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【 CASE REPORT 】

Rapid Eye Movement Sleep Behavior Disorder-like Symptoms Due to Arousal Responses Associated with Severe Obstructive Sleep Apnea-hypopnea

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Abstract:
A 78-year-old man suspected of having α-synucleinopathies received a high score on a validated questionnaire for rapid eye movement (REM) sleep behavior disorder (RBD). Although he did in fact have unpleasant dreams and vigorous behaviors, polysomnography (PSG) found only obstructive sleep apnea-hypopnea (OSAH). The RBD-like symptoms corresponded with arousal responses, namely augmented inspiratory effort and leg movements, to his frequent apnea-hypopnea events during REM sleep. Thus, severe OSAH might cause RBD-like symptoms. PSG can discriminate real RBD from RBD-like symptoms associated with severe OSAH and therefore may be essential for determining an appropriate course of treatment in certain patients.

Key words: REM sleep behavior disorder (RBD), REM sleep without atonia (RWA), questionnaire, polysomnography, obstructive sleep apnea, brainstem

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Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is the prodromal stage of α-synucleinopathies and REM sleep parasomnia, clinically characterized by unpleasant dreams and vigorous behaviors during REM sleep (1, 2). Although the detection of REM sleep without atonia (RWA) on polysomnography (PSG) provides a definitive diagnosis of RBD (3), PSG is costly, demands specialized training, and is not widely available (1). Thus, several validated questionnaires have been proposed to screen for RBD (1, 2).

We herein report a case of severe obstructive sleep apnea-hypopnea (OSAH) whose clinical symptoms were remarkably similar to those of RBD. Although an RBD questionnaire that had a high specificity suggested the diagnosis of RBD, PSG showed no RWA but instead frequent arousal responses associated with OSAH-related oxygen desaturation.

Case Report

A 78-year-old man was referred to our hospital due to unsteadiness of gait and festination. He had a history of hypertension, diabetes mellitus, prostatic enlargement, rotator cuff tear of the left side and osteoarthritis of the left knee. Neurological findings revealed clumsiness of the left upper and lower limbs and a short-stepped gait. The muscle tone of the limbs was normal, and no resting tremor was observed. Tendon reflexes were preserved, and his plantar responses were indifferent. Tandem gait was unstable. Autonomic dysfunction was not observed, except for with regard to urinary frequency. He had a Montreal Cognitive Assessment score of 23/30.

Given the possibility of α-synucleinopathies, the olfactory function was assessed, and an RBD screening questionnaire (Japanese version; RBDSQ-J) was administered (4). Odor identification with Open Essence (Wako, Japan) showed a score of 6/12 (cut-off value, 6) (5). RBDSQ-J showed a

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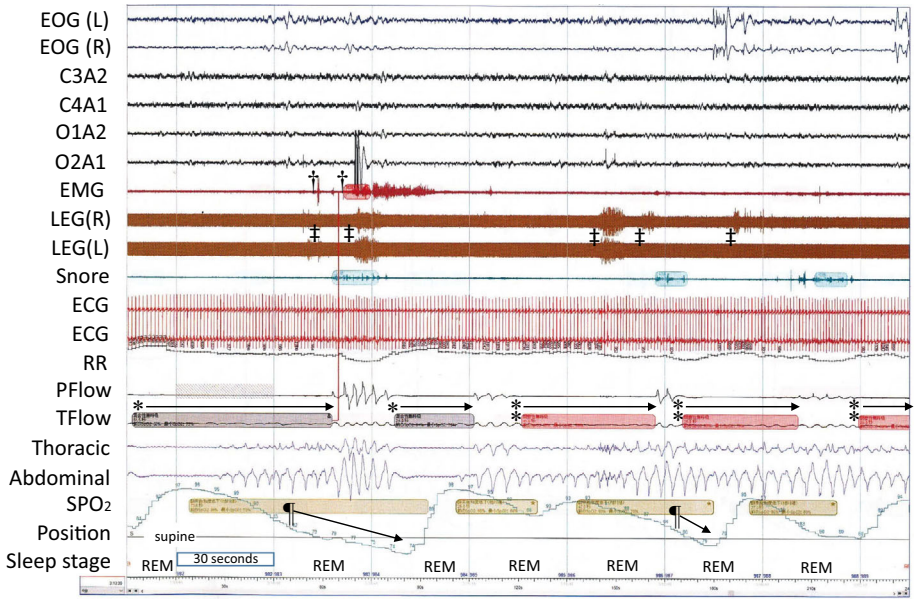

Figure. PSG findings during REM sleep. The first and last halves of the record showed apnea of mixed type (*) and obstructive type (⁑), respectively. Most of the episodes of apnea induced severe hypoxemia (¶) and thus an arousal response with submandibular tonic and phasic EMG activity (†). Leg movements were also observed (‡).

score of 8/13 (cut-off value, 4.5). In the RBDSQ-J, 2 of the 4 questions (items 3, 6.1, 6.2 and 6.3) focusing on dream enactment received "yes" responses (items 6.1 and 6.2), indicating RBD (≥1=RBD positive) (6). Further inquiry revealed a history of unpleasant dreams (being chased by a snake, fighting a dog, being killed by someone, etc.) and vigorous behaviors (punching, kicking a bedside cabinet, etc.). He also had excessive daytime sleepiness and loud snoring.

PSG showed an apnea-hypopnea index (AHI) of 71.2 (66.4 during REM and 61.5 during non-REM), an arousal index of 52.8 (34.8 associated with sleep disordered breathing), and a 3% oxygen desaturation index of 70.2. During REM sleep, the longest period of apnea was 73.6 seconds, and the minimal oxyhemoglobin saturation was 73. Three-quarters of the apnea-hypopnea events were apnea (central type 1%, obstructive type 36% and mixed type 63%). During REM sleep, almost half of the apnea-hypopnea events with oxygen desaturation induced arousal responses showing tonic and phasic submental electromyography (EMG) activity. In addition, 12 of 17 arousal responses (71%) were associated with leg EMG activities (Figure). There was no tonic EMG activity, defined as increased sustained EMG activity (amplitude more than the minimum non-REM amplitude) in the mentalis muscle in more than 50% of the 30-second epoch periods (7). In addition, there was no phasic EMG activity, defined as a burst of EMG activity (exceeding 4 times background EMG amplitude) in the mentalis and limb muscles in more than five 3-second miniepochs over any 30-second epoch period (7). Thus, except for the EMG activity associated with arousal responses, neither tonic nor phasic EMG activity fulfilling the decision criteria for RWA was observed in the mentalis or limb muscles.

His periodic limb movement disorder index was 5.7 (standard value in adults: <15) (3). Magnetic resonance imaging of the brain showed no abnormalities except for a small infarction in the left corona radiata. ^{123}Iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy showed a normal heart-to-mediastinum (H/M) ratio (early phase 2.63, late phase 3.52; cut-off value, 2.2) (8). ^{123}Iodine-ioflupane single-photon emission computed tomography (SPECT) showed a slight decrease in the right specific binding ratio (SBR) (right 4.02, left 4.54; cut-off value, 4.5) (9). The visual assessment of the dopaminergic degeneration pattern was grade 4 (eagle wing) (10).

Oral medicine for prostatic hypertrophy and operative treatment for the shoulder and knee ameliorated the neurological findings presented at the first visit. ^{123}Iodine-ioflupane SPECT showed a slight change, but he had not yet developed α-synucleinopathies, such as Parkinson's disease (11), Dementia with Lewy bodies (12) or multiple system atrophy (13). Thus, his chief complaints seemed to have arisen from urologic and orthopedic problems; the array of symptoms suggestive of α-synucleinopathies appeared to be unrelated. Although treatment with continuous positive airway pressure was recommended for his severe OSAH, he refused the treatment due to the discomfort of the airflow.

Discussion

Although the scores of RBDSQ-J and subpart of RBDSQ-J indicated a diagnosis of RBD in this patient, PSG failed to show the RWA that is essential for a diagnosis of RBD. Instead, PSG demonstrated frequent arousal responses associ-

ated with oxygen desaturation due to severe OSAH. Most of the arousal responses were accompanied by leg movements. These findings suggest that severe OSAH but not RBD might cause unpleasant dreams and vigorous behaviors during REM sleep.

Even though the RBDSQ-J can discriminate RBD from OSAH with high sensitivity (88.5%), specificity (90.2%) and reliability in the elderly Japanese population (4), it was reaffirmed that the specificity of the questionnaire is limited by severe OSAH (1, 2). Thus, PSG should be used to avoid a misdiagnosis of individuals with unpleasant dreams and vigorous behaviors due to OSAH. It has been revealed that RBD and OSAH share clinical characteristics, including sleep behaviors (punching, jumping out of bed or shouting), dreams (being attacked or robbed) and a predilection for older men (14). RBD-like symptoms due to OSAH are only seen in patients with a high AHI and severe oxyhemoglobin desaturation (14). Indeed, this patient showed severe OSAH (AHI 71.2, minimal oxyhemoglobin saturation 73).

Although the precise mechanism underlying the RBD-like symptoms in patients with OSAH remains unknown, there are several possibilities. First, the termination of apneic events is associated with arousal responses, which directly depend on augmented inspiratory effort (15). In this patient, almost half of the apnea-hypopnea events with oxygen desaturation induced arousal responses, 71% of which were associated with leg EMG activity. The frequent augmented inspiratory effort and leg movements were at first difficult to differentiate from vigorous RBD behaviors. However, in questions focusing on dream enactment, the match between dream contents and nocturnal behavior (item 3) received a "no" response. These findings suggest that a mismatch in content between vigorous behaviors and dream content in patients might reflect body movement caused by OSAH arousal responses rather than RBD dream enactment. Second, in some patients, OSAH might coexist with real RBD (16), although that was not the case in our patient. An animal model of recurrent apnea simulating OSAH developed apoptotic neurons and glia in the brainstem regions involved in the control of REM sleep and wakefulness as well as the respiration and cardiovascular functions (17). Degeneration of the subcoeruleus nucleus releases the inhibition of spinal motor neurons via the medullary reticular formation and the spinal ventral horn interneurons, thereby introducing the pathological movements of RBD (2). In addition, degeneration of the medullary reticular formation circuit of the subcoeruleus nucleus releases inhibition of the red nucleus, which is followed by the generation of muscle twitches (2). These twitching limbs might induce dream images and content via motor-sensory feedback (18). Progression of the brainstem lesion due to long-term repeated OSAH might explain the finding that RBD symptoms have been observed in OSAH patients.

In conclusion, severe OSAH might result in unpleasant dreams and vigorous behaviors remarkably similar to those of RBD. The RBD-like symptoms due to OSAH might be caused by arousal responses associated with augmented inspiratory effort and leg movements. In the case of OSAH complicated by real RBD, brainstem dysfunction after exposure to long-term repeated apnea might play an important role in the development of RBD symptoms. Although a validated questionnaire is useful for screening RBD, PSG is essential for discriminating real RBD from RBD-like symptoms associated with severe OSAH and thus for deciding on the course of treatment. In our case in particular, the array of suggestive symptoms could have easily led to the wrong diagnosis without PSG.

The authors state that they have no Conflict of Interest (COI).

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