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Improvement of dream enactment behavior associated with levetiracetam treatment in dementia with Lewy Bodies

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Introduction

Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) is a parasomnia characterized by dream enactment behavior associated with abnormal augmentation of muscle tone during REM sleep. Dream enactment is highly variable, ranging from simplex vocalizations to violent thrashing in bed, and can lead to falls and injuries to the patient or bed partner. RBD can be a harbinger of neurodegenerative disease in up to 90% of cases, most commonly synucleinopathies such as Multiple System Atrophy, Dementia with Lewy Bodies (DLB), or Parkinson's disease[1]. Though the underlying affected neural circuitry is imperfectly understood, animal and human studies implicate pontine centers involved in the generation of sleep atonia[2]. Medications from various classes have been found to be efficacious in RBD, including benzodiazepines, melatonin, cholinesterase inhibitors, dopamine agonists and others[3], suggesting these pathways can be influenced in diverse ways. Among anticonvulsants, only carbamazepine has been reported to ameliorate the symptoms of RBD[4]. Here we report the apparent efficacy of levetiracetam in the treatment of dream enactment behavior in a man with probable DLB.

Case Description

A 64 year-old man with a history of alcoholism, depression, and 10 year history of anosmia began having progressive worsening of memory and word-finding problems. Concurrently, he began having episodes during sleep in which he would kick and lash out consistent with reported dream content, falling out of bed as a result on at least one occasion. These episodes occurred around 6 times per month and were frequently associated with crying out. At age 65 he underwent an ambulatory electroencephalogram (EEG) which showed diffuse slowing and non-specific sharp waves. The patient was placed on lamotrigine but developed a severe rash. He was then placed on levetiracetam which was gradually increased to 1000

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mg twice a day. According to his wife, the frequency of nocturnal episodes decreased to 3 times per month with the initiation of levetiracetam and their severity was diminished such that when he had episodes he was described as “still moving around” but no longer “acting out” or “screaming.” Concurrent medications included atorvastatin, escitalopram, aspirin, fexofenadine, folate, and vitamin B12 supplements.

He was assessed by a neuropsychologist at age 66 by which time he needed assistance from his wife in paying bills and managing his medications. During testing he revealed the false sensation that someone was sitting next to him and that he had experienced this same sensation in the past. He was found to have moderate to severe impairment in multiple areas of cognition with particularly poor visual-spatial abilities, attention, memory, and distractibility. It was the neuropsychologist's impression that the patient's diagnosis was most consistent with dementia with DLB.

The patient was referred to an epileptologist who ordered a repeat EEG, MRI, and fluorodeoxyglucose positron emission tomogram (FDG-PET) scan. The EEG confirmed left temporal interictal epileptiform discharges and focal attenuation of fast activity over the left posterior quadrant. The MRI showed mild diffuse atrophy without obvious focal (medial temporal or lobar) involvement or any ischemic changes. FDG-PET showed decreased FDG uptake in the frontal, parietal, temporal, and occipital lobes, particularly in the left occipital lobe, interpreted as being consistent with a diagnosis of DLB. In light of the potentially epileptiform abnormalities on EEG, the patient was advised to stay on levetiracetam and referred to a dementia specialist.

At age 67 the dementia specialist verified ongoing sensations of the presence of non-existent persons and objects. On the Mayo Sleep Questionnaire (MSQ)[5] the patient's spouse endorsed the patient appearing to “act out his dreams,” resulting in him being injured on one occasion, and telling her “about dreams of being chased, attacked, or that involve defending himself,” and that “the details of the dream matched the movements made while sleeping.”There was no clear history of fluctuations in cognition or arousal state. Mini-Mental Status Score was 20/30. No Parkinsonism was appreciated. To help clarify the diagnosis, an iodine ioflupane SPECT (I-123 DATscan) was obtained. This showed severely decreased activity in the left putamen and caudate with moderate to severe decreased activity in the right putamen consistent with a Parkinsonian syndrome. Therefore, despite the lack of clinical Parkinsonism and fluctuations, it was felt that the most likely diagnosis was probable DLB. In light of the absence of episodes suggestive of epileptic events, the patient was advised to taper off levetiracetam. When levetiracetam was discontinued, the severity and frequency of nocturnal episodes increased again to approximately 8 times per month. The rivastigmine patch was then started without significant impact on his nighttime behaviors. At the time of last contact he continued to have episodes consistent with probable RBD 3 to 4 times per month. As it was not felt that these episodes were overly troubling, no further assessment or treatment was instituted.

Discussion

We report a case of a man with a presentation consistent with a neurodegenerative dementia and nocturnal episodes consistent with probable RBD that had a partial response to levetiracetam. Though we did not obtain polysomnographic verification of the diagnosis of RBD, the wife's responses on the MSQ were consistent with this diagnosis. Such responses have been demonstrated to have a sensitivity of 100% and specificity of 95% for a diagnosis of RBD in a validation study using polysomnography as the gold standard[5]. Despite the epileptiform EEG abnormalities, there was no suggestion of clinical seizures in the patient's history. Though our patient had only one of the core features of DLB (visual hallucinations) with substantial fluctuations in cognition and arousal state and Parkinsonism being absent, the presence of probable RBD and a DATscan characteristic of that diagnosis qualifies him as having probable DLB by the McKeith et al criteria[6]. Further supportive features for this diagnosis were cognitive decline, anosmia, delusional ideas, and an FDG-PET with pronounced occipital hypometabolism.

Drugs from diverse classes have been shown to have efficacy in RBD[3], indicating that the underlying neural circuitry is complicated and incompletely understood. There is, to our knowledge, only one prior case report of a non-benzodiazepine anticonvulsant (carbamazepine) being effective in uncomplicated RBD[4]. As such, beneficial effects in RBD do not appear to be a characteristic of this class of drugs overall. The apparent efficacy of levetiracetam reported here is noteworthy in light of its unique pharmacology. Levetiracetam is a pyrrolidone derivative, chemically similar to piracetam, approved by the FDA for the treatment of seizures. It is effective in some, but not all pre-clinical seizure models and does not appear to act through traditional anti-epileptic mechanisms. The lead theory regarding its mechanism of action involves effects on regulation of calcium signaling through binding to synaptic vesicle protein 2. Studies of the influences of levetiracetam on sleep indicate that it reduces time spent in REM sleep[7]. In addition, another study of levetiracetam administration to patients with partial onset seizures on carbamazepine and healthy volunteers found an increase in stage 2 of NREM sleep. In the healthy volunteers, there was an increase in REM latency[8]. However, at least one other study of patients treated with levetiracetam failed to demonstrate changes other than increased sleep efficiency on polysomnogram[9].

It is possible that the improvement in dream enactment behavior seen in this case was either random fluctuation (as can occur in DLB-related symptoms) or due to some other confounding cause. Indeed, our patient was known to be a heavy alcohol consumer and was on escitalopram. Both alcohol consumption/withdrawal and selective serotonin-reuptake inhibitors are known to have effects on sleep architecture and RBD symptoms. However, there was no association of changes in the dose or pattern of consumption of these agents with his dream enactment behavior. There was such an association with the initiation and discontinuation of levetiracetam.

Though 80% of patients with RBD respond to clonazepam, early-morning sedation and, in the elderly, gait and memory problems can limit its use. There is increasing evidence for efficacy of melatonin in RBD, which appears to be better tolerated[3]. There are several reasons to consider levetiracetam to supplement the treatment of RBD in elderly demented

persons. In the context of epilepsy in Alzheimer's disease, levetiracetam was found to have the best side effect profile relative to lamotrigine and phenobarbital in a prospective and randomized trial, and there was even a suggestion of improvement in cognition associated with levetiracetam use[10]. Furthermore, in a mouse model of AD, levetiracetam was shown to ameliorate synaptic dysfunction and cognitive deficits, possibly by suppressing neuronal network dysfunction[11].

We describe a beneficial effect of levetiracetam, a medication with proven safety in the elderly, on dream enactment behavior in a patient with probable DLB. Though objective documentation of loss of REM sleep atonia with polysomnography and it's improvement with levetiracetam would strengthen the case, we feel the clinical history provides preliminary evidence for the efficacy of levetiracetam in RBD. Such improvement may have occurred via suppression of REM sleep, although more data are needed to confirm this. Though not approved by the U.S Food and Drug Administration for this purpose, further study of levetiracetam's effectson RBD in larger cohorts of elderly patients afflicted with this sleep disorder is indicated.

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