5, 11, 12; Table 2).

The ICARS was found to be inversely correlated with sleep efficiency (correlation coefficient: −0.786, p = 0.001) and REM sleep percentage (correlation coefficient: −0.595,

Table 2
Sleep architecture observed in the patients with SCA3 in this study.

Patient number/sex	Sleep efficiency (%)	SWS (%)	REM sleep (%)	REM onset sleep latency (min)	RSWA (%)	REM sleep with phasic chin density (%)	Clinical RBD before PSG	RDI	Age at PSG (yrs)
1/F	69.7	1.5	14.6	55.5	11.21	14.99	−	0.8	61
2/F	64.9	9.2	5.4	177.5	9.52	18.41	−	8.9	45
3/M	80.6	2.8	2.1	272.5	23.53	21.57	+	24.0	42
4/M	79.8	6.0	13.8	107.0	20.13	25.97	+	2.7	50
5/M	37.2	2.0	0	REM−	REM−	REM−	−	0	47
6/M	83.7	5.5	9.2	202.5	12.04	10.88	+	10.3	58
7/M	53.5	8.7	3.1	106.5	0	6.41	+	0.2	59
8/M	89.5	5.3	16.6	63	1.61	12.15	+	2.3	54
9/M	57.8	16.9	2.3	282.5	19.61	19.61	+	0	26
10/M	89.8	13.2	7.8	97	5.29	12.70	−	6.4	34
11/M	44.7	3.3	0	REM−	REM−	REM−	−	1.0	43
12/F	63.3	0	0	REM−	REM−	REM−	−	11.8	52
13/F	52	5.9	1.2	253	25.0	23.33	+	2.8	41
14/F	73	0	14.5	114	7.6	11.23	−	0.2	32
15/M	76.3	1	10.7	141	5.24	12.36	+	0	34

PSG = polysomnography; RBD = REM sleep behavior disorder; RDI = respiratory disturbance index (abnormal: ≥5), REM = rapid eye movements; RSWA = REM sleep without atonia; SWS = stage III-IV slow wave sleep; − = absent; + = present.

Table 3
Comparison of sleep architecture between the patients with SCA3 and controls.

	SCA3 ($n = 15$)	Controls ($n = 16$)	p
Age (yrs)	45.2 ± 10.6	43.4 ± 11.4	0.61
Total sleep time (min)	285.3 ± 63.9	309.6 ± 50.0	0.281
Sleep efficiency (%)	68.4 ± 15.7	82.8 ± 9.3	0.007
Arousal index	33.6 ± 14.1	18.8 ± 5.4	<0.001
Sleep onset latency (min)	29.7 ± 35.8	21.9 ± 21.1	0.808
Stage shifts	217.9 ± 71.9	157.9 ± 40.6	0.012
Wake time after sleep onset (min)	26.2 ± 15.1	10.2 ± 7.2	0.001
Stage I (%)	22.2 ± 7.8	12.9 ± 6.4	0.001
Stage II (%)	38.8 ± 13.5	51.7 ± 8.0	0.002
SWS: Stage III - IV (%)	5.4 ± 4.9	8.8 ± 8.1	0.286
REM sleep (%)	6.8 ± 6.1	15.0 ± 4.9	<0.001
REM sleep onset latency (min)	156.0 ± 80.2 ($n = 12$)	76.7 ± 35.4	0.003
RSWA (%)	11.7 ± 8.5 ($n = 12$)	1.8 ± 2.3	<0.001
REM sleep with phasic chin density (%)	15.8 ± 5.9 ($n = 12$)	5.8 ± 4.3	<0.001
BMI	21.6 ± 3.8	22.3 ± 2.8	0.718
RDI	4.8 ± 6.7	1.6 ± 2.2	0.225
Incidence of respiratory disturbance	5/15 (33.3%)	2/16 (12.5%)	0.220
ESS	5.6 ± 3.5 ($n = 14$)	3.9 ± 2.2 ($n = 14$)	0.296
Prevalence of EDS	2/14 (14.3%)	0/14 (0%)	0.481

BMI = body mass index; ESS = Epworth sleepiness scale; EDS (excessive daytime sleepiness) = ESS ≥ 10; RDI = respiratory disturbance index (respiratory disturbance: RDI ≥ 5); REM = rapid eye movements; RSWA = REM sleep without atonia; SWS = stage III-IV slow wave sleep.

$p = 0.019$; Fig. 1). The expanded length of trinucleotide repeat and disease duration, however, did not correlate with any PSG parameter.

4. Discussion

The patients with SCA3 apparently had lower sleep efficiency and REM sleep structure disruption. Furthermore, the severity of ataxia, measured with ICARS, seemed to be inversely correlated with sleep efficiency and REM sleep percentage, suggesting that they had more sleep disruption and REM sleep disturbance as the disease progressed. To our knowledge, this feature has never been reported before, and the mechanism of sleep disruption in spinocerebellar ataxia has rarely been discussed.

Poor sleep efficiency has been documented in Parkinson disease,[23,24] Alzheimer disease,[23,25] and SCA2.[26,27] In Parkinson disease, frequent awakening during sleep may be attributed to bradykinesia and difficulty turning over in bed. The shorter, shallower, and fragmented sleep in patients with other neurodegenerative diseases, including SCA2 and SCA3, may similarly stem from the same pathomechanism. Besides bradykinesia, ataxia-related symptoms, such as vertigo while turning on the bed and inadvertent and excessive collision, might also play a significant role in their sleep disturbance. In Parkinson disease, the reduction of REM sleep duration was caused by the degeneration of dopaminergic nigrostriatal pathway with compensatory activation of monoaminergic neurons in the brain stem.[28] Reduced concentration of dopaminergic transporter in the nigrostriatal pathway has also been reported in SCA2[29] and SCA3.[3,4] Therefore, it is conceivable that the REM sleep reduction in Parkinson disease, SCA2 and SCA3 may have similar pathomechanism.

EDS was reported in only few patients with SCA3 (Table 3), which might be due to a poor sleep efficiency and OSA.[12] EDS is frequently observed in patients with Parkinson disease,[30,31] and has been attributed to the use of anti-parkinsonism medicines, i.e., dopaminergic agonists,[32] which are not prescribed to most patients with SCA3.

Table 4
Comparison of the characteristics of REM sleep between SCA3 patients with RBD and without.

	Patients with RBD ($n = 8$)	Patients without RBD ($n = 7$)	p
Age (yrs)	45.5 ± 11.8	44.8 ± 10.0	0.981
Disease onset duration	9.5 ± 4.8	10.9 ± 5.2	0.590
ICARS	38.6 ± 20.9	47.7 ± 21.3	0.613
Trinucleotide repeat number	73.9 ± 6.9	74.0 ± 5.4	0.757
Sleep efficiency (%)	73.0 ± 13.2	63.2 ± 17.6	0.397
REM sleep (%)	7.4 ± 6.0	6.0 ± 6.6	0.533
REM sleep onset latency (min)	178.5 ± 85.2	111.0 ± 50.7 ($n = 4$[a])	0.214
RSWA (%)	13.4 ± 10.1	8.4 ± 2.5 ($n = 4$[a])	0.570
REM sleep with phasic chin density (%)	16.5 ± 7.0	14.3 ± 3.1 ($n = 4$[a])	0.808

ICARS = International Cooperative Ataxia Rating Scale; RBD = REM sleep behavior disorder; REM = rapid eye movements; RSWA = REM sleep without atonia.

[a] No REM sleep during PSG in three of the seven patients without RBD.

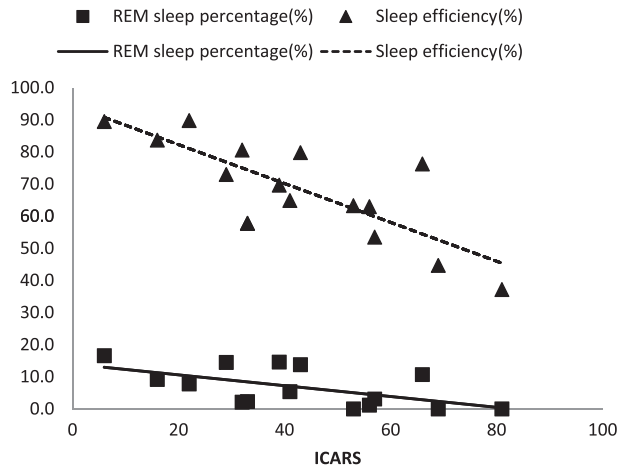

Fig. 1. Correlation between ICARS and two polysomnographic parameters: sleep efficiency (diamond) and REM sleep percentage (circle). ICARS = International Cooperative Ataxia Rating Scale; REM = rapid eye movements.

Previous studies have revealed that the percentage of RSWA and REM sleep phasic chin/legs densities significantly increased in SCA3 with RBD, but not in SCA3 without RBD.[8,9] However, in this series, reduction in REM sleep percentage and increase in REM sleep latency, percentage of RSWA and REM sleep phasic chin densities were similarly found in all patients with SCA3, regardless of the absence of RBD (Table 4). The calculation of RSWA percentage might have been less accurate in those patients who had very short REM sleep. It may not be appropriate to compare RSWA or REM sleep with phasic chin density percentage in patients with extremely short REM sleep. Furthermore, four patients without clinical RBD had no REM sleep at all during the single-night PSG and therefore couldn't be included in the analysis of RSWA. Since the REM sleep duration seem to diminish as the disease progresses, a patient with real RBD may not be correctly diagnosed if REM sleep becomes absent in advanced stage. A longitudinal study would be needed to follow the clinical manifestation and PSG changes as the disease evolves.

Snoring and sleep apnea have been reported in patients with SCA3 in a questionnaire study.[15] Several patients in our study had respiratory disturbances recorded by PSG, but neither the average RDI nor the incidence of respiratory disturbance was significant higher than control. Therefore, the relationship between sleep apnea and SCA3 was not corroborated in this study based on PSG. Further studies in larger population may be needed.

Because of the difficulty in recruitment and limited sample size, only non-parametric statistical method could be used and multivariate analysis could not be carried out to adjust confounding factors of sleep. Besides, the study group and controls could not be perfectly matched in age and sex, although the average age was not significantly different. Furthermore, the PSG should have included anterior tibialis EMG recording in most patients and controls, although it was not a standard operating procedure in our sleep laboratory. Medication effects to sleep could not be avoided in some patients with their insistence of continuous use of hypnotics at the time of PSG.

In conclusion, this genetic and polysomnographic study provided evidence that, in SCA3, sleep efficiency and REM sleep percentage inversely correlate with the progression of ataxia symptom. REM sleep reduction occurs regardless of the presence of RBD, which may have significant influence in RBD assessment. Neither daytime sleepiness nor respiratory disturbance during sleep is the feature of SCA3.

Acknowledgments

We are grateful to the patients with SCA3 whose collaboration was essential to the success of this study. This work was supported by grants from the National Science Council (NSC98-2314-B-010-036-MY3), Taipei Veterans General Hospital (V99-C1-052), Yen Tjin Ling Medical Foundation (CI-98-3), and Taiwan Ataxia Patient Support Group, Taiwan, R.O.C.

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