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Case report

Excessive daytime sleepiness with multi-factorial etiologies: a case report and brief review of literature

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Abstract

A 42-year-old hypertensive diabetic white female with a history of excessive daytime sleepiness (EDS), snoring, and obesity exhibits several risk factors for the obstructive sleep apnea syndrome. In addition, the patient has periodic leg movements in sleep and central sleep apnea. Renal insufficiency, with raised blood urea nitrogen, likely made a contribution to the EDS.

Background

While the combination of excessive daytime sleepiness (EDS), snoring, a narrow oropharynx, and obesity are increasingly found to be associated with male dominated obstructive sleep apnea (OSA), this same constellation of clinical features can also induce OSA in females. Hypertension (HTN) is often noted in OSA patients of both sexes. Nocturnal polysomnography (PSG), daytime multiple sleep latency testing (MSLT), and the determination of concomitant medical, neurological and/or psychiatric disorders are required in evaluating these patients. Forme fruste or full blown narcolepsy, central sleep apnea (CSA), hypoventilatory syndromes and movement disorders disrupting sleep can further impact upon an EDS problem discovered in an OSA patient.

Case presentation (part I)

A 42-year-old white female presents with a history of daytime sleepiness since her teens. The patient describes falling asleep while driving, inability to stay awake during any movie she attends and frequent spells of "daydreaming" that interrupt her concentration in all situations. The patient also describes the following:

- A 10 year history of HTN and type 2 diabetes for which she takes a diuretic and an oral hypoglycemic (no other meds).
- A 20 year history of obesity.
- A family history of excessive sleepiness (her parents and only sibling).
- A history of loud snoring (also noted in both parents and brother).
- A history of insomnia over the past five years manifested by inability to return to sleep after nocturnal awakenings.
- A history of nocturnal leg jerking without leg discomfort or restlessness at any time (noted by two bed partners in last decade).
- A history of chronic 2-3 cups/day coffee drinking but no major changes in amounts (no alcohol or other drug use).
- A history of fatigue and depression (related to her increasing weight which has made her very tearful).
- A history of a recent head injury (bumped her head exiting her car without loss of consciousness).
- A history of general muscle weakness (associated with her tiredness, particularly late in the day).

Discussion (part I)

This is a case packed with commonly noted historical data to explain EDS such that one is hard pressed to eliminate what is important and what is not in terms of the somnolence complaint.

Distinguishing between sleepiness and fatigue is often difficult historically (1,2). In fact, it is a critical distinction to make. The differential diagnosis for fatigue would be at least as long as the thousands of chronic diseases seen in man. However, true EDS is a label that is given only to those fulfilling certain

criteria by questionnaire and via polysomnographically derived MSLT (3).

So given the history of frequent inappropriate sleep attacks that have become socially debilitating, let us assume that the patient has true EDS.

This patient's array of problems argues for a checklist approach as related to risk factors for EDS. Here are some initial historical considerations:

HTN: Medication for HTN can cause EDS, particularly those that are lipid soluble and can act to depress mood and respiration such as the beta-blockers. The patient however is on diuretic medication only. However, HTN is independently associated with stroke risk, which can induce impairment in nocturnal respirations, which in turn can induce poor quality nocturnal sleep and EDS (4). HTN is also linked to snoring and obstructive sleep apnea, both linked to EDS (1).

Diabetes: Diabetes can be associated with EDS via brain edema issues related to hyperosmolarity. Diabetes is also independently linked to OSA and therefore EDS (5-7).

Obesity: Numerous studies on obesity-sleepiness-respiratory issues have been compiled over decades. The Pickwickian syndrome and CSA can occasionally be seen in the obese and in turn can be linked to EDS (8-11). The mechanism involves abnormal response to low CO2 levels particularly at night inducing apneic breathing and impaired depth of sleep leading to daytime sleepiness.

Loud snoring: This complaint, in the category of sleep disordered breathing, is extraordinarily common and is independently associated with HTN and stroke (12). However, the combination of loud snoring and obesity is particularly associated with OSA, the leading cause of excessive daytime sleepiness (1).

Insomnia: Sleep lack at night can induce EDS (13). In this case, the patient describes a disorder of maintaining sleep, not initiating it.

Stimulant history: Chronic use of caffeine, amphetamines, or alerting drugs such as modafinil and then cessation of these agents can induce EDS.

Fatigue/depression: This combination is extremely common and can be associated with hypothyroidism, collagen vascular disease, systemic cancer, brain tumor, chronic fatigue syndrome, fibromyalgia, or long standing infection such as TB (12). However, the most common fatigue/depression etiology would be clinical depression and the tiredness so often related to it. These concomitant complaints are not typically linked to EDS. Idiopathic hypersomnia can be linked to more general complaints of fatigue and sadness (14).

Head injury: This finding in the history can be tied to hypersomnolence, either by way of a post-concussion syndrome or the induction of a brain intra- or extra-axial hemorrhage.

Muscle weakness: Fatigue of muscles could be part of a dystrophy which in turn can be tied to hypotonicity of pharyngeal musculature (increasingly seen in the elderly) and OSA (15). However, muscle weakness associated with a disorder such as myasthenia gravis or multiple sclerosis is not commonly linked to OSA/EDS though both have some association with OSA (16, 17); even diffuse muscle fatigue does not connote EDS.

Case presentation (part II - physical exam)

Vital signs: BP 150/98; pulse 88 irregular; respiration rate 12/min; temperature 98.6°F

Highlights of general physical and neurological exam:

- Obese 5'7", 279 lbs.
- 2+ leg edema, clear chest, no murmurs.
- Narrow oropharynx, atrophic tonsils, short fat neck, Mallampati Score III.
- Falls asleep during interview and reports formed visual hallucination on being awakened.
- Short term memory and poor attention.
- Diffuse hyporeflexia, otherwise no nervous system abnormalities.
- No cataplexy.

Discussion (part II)

The broad differential reviewed initially does not appear to be much narrower after the physical examination. This would appear to be an obese hypertensive female with physical stigmata for OSA. The patient reveals a crowded or narrow oropharnx based upon a Mallampati score of III. This rating scale is used for assessing intubation difficulty and can be applied to the initial evaluation of any sleep apnea patient. (18) She may have atrial fibrillation and a variety of causes for leg edema including right heart failure or some kind of oncotic pressure problem.

Although the patient does not have cataplexy on this exam, she could have narcolepsy (19) as her sleepiness history extends into her adolescence. Her

family history of sleepiness is of note, but could this could also be a feature of sleep apnea in anatomically predisposed family members. In this patient, a rapid eye movement (REM) sleep attack with presumed dream related imagery (i.e., a hypnopompic hallucination) (20) was noted. This is classic for narcolepsy but does not rule out OSA which could be present in this obese patient with loud snoring and a congenitally narrow oropharynx complicated by fat accumulation in the region. REM sleep can be diminished in OSA and a sleep attack induced REM intrusion can be what was noted here (21). The obesity could also be linked to concurrent primary hypoventilation and CSA, the latter condition being increasingly noted with atrial fibrillation (22).

Hydrocephalus can also be tied to OSA or CSA (23). The question arises as to the cause of the abnormal mental status. The clinical surmise is that it represents a depressed level of consciousness due to the sleepiness. Could this patient have systemic disease, another CNS disorder, or both? The answer would be absolutely on both counts. The non-focality of the neurological exam does not rule out a brain mass. Sleep apnea can be linked to multi-system atrophy, olivopontocerebellar degeneration, myotonic dystrophy, or other neuromuscular disease such as Charcot Marie Tooth disease but there appears to be no evidence for any of these. There were no involuntary movements on exam, but that does not rule out such problems nocturnally. Dystonia and chorea rarely and limb myoclonus occasionally can be disruptive influences during sleep (24). The latter is often absent during wakefulness though in some, it can be associated with restless leg syndrome (25). Also lurking in one's mind is the fear that the patient has a vasculopathy as part of her diabetes and HTN. Could occult cerebrovascular disease be inducing a sleep disorder? Relatively silent right hemispheric or brain stem strokes can induce neurogenically disordered breathing during sleep.

Final workup

CBC: normal

ESR: normal

ANA: negative

T3, T4: normal

SMA20: normal except fasting glucose of 254 (high) and albumin 3.2 (slightly low)

BUN: 89 (high)

Creatinine: 5.2 (high)

EKG: atrial fibrillation at around 90

ABG: normal

U/A: 3+ proteinuria

Brain MRI: normal

Nocturnal PSG (representative sample in Figure 1- see below the references) showing no airflow in channel labeled FLW with some preservation of chest (THO) and abdominal (ABD) muscles because of sustained respiratory effort): moderate OSA (30 apneas/hour); occasional CSA (5/hour); moderate oxygen desaturation; tachycardia/bradycardia associated with apneic events; periodic leg movements (PLM) (55/hour) with both legs associated with awakenings (PLM arousal index 15/hour); poor quality sleep with little stage 3-4 or REM sleep

Daytime MSLT: 1/5 nap opportunities yielded sleep onset REM (SOREM) attack; overall average latency to sleep is 5 minutes (normal at least 15 minutes)

Gene testing: no narcolepsy associated genes

Epworth sleepiness scale score (ESS): 15 (moderate sleepiness)

Final discussion

EDS is confirmed by the results of the MSLT and the ESS. This is extremely important in proving that the sleepiness complaint equals objective sleepiness. The normal brain MRI and ABG are also noteworthy. A structural brain lesion is ruled out. CO_2 narcosis as part of an obesity/hypoventilation syndrome is not apparent (11).

The presence of a hypnopompic hallucination does not by itself allow for a narcolepsy diagnosis. This patient does not have that disease based on MSLT criteria, although she has a REM sleep disturbance (i.e., the reported dream fragment) likely due to nocturnal REM suppression. Post-traumatic narcolepsy can occur without the typical narcolepsy gene association (26). Additional work-up for narcolepsy with CSF for decreased levels of hypocretin/orexin would be warranted in cases where MSLT results are equivocal and no other cause of EDS is apparent (27).

However, this patient has a cavalcade of common diseases that have induced EDS. Heading the list is the most likely cause for EDS, OSA. The combination of middle age, a narrow hypopharynx, and obesity in a hypertensive snoring patient is classic for OSA. Obese female patients can be at risk for both sleep apnea and hypoventilatory syndrome. Testosterone producing tumors in women have been associated

with sleep apnea induction; this is presumed to be due to increased collapsibility of the airway (28). However, this patient has not only OSA but a component of CSA which may be of genetic origin or associated with her significant obesity, atrial fibrillation, diabetes, and renal insufficiency. Sleep disrupting PLM (associated with both sleep apnea and narcolepsy) is also a factor in her EDS.

She may indeed have a protein wasting diabetic nephropathy complicated by her long standing HTN. Though the correlation with end stage renal disease/hemodialysis and sleep apnea/PLM in sleep is well established though incompletely understood (29-31), it has recently been shown that earlier chronic renal insufficiency is associated with sleep disruption and secondary EDS (32-36). The apneas and the PLM are both major contributors to this patient's poor quality nocturnal sleep that includes REM suppression (1, 37-40). Her renal dysfunction, particularly if the elevated BUN is chronic, is likely feeding into the hypersomnia problem through the induction of a urea mediated encephalopathy or as a trigger for the sleep disordered breathing/leg jerking. This raises another important issue. When a patient has a depressed level of consciousness inducing hypersomnolence, disorders such as uremia, hepatic shut-down, sepsis, drug/alcohol intoxication, and hyperosmolar states must be ruled out.

The good news for the patient is that she has many aspects of her EDS condition that are fully or partially reversible. These include her excessive weight, sleep debt related attentional/memory impairment, hyperglycemia, HTN, and presumably renal insufficiency. Improvement in all of these parameters could significantly decrease the sleep apnea syndrome severity. If we are to assume some permanent metabolic dysfunction, particularly obesity in the setting of oropharyngeal narrowing, nasal continuous positive airway pressure (CPAP) could be quite helpful for this patient's apnea and EDS. The PLM disorder can improve with better renal function, but may require clonazepam therapy at night.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

List of abbreviations

ABG - arterial blood gases

ANA - anti-nuclear antibody

BUN - blood urea nitrogen

CBC - complete blood count

CNS - central nervous system

CPAP - continuous positive airway pressure

CSA - central sleep apnea

EDS - excessive daytime sleepiness

EKG - electrocardiogram

ESR - erythrocyte sedimentation rate

ESS - Epworth sleepiness scale score

HTN - hypertension

MRI - magnetic resonance imaging

MSLT - multiple sleep latency testing

OSA - obstructive sleep apnea

PLM - periodic leg movements

PSG - polysomnography

REM - rapid eye movement

SMA20 - sequential multi-channel analysis with computer-20

SOREM - sleep onset rapid eye movement

T3 - triiodothyronine

T4 - thyroxine

TB - tuberculosis

U/A - urinalysis

Competing interests

The authors declare that they have no competing interests.

Author's contributions

SL and KG secured the case, conducted the literature review, and participated in the preparation of the manuscript. All authors read and approved the final manuscript.

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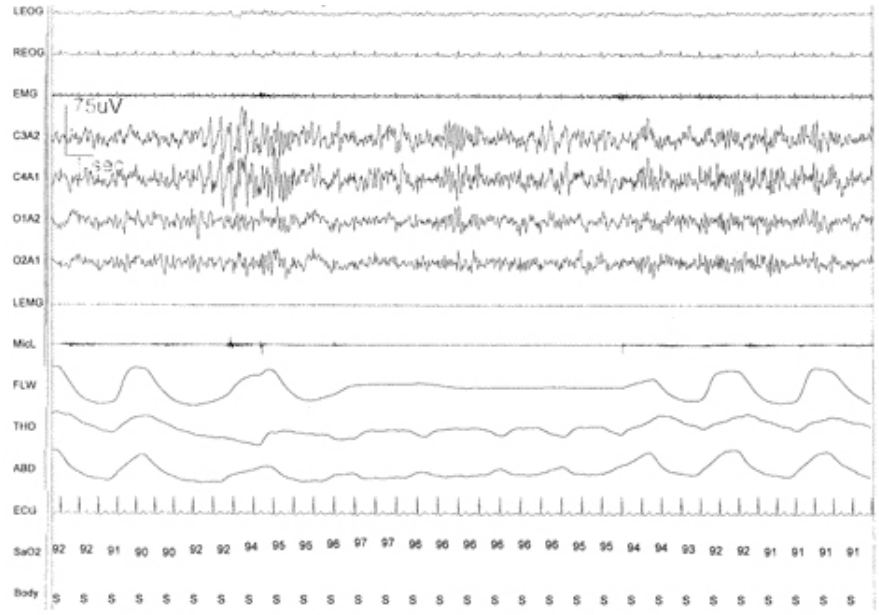
Figure 1. Nocturnal polysomnogram showing OSA event.



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