REVIEW ARTICLE

Is there a relation between the physiopathological mechanism of prostate cancer and REM sleep behavior disorder?

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Abstract

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by loss of muscular atonia and prominent motor behaviors during REM sleep, associated with excessive motor activity while dreaming. Behaviors can cause injuries to the patient or sleeping partner. RBD is associated with neurodegenerative diseases, such as multiple system atrophy, Parkinson's disease, dementia with Lewy bodies, and progressive supranuclear palsy. In many cases, the symptoms of RBD occur before other symptoms of these neurodegenerative disorders by several years. RBD was noted for the first time after the patient developed cancer of the prostate. The fact that PCa develops one year after the onset of RBD is of significance. Could RBD be a forerunner for PCa, or could a PCa that has not yet clinically surfaced have given rise to RBD? Some diseases associated with voltage gated potassium (K) channel antibody also had RBD. The possible contribution of voltage gated K channel activity in metastatic process was emphasized in PCa model in rats. Apparently, being able to explain the development mechanism of RBD by PCa and K channel antibody might be a possible viewpoint. Although our hypotheses can be explained by voltage gated K channel activity, yet there are still numerous ambiguities. This case brings to focus several unanswered questions related to the pathogenesis of RBD.

Keywords: Prostate cancer, REM, behavior disorder, K^+ ion channels

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Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a clinical presentation with the intermittent loss of atonia during REM sleep but with vivid dreams. Even though the prevalence is not known, its frequency in the general population was reported as 0.38% and 0.5% (1, 2). The severity prevalence related to sleep is 2.1%, and 0.38% of this rate is related to the vivid dreams, which takes the RBD prevalence to 0.8% (3). Atony in REM sleep occurs via the active inhibition of the motor activity of the peri-locus coeruleus (PLC) region in pons. This inhibition of the PLC region stimulates the nervus reticularis

magnocellularis (NRMC) in the medulla through the lateral tegmentoreticular tract. The stimulated NRMC hyperpolarizes the ventrolateral reticulospinal tract and spinal alpha motor neurons, thus leading to REM atony (4). Patients are often males at the age of 50 and above (5, 6). The clinical picture can be observed around 90 minutes following the beginning of sleep, or during the period in which REM appears first in a normal sleep or at later REM phases. The most typical clinical findings are calling names, talking, laughing, and some simple and complex movements. Punching and/or kicking, jumping, running, talking, and shouting are the most common moves. These behaviors are often linked with the events occurring during the dream. This means that the dream is being animated. Even prolonged aggressive talking and ranting can be observed during the sleep. The complexity of these behaviors, their content of violence and frequency increases with time. Dreams are mostly of violent content. It produces the feeling of fear more than anger. The most frequent unpleasant dreams are: running away from a creature or an unusual appearing person, being attacked, chased by them, fighting and scuffling with them. Animals in these dreams are often snakes, spiders, and dogs. These dreams rarely have adventurous or sports contents. Sexual or appetizing dreams concerning eating are not common. Sometimes, these dreams may be connected with the aggressive feelings that the person might have experienced during the day (7). If the person is woken up or wakes up by himself/herself, he/she may clearly remember the dream. Interestingly, such patients do not demonstrate aggressive behaviors or personality characteristics during the day (8).

Brief case history

Our patient presented with the history of beating and kicking his wife during sleep for the last 5-6 months. He was embarrassed of the situation. His mother had died from dementia and he feared developing the same. Going into the history it was found out that our patients complaints began about 10 years back with history of sleeplessness and increasing drowsiness during the day. About four years later the patient complained of talking, sitting up and first showed violent behavior of ranting/ irrelevant talk during sleep. He associated his symptoms with his son's quitting of school around that time. This was the period when he noticed injuries (bruised knees)following sleep (later he learnt that during this period he started sleep walking/ sleep talking, often falling or bumping into the furniture). Later on, he developed frightful dreams-chasing /being chased by animals/ creatures. He dreamt coming face to face with the 'angel' of death. However, he never felt pain or fear. This was the time when he recollected kicking/punching his wife or the wall. Interestingly he always remembered his dreams. He recollects his neighbors being disturbed by his noise/cries during sleep. Surprisingly, such dreams never occurred when he slept during the day time. It was at this point he consulted a psychiatrist who prescribed him antidepressants. Unfortunately, this only increased his complaints. The patient then visited our centre, clinical examination including neurological examination, biochemical investigations and MRI of the brain were found to be normal. Video polysomnography (VPSG) revealed REM episodes without atony. Video imaging detected his talking during sleep and sitting up on the bed. Patient was diagnosed with RBD, and was started on clonazepam in the dose (0.5 mg/day, then 1 mg/day). His complaints shortly disappeared. The patient was a 64-year-old man who also had symptoms of the lower urinary tract with an elevated prostate-specific antigen (PSA) level of 9.0 ng/mL. His rectal examination revealed a firm nodule at the left base of the prostate gland. Transrectal ultrasound guided biopsy revealed prostatic adenocarcinoma score 7 (Gleason score 3+4) in the right and left lobes of the prostate. He underwent a radical prostatectomy.

The hypothesis

There are numerous diseases associated with RBD (2, 9). The connection of RBD with numerous neurological diseases is commonly known, and its pathogenesis is accounted for by the association with these diseases. Pathogenesis of several diseases appearing in combination with RBD is as yet unexplained. Diseases that accompany RBD might be of vascular, neoplastic, toxic, metabolic, infectious, degenerative, traumatic, or congenital origin. Among these are mitochondrial encephalomyopathy, normal pressure hydrocephaly, Tourette's syndrome, cerebellopontine angle tumors, brain stem neoplasm's, group A xeroderma, ischemic or hemorrhagic cerebrovascular diseases, autism (9-11). Parkinson's disease (PD) is the leading disorder among them, and RBD is reported in 15-34% of patients with PD (12-14). The clinical finding giving rise to the suspicion of RBD in 25% of the Parkinson's patients is injuries occurring while sleeping, and RBD was reported

in 47% of PD patients with sleep complaints whose VPSG were examined (12). RBD in multisystem atrophy (MSA) patients are more prevalent compared to PD (15); 90% of MSA patients were reported to have REM sleep episodes without atony, and clinical RBD was found in 69% of these patients (16). The fact that MSA shows more common degeneration than PD and involvement of the region of the brain stem explains the occurrence of REM atony. The presence of a strong relationship between RBD and Lewy Body Dementia is also known (6, 17, 18). RBD may also be seen in patients with Parkin gene mutation (19, 20). The relation between progressive supranuclear palsy-Alzheimer's disease, progressive dementia and frontal syndrome, corticobasal degeneration, Machedo-Joseph Disease (SCA-3), multiple sclerosis and RBD might be of possibility (21-26). Thus, the pathogenesis of RBD can be explained in different ways. In some cases RBD may predate the diagnosis of prostatic cancer by several months or more. Cases of limbic encephalitis (LE) are associated with paraneoplastic antibody. But, the ones that are associated with RBD were voltage-gated K tract antibody positive. Five of the six patients with LE associated with voltage-gated potassium (K) channel antibody had RBD. Pathologies of limbic structures were reported in cases with PD, multiple system atrophy (MSA), and Lewy Body Dementia (LBD). The highlighted fact was that the limbic system might play a role in the occurrence of unpleasant and dreadful dreams (27). The possible contribution of voltage-gated K channel activity in metastatic process was emphasized in PCa model in rats (28). This view is also affirmed by the studies concerning the relation of human PCa with K channels and the fact that K channel blockers inhibit the RBD (29). The role of K channel antibody in the mechanism for development of RBD is one of the most probable hypothesis.

Discussion

Rapid eye movement (REM) sleep behavior disorders (RBD) was first identified in the written literature in 1600s with the Don Quixote de la Mancha figure by the renowned Spanish author Miguel de Cervantes, but was not till then known as a sleep disorder (30). The fact that RBD might surface as a clinical picture in humans was first reported by Schneck (31). Sleeplessness at night and excessive daytime sleepiness (EDS) complaints of our patient since 10 years is compatible with RBD. Months or years before the clinical picture appears, about 25% of the patients had history of talking, shouting, or running/kicking/ punching during sleep (6, 32, 33). Their complaints are in accordance with the previously reported RBD symptoms. As a result of these behaviors, injuries, ecchymosis, lacerations, and even subdural hematomas may occur. The patient may punch and kick his/her partner, or even pull his/her hair, etc. (6, 34, 35). Voltage-gated K+ channels (VGPC) have been noted to effect cellular functions in both excitable and non-excitable cell types. These functions consist of resting membrane potential, solute and water transport, cell volume regulation, cell adhesion, apoptosis, and lymphocyte activation. These processes may have the possibility that cells disseminating from a primary tumor to distant areas in the body. VGPC are expressed in cell lines derived from several cancers, such as prostate, lung, astrocytoma and melanoma. Furthermore, VGPC can be controlled by mitogens and oncogenes, and their expression can influence several essential characteristics of cancer cells, including invasion, apoptosis, lateral motility, morphological development and proliferation (28).

Conclusion

Although our hypotheses can be explained by voltage-gated K channel activity, yet there are still numerous ambiguities. This case brings to focus several unanswered questions related to the pathogenesis of RBD.

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