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SLEEP MEDICINE PEARLS

A Patient With Rapidly Progressing Early-Onset Dementia and Insomnia

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A 51-year-old woman presented with insomnia for 2 months and daytime sleepiness for 6 months. The patient attributed the insomnia to stress from recent life events. Her Epworth Sleepiness Scale score was 18 of 24. Observers of the patient reported loud snoring, apneas, kicking, and dream enactment. The patient had hyperhidrosis during sleep.

Family history was positive for hypertension and dementia. Social history excluded tobacco, alcohol, or illicit drug usage. Review of symptoms was significant for heart palpitations, headaches, and depression. The patient's medical history was negative with no medications.

Physical examination revealed a blood pressure of 140/90 and body mass index of 30.3 kg/m^2. The patient's Mallampati score was class IV. Physical examination was otherwise unremarkable. Neurological examination showed normal reflexes, gait, and intellect with good recent and remote memory recall.

Diagnostic polysomnography (PSG) showed apnea-hypopnea index, 84.4 events/h; periodic limb movement index, 10.7 events/h; reduced total sleep time (140 minutes); increased stage N1 sleep; and no stage N3 or R sleep. Minimum oxygen saturation was 80%. Sleep spindles were absent.

The patient refused an in-laboratory positive airway pressure (PAP) titration, and was placed on auto-adjusting PAP therapy for her severe obstructive sleep apnea.

At follow-up, 8 weeks after starting auto-adjusting PAP therapy, the patient demonstrated cognitive impairment not apparent on the original visit. She came with a family member who reported sudden onset and rapid worsening of the patient's cognition with new issues of confusion and disorientation. Short-term memory was poor, but long-term memory remained intact. Mini-Mental Status Examination yielded 2 out of 3 correct for recall. Hyperhidrosis was more prominent occurring during wakefulness hours as well as during sleep.

The patient's sleep-wake schedule was erratic with intermittent brief dozing day and night. Her sleep behaviors, such as dressing herself, combing her hair, and tying her shoes, were more complex. Initially dream enactment behaviors were simpler with calling out and sitting up in bed. She was unresponsive during these periods, amnestic for her actions in sleep, but awoke oriented. Despite efforts to use PAP, the patient would disassemble her interface while asleep. She reported horizontal diplopia, new-action tremor, and a 12-lb weight loss. Her pertinent vital signs were blood pressure 164/108 and heart rate 110 bpm. Comprehensive metabolic panel, thyroid function tests, urinalysis, and head computed tomography were unrevealing. Repeat PSG was attempted on continuous positive airway pressure with the patient demonstrating little sleep (**Table 1**).

QUESTION: What diagnosis should be considered in this patient and what additional history might be helpful?

Table 1—Baseline and follow-up PSG.

	Baseline PSG	Titration PSG 10 Weeks After Presentation
Total sleep time	140 minutes	16 minutes
Sleep efficiency	27%	4%
Stage N1 sleep	60.8%	100%
Stage N2 sleep	39.2%	0%
Stage N3 sleep	0%	0%
Stage R sleep	0%	0%
AHI	84.4	28.8
REM AHI	NA (no stage R sleep)	NA (no stage R sleep)
PLMI	10.7	0.0

AHI = apnea-hypopnea index, PLMI = periodic limb movement index, PSG = polysomnography.

ANSWER: Fatal familial insomnia should be considered. A thorough family history is essential to make the diagnosis.

DISCUSSION

This patient presented with daytime sleepiness, insomnia, sleep-disordered breathing, and abnormal sleep behaviors. PSG revealed severe sleep apnea and loss of sleep spindles; the patient was started on auto-adjusting PAP therapy. At follow-up, she had advanced symptoms of dementia with additional findings supporting fatal familial insomnia (FFI) including hypertension, tachycardia, and changes in sleep architecture (increased stage N1 sleep with no stage N3 and R sleep). A more detailed family history revealed her mother died at age 59 years after suffering with insomnia that progressed to no sleep, confusion, and hallucinations. One brother (age 43 years), one grandmother (age 46 years), and two uncles (ages 36 and 40 years) suffered similar clinical courses resulting in death within 12 months of symptom onset. Thus, a more detailed family history gave a clear story for insomnia, and altered mental status with rapid progression to death at a young age, which raised the possibility of FFI.

FFI is a prion disease with autosomal dominant inheritance of mutation in the prion gene *PRNP*.[1] Symptoms usually appear between ages 32 and 62 years with unrelenting insomnia, poor appetite, weight loss, temperature dysregulation, and dementia.[1] The initial symptom is sometimes dementia, not insomnia. Autonomic manifestations can include hyperventilation, hyperhidrosis, hypertension, tachycardia, and excessive drooling.[2] Our patient also presented with hyperhidrosis, loss of sleep spindles, and sleep-disordered breathing similar to signs and symptoms noted in the series by Wu et al.[3] With disease progression ataxia, hallucinations, delirium, and myoclonus may develop. Initial confusion and forgetfulness progress to aphasia or immobility with eventual total inability to sleep with end-stage FFI.[1] Additional supporting history includes a family history of unexplained dementia occurring at a young age.

Evaluation includes PSG and positron emission tomography (PET) scanning to confirm thalamic hypometabolism.[2,3] Genetic testing in the United States is available if 1 of 3 criteria are met (family history of FFI, abnormal PSG or PET scan with high suspicion for FFI, diagnosis of FFI by PSG and PET scan).[1] Genetic evaluation examines for a mutation at codon 178 on chromosome 20, resulting in an asparagine instead of aspartic acid combined with a methionine codon at position 129.

Currently there is no cure or effective treatment for FFI. The prognosis is poor, with death occurring in 12 to 72 months (range, a few months to several years).[2]

In our patient, a PET scan confirmed decreased thalamic activation. Genetic testing showed the D178N-129M mutated allele in the prion protein gene linked to FFI. The patient died 10 months after symptom onset. Her daughter (age 35 years), son (age 30 years), and cousin tested positive for the FFI gene.

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1. FFI can present as insomnia associated with rapidly worsening dementia.
2. A hallmark of FFI is a progressive change in sleep architecture (loss of sleep spindles and slow wave sleep) with eventual loss of distinct sleep stages, with progressive flattening of the electroencephalogram until death occurs.[2]
3. A family history of dementia occurring at an early age with a rapid course to death is suggestive of FFI. Patients who are methionine homozygous at the 129 codon present at an early age and have a rapid course.[2]
4. Comorbid sleep disorders such as obstructive sleep apnea may confuse the initial evaluation of FFI.

ABBREVIATIONS

AHI, apnea-hypopnea index
FFI, fatal familial insomnia
PAP, positive airway pressure
PET, positron emission tomography
PLMI, periodic limb movement index
REM, rapid eye movement

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DISCLOSURE STATEMENT

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