CLINICAL VIGNETTE

A New Name for an Old Insomnia: What is WED?

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A 56-year-old female presented with a complaint of insomnia for over 20 years. She developed sleep problems after the birth of her son that never resolved. She decribes frequently lying in bed for 1-2 hours before falling asleep. She reports fragmented sleep, waking up every two hours on average, three times nightly. During these nocturnal awakenings, she wakes up feeling alert but is able to fall back asleep easily. She gets into bed between 9-10pm and usually arises at 6am. Her schedule does not change significantly on the weekends. She works from 9am until 4:30pm and does not drink caffeine or smoke tobacco. She does not exercise regularly and does not nap.

She had no difficulty sleeping as a child. She was always comfortable going to bed early and rising early. There is no history of frequent childhood tonsillitis or consideration for tonsillectomy. She denies any sleep problems in her early adult life and has never experienced sleep paralysis, hypnagogic or hypnopompic hallucinations, or cataplexy. There is no history of snoring or witnessed apneas. She denies waking with headache or dry mouth and has not gained weight recently.

There is no history of excessive movements during sleep or any injuries during sleep. She responds negatively about questions regarding uncomfortable sensations in the limbs prior to sleep. She did report episodes of sleep walking and waking up in the morning to find that she had eaten food in the kitchen during the night. She usually does not recall these episodes and often eats high carbohydrate foods. She denies any other known complex behavior while asleep, and she believes that the sleep eating episodes were all during times in which she was taking zolpidem. She denies having an eating disorder otherwise.

She reports occasional nightmares and has reportedly yelled in her sleep, but she has never had a night terror. She has a history of a prior abusive relationship, but the evaluation for post- traumatic stress disorder was negative. The sleep difficulties started prior to the abusive relationship. She is currently in a healthy relationship and does not feel that the prior issues are currently bothering her. She denies current depression or anxiety.

She reports improved sleep during a recent trip away from home. She felt that the increased physical activity may have helped her sleep. At home, she sleeps in a different bedroom from her husband due to his excessive snoring (he has not yet been evaluated).

On the Epworth Sleepiness Scale, she scored 5 out of 24, which suggests that she does not have pathological daytime sleepiness. The patient is currently taking three hypnotic medications. On this regimen, she believes she is not sleep deprived. She notes that when she does not sleep well, she is functionally limited the next day. She reports worsening problems with memory and concentration over the last few years, exacerbated by lack of sleep.

The patient has an extensive history of medication use for insomnia. She currently is taking doxylamine, clonazepam, and 5-HTP (herbal). In the past she used zolpidem (stopped due to sleep related eating), temazepam (actually led to increased alertness at night), clonidine, trazadone, diphenhydramine, mirtazapine, and ramelteon; none of these medications worked. She has also taken alprazolam but stopped this medication because of the potential for addiction. Of all of the medications she has used for sleep, she has found alprazolam to be the most effective. Alprazolam was initially prescribed for anxiety, but she denies any anxiety symptoms for years.

She has a past history of hypothyroidism, hypertension and allergies, all of which are well controlled. Current medications include irbesartan, levothyroxine, esomeprazole, conjugated estrogen, and furosemide. She is a former smoker with no symptoms of pulmonary disease. There is no family history of any sleep disorder. She works as a nurse manager. She is 5’1” and weighs 156 lbs with a BMI of 29.4 and has a 14.5 inch neck circumference. On physical exam the upper airway is notable for a Mallampati grade 3 view with a mildly enlarged tongue and tonsillar pillars that are more medial than

normal. The lungs are clear and heart sounds are normal without a murmur. The last TSH was in the normal range and an echocardiogram was reportedly normal.

Differential diagnosis of the insomnia

The patient has both sleep onset and sleep maintenance insomnia for many years. Although she does not have the most common features of obstructive sleep apnea such as snoring, witnessed apneas or waking with a dry mouth, she does exhibit some features that are suggestive of sleep disordered breathing. The cyclic waking on a 2-hour schedule may represent REM related sleep apnea since REM cycles about every 1 and a half to 2 hours on average. Additionally the oral airway exam suggests the possibility of restricted airflow due to anatomic considerations as well.

She is an early riser and has a consistent morning wake time, features arguing against a circadian rhythm disorder. Another disorder low on the differential is narcolepsy. Although she describes fragmented sleep during the night, this is somewhat controlled with hypnotic medications. She does not have daytime sleepiness and does not feel the need to nap. The age of onset in the mid 30's and the lack of cataplexy or other associated features make narcolepsy unlikely.

The patient does not seem to be depressed or have post-traumatic stress disorder. Although these features may have been present in the past, she does not describe active conscious manifestations that are currently limiting her sleep.

A clear abnormality is the nocturnal eating that occurs while asleep. She believes that this was strongly correlated with the use of zolpidem, but acknowledged that it may have happened at other times. This may represent a sleep related eating disorder, although the effect of the medication must be considered as well. Due to this behavioral aspect occurring during sleep, it is possible that she may have another movement or behavioral disorder as well. The lack of injuries during sleep and the lack of vivid dreams lead one away from REM behavior disorder, but other parasomnias or movement disorders are possible.

She clearly relates the onset of the insomnia after the birth of her son. The sleep pattern was disrupted during this time, and never returned to a healthy pattern. It is likely that she has associated sleep, the bed and the bedroom with negative feelings about sleep, exacerbating anxiety about insomnia and the consequences of sleep deprivation. This is evidenced by her improved sleep when away from home. This presentation meets the criteria for psychophysiologic insomnia, a common condition often sparked by a disruption in the sleep schedule with subsequent conditioned sleep difficulty and a perpetuation of anxiety about sleep. The resulting insomnia may last for decades[1].

The differential diagnoses includes psycho-physiologic insomnia as the most likely, with other possibilities such as sleep related breathing disorder (particularly REM related) and parasomnia or movement disorder possible as well. Due to these possibilities, polysomnography was ordered.

The patient completed a polysomnogram. She took trazadone and alprazolam that night to ensure that she slept. Her Epworth Sleepiness Scale was 5 (normal range). The sleep study showed a sleep latency (time to fall asleep) of 13 minutes and a sleep efficiency of 90%. The apnea-hypopnea index (AHI) was only 2/ hour, and the REM-related AHI was 5/hr. There were a total of 10 hypopneas during the entire night. The respiratory disturbance index (RDI) measured only 9/hr. events per hour. There periodic limb movements during sleep (PLMS) was 53/hr with an associasted PLMS arousal index of 14/hr.

While reviewing the sleep study report with the patient, she reflected about the questions regarding periodic limb movements. She reports that for many years prior to going to sleep, she would move her ankles and legs in bed in a writhing motion. He husband often brought this to her attention. She would perform these motions without thinking about it much, but without the movement she would be uncomfortable. She often gets out of bed to walk and move around, after which the need to move her legs in bed subsides. In re-discussing her recent trip, she felt that the increase in daily activity and walking may have decreased this limb sensation at night, leading to better sleep. Based on this information, the patient was diagnosed with primary Willis-Ekbom syndrome with PLMS Disorder.

Primary Willis-Ekbom syndrome with Periodic Limb Movement Disorder

The nomenclature has recently been revised and the entity known as Restless Legs Syndrome is now referred to as Willis-Ekbom Disease. The name change was recommended by the Restless Legs Syndrome Foundation, now the Willis-Ekbom

Disease Foundation, in an effort to honor the original descriptors of the process.

Willis-Ekbom Disease (WED) is a clinical diagnosis based on four factors: 1) an uncomfortable sensation leading to an urge to move the legs; 2) the process begins or worsens at rest; 3) the process worsens or occurs exclusively at night; and 4) the sensation is partially or completely alleviated by movement. Severe conditions can lead to a total sleep time of less than 5 hours per night with daytime adverse consequences of decreased energy, depression, and anxiety[1]. WED traditionally has been estimated to have a prevalence of about 5% in a Northern European population, but only about 1% reported in a Korean population[2]. Women manifest Willis-Ekbom about twice as commonly as men. More than 50% of patients with primary Willis-Ekbom report a family history and the risk in a first-degree relative is 3 to 6 times greater than the general population[1]. COPD patients have a 3 to 4 times greater risk of WED than the general population[3]. Type 2 diabetic patients were reported having a 17% prevalence of WED with neuropathy being a contributing factor[4]. Patients with liver disease also had an elevated risk by self-report[5]. Depression is associated with WED but causality is not established[6]. Pregnant women have been found to have a prevalence of 20%[7] and the elevation of estradiol appears to be a mechanistic factor[8]. A recent review of the Tucson cohort of the Sleep Heart Health Study confirmed prevalence in a Caucasian population of 4.1 to 7.7% and supplemental estrogen use and COPD were identified as independent risk factors[9]. Medications such as olanzapine have also been implicated in the development or exacerbation of WED[10]. Onset of WED may occur at any age, but those presenting before age 45 often have intermittent symptoms that worsen over time. The symptoms usually start in the legs but sometimes begin in the ankles or feet first. The symptoms may progress over time, and although the severity can vary substantially, sedentary activities may precipitate the symptoms[1].

The pathophysiology of Willis-Ekbom involves the dopaminergic neurotransmitter pathways and the co-factor iron is particularly important. The role of dopamine remains incompletely identified, and the strongest evidence for its role stems from pharmacologic studies and the clinical efficacy of dopamine agonists in reducing or eliminating the symptoms[1]. Conversely, dopamine antagonists may exacerbate or even elicit symptoms of Willis-Ekbom. Nevertheless, imaging and CSF studies have not provided conclusive evidence regarding the nature of the dopamine abnormality[11]. Iron, specifically neurologic iron deficiency, appears to be a significant factor in primary Willis-Ekbom. Both MRI and CSF studies have shown iron deficient states in the CNS[12]. Postmortem studies have shown reduced iron transporters and reduced or abnormally distributed ferritin in the substantia nigra. Studies of iron metabolism in lymphocytes have shown abnormal metabolic pathways in WED patients compared to controls[13]. Patients with ferritin levels less than 50, even without the other laboratory findings of iron deficiency, reported reduced symptoms with iron supplementation. Intravenous iron at doses of 200 to 1000 milligrams can induce remission of symptoms for months in primary Willis-Ekbom[1].

Periodic limb movements during sleep occur in at least 80% of patients with Willis-Ekbom. Periodic limb movements during wakefulness (PLMW) may be noted at the transition to sleep, disturbing the smooth transition and leading to sleep onset insomnia. PLMW may be noted during time awake on a nocturnal polysomnogram or during a Suggested Immobilization Test (SIT), a one hour polysomnogram recording performed just before the usual bedtime with the patient sitting in bed in the upright position with legs stretched out on the bed. PLMS can be determined by the traditional polysomnogram overnight study. The periodic movements are defined as 0.5 to 5 seconds in duration with a sequence of 4 or more movements that are separated by at least 5 seconds but no more than 90 seconds between movements. The usual interval is 20 to 40 seconds spacing between the movements, and these phenomena occur during non-REM sleep. In adults, a frequency of 15 PLMS per hour is considered abnormal. The PLMS arousal index specifies the association of EEG evidence of cortical activity signifying an arousal with the PLMS event. Some patients with high PLMS indices may experience daytime fatigue and insomnia without documented cortical arousals, and in some of those patients the clinical significance of the PLMS may be operative, even without documentation of cortical activity changes. Another measure of the clinical impact of PLMS is autonomic arousals, identified by HR, BP or pulse transit time measures. These arousals may also contribute to sleep disruption and poor quality sleep, but may be more difficult to quantify on the polysomnogram. Evidence suggests that the sympathetic overactivity in both PLMD and WED may predispose patients to hypertension, heart disease and stroke[14].

Clinically, patients are usually unaware of these movements. The movements are often partial flexion of the hip, knee, or ankle with extension of the toe and may not lead to significant disruption of bed

covers or the bed partner's sleep. PLMS may occur secondary to the cortical activation of sleep related breathing disorders (SRBD), so exclusion or treatment of SRBD is necessary before consider PLMS to be the causative factor in sleep disruption. PLMS alone leading to symptomatic sleep disruption is considered to be relatively uncommon, but have been reported in up to 15% of insomniacs. PLMS is most often associated with Willis-Ekbom, but has also been described in REM behavior disorder and in narcolepsy. Interestingly for our patient, PLMS has also been described in conjunction with Sleep Related Eating Disorder, and both entities, when co-existing, respond to dopaminergic therapy.

Treatment

The mainstay of treatment for Willis-Ekbom with PLMD is generally dopaminergic therapy unless the iron stores are low based on serum ferritin. Iron replacement may be considered as monotherapy in the event of a ferritin less than 50. Dopaminergic therapy is regarded as first line in WED[15]. The main adverse effects of dopaminergic medications are impulse control behaviors, nausea, sedation, and augmentation (increase in symptoms often occurring earlier in the day). Another option is gabapentin enacarbil (a different formulation that generic gabapentin) with efficacy being demonstrated in 3 short-term trials. The main side effect is sedation and dizziness, but this can be significant for some patients[15]. Other treatments include chronic opioids and benzodiazepines, but the long term use of these medications may pose greater difficulties for many patients.

In our patient, we discussed the polysomnogram data in detail. The discussion addressed the possibility that a sleep related breathing disorder could still be operative. The AHI of 2/hr is within the normal range, but the REM AHI of 5/hr may be borderline. Since PLMS can be elicited by the neurologic activation of respiratory airflow limitation, the possibility of a sleep related breathing disorder must always be considered strongly. In this case, the frequency of PLMS was far in excess of respiratory events and in reviewing the data, the PLMS that were identified were independent of airflow limitation. Therefore, the patient was started on dopaminergic therapy. Her ferritin level was over 100 so iron therapy was not considered. She developed agitation and irritability on the dopamine agonist therapy, so she was changed to gabapentin enacabril. She developed nausea after increasing to a therapeutic dose and discontinued treatment. She also started a regular exercise program in the afternoons with mild improvement in her symptoms.

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