Part I

Sleep-related breathing disorders

Case 1

Opioid-induced central sleep apnea

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Clinical history and examination

A 42-year-old man presented for evaluation of frequent breathing pauses during sleep, which had been witnessed by his wife for 5 years along with intermittent mild snoring. He also reported excessive daytime sleepiness (EDS), but his Epworth Sleepiness Scale score was only 6/24 (see Appendix). He would wake up unrefreshed in the morning with a dry mouth. He also reported having had difficulties initiating and maintaining sleep for 10 years. He was treated with multiple medications with incomplete resolution of his insomnia. He was taking temazepam 7.5 mg to help him to maintain sleep.

He had been going to bed between 1 and 4 am and waking up between 12 and 2 pm. His sleep latency was less than 5 minutes and his average sleep time was 8–9 hours per night, but he reported three to four nocturnal awakenings with no known triggers. He had problems returning to sleep after these awakenings and usually spent his time reading. He would take one unintentional nap per day of around 60–90 minutes' duration and felt refreshed upon awakening. There were no symptoms suggestive of narcolepsy, parasomnias, leg kicking, restless legs syndrome (RLS), nightmares or post-traumatic stress disorder (PTSD). He denied having any motor vehicle accidents or near accidents related to somnolence.

His past medical history revealed depression and resection of a schwannoma abutting on the cervical spinal cord in 1992, leaving him with Brown–Séquard syndrome characterized by motor deficits on the left, leading to use of a cane, and pain and paresthesia on the right side of his body. He also remained with a partially paralyzed diaphragm.

His social history was negative for alcohol or other substance abuse, but he was an ex-smoker and he drank 12 cups of coffee per day. His medications included bupropion 150 mg BID, temazepam 7.5 mg QHS, docusate 50 mg TID PRN, baclofen 30 mg TID, pregabalin 200 mg BID, tramadol 100 mg TID and morphine

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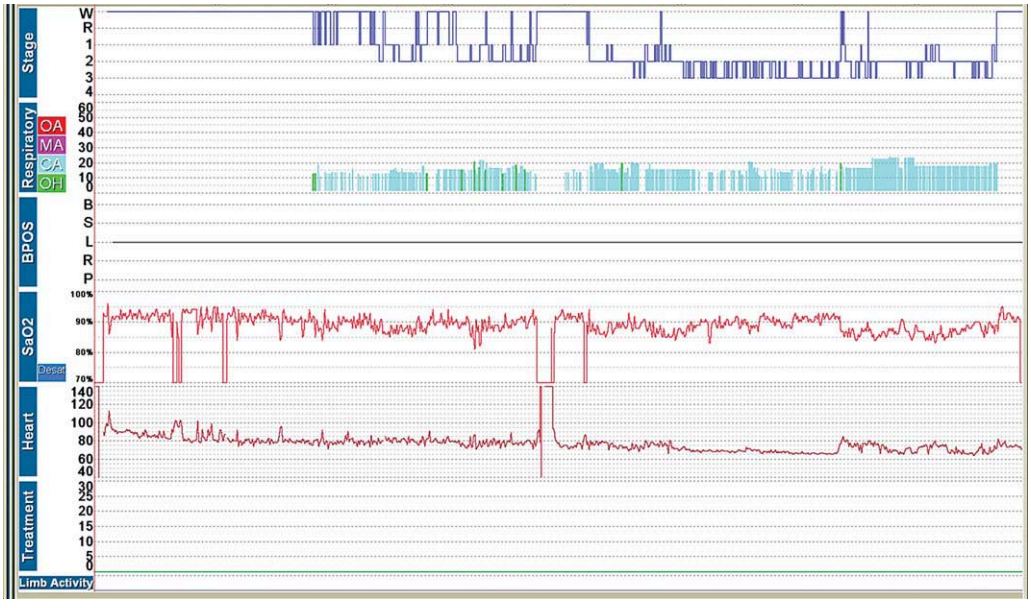

Figure 1.1 Sleep/wake hypnogram of the baseline PSG. Note the severity of central apnea. Central events were prevalent throughout the night (except in the wakefulness stage), with associated O_2 desaturation. OA, obstructive apneas; MA, mixed apneas; CA, central apneas; OH, obstructive hypopneas; BPOS, body position.

sulfate SR 60 mg TID. The patient had been maintained on narcotics for treatment of his chronic pain following the laminectomy, for a period of 8 years. He started with morphine for 3 years, was switched to oxycodone for a few years and then switched back to morphine 5 months prior to his current presentation to the sleep clinic. His family history was negative for obstructive sleep apnea (OSA), narcolepsy, RLS and other sleep disorders. The physical examination revealed a BMI of 18.8 kg/m^2 and an oropharyngeal Mallampati score of 2. He had decreased motor power in the left leg and mild foot drop, and had left arm flaccid paralysis and wrist drop. He was hyperreflexic on the left. He had no other pertinent physical findings.

Special studies and results

In view of his sleep respiratory symptoms, polysomnography (PSG) was performed (Figure 1.1). This revealed a delayed sleep onset (88 min), low sleep efficiency (60.3%) and 340 apneas with an apnea–hypopnea index (AHI) of 89.6 per hour and a central apnea index of 86.8 per hour (Table 1.1). A continuous positive airway pressure (CPAP) titration was scheduled and, after having a discussion with the patient about the potential effects of his medication on

Table 1.1 Summary of the baseline PSG results

Sleep architecture	
Time in bed (min)	390
TST (min)	235
Sleep efficiency (%)	60.3
WASO (min)	58.5
Sleep latency (min)	88
REM sleep latency (min)	N/A
TST supine (min, %)	0 (0)
STAGING	
Stage N1 (min, %)	39 (16.6)
Stage N2 (min, %)	142.5 (60.6)
Stage N3 (min, %)	53.5 (22.8)
Stage REM (min, %)	0 (0)
Respiratory parameters	
Total apneas (no.)	340
Obstructive apneas (no.)	0
Central apneas (no.)	340
Hypopneas (no.)	11
AHI (/h)	89.6
Central apnea index (/h)	86.8
Lowest SaO_2 (%)	81
Waking SaO_2 (%)	91–96

Note: TST, total sleep time; WASO, wake after sleep onset; REM, rapid eye movement; N/A, not applicable; AHI, apnea–hypopnea index.

the results of the obtained sleep study, morphine sulfate was discontinued for 3 months prior to the CPAP titration. A CPAP pressure of 6 cmH_2O resulted in complete resolution of the sleep-disordered breathing and improved his sleep morphology (Table 1.2, Figure 1.2).

Question

Why does this patient have central sleep apnea?

General remarks

This case is a good example of opioid-induced central sleep apnea. During the last decade, there has been a marked increase in opioid use following the release of a joint statement from the American Academy of Pain Medicine and the American

Table 1.2 Summary of the CPAP titration results

Sleep architecture	
Time in bed (min)	424.5
TST (min)	302
Sleep efficiency (%)	71.1
WASO (min)	19.5
Sleep latency (min)	103
REM sleep latency (min)	138.5
TST supine (min, %)	0 (0)
STAGING	
Stage N1 (min, %)	16 (5.3)
Stage N2 (min, %)	250 (82.8)
Stage N3 (min, %)	28 (9.3)
Stage REM (min, %)	8 (2.6)
Respiratory parameters	
Total apneas (no.)	0
Obstructive apneas (no.)	0
Central apneas (no.)	0
Hypopneas (no.)	2
AHI (/h)	0.4
Central apnea index (/h)	0
Waking SaO_2 (%)	93–96
Lowest SaO_2 (%)	90% (in NREM)

Note: TST, total sleep time; WASO, wake after sleep onset; REM, rapid eye movement; AHI, apnea–hypopnea index; NREM, non-rapid eye movement.

Pain Society in 1997, which advocated the aggressive use of opioids. This has been accompanied by recognition of the undertreatment of pain and the adoption of pain as another vital sign alongside temperature, heart rate, blood pressure and respiration. Indeed, pain units have now become commonplace in academic centers and community hospitals alike.

Opioid receptors are located in various areas of the brain but particularly in the brainstem where they are found in or around respiratory centers such as the medullary pattern generators and the nucleus of the tractus solitarius. There are three types of opioid receptors: mu, delta and kappa. Most of the opioid medications used for pain control target the mu receptors and these receptors have an inhibitory effect on breathing rate and amplitude.

Although the effects of opioids on waking respiration have long been recognized, awareness of their effects on respiration during sleep is a relatively recent development. Wang *et al.* (2005) studied a group of 50 patients on methadone

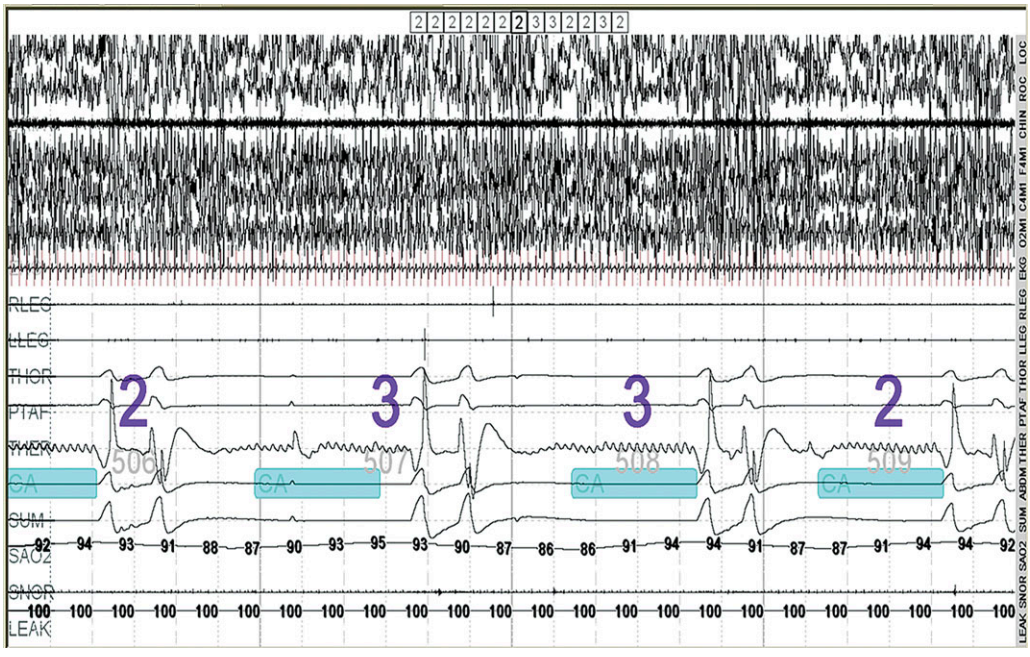

Figure 1.2 A 120-second segment from the patient's PSG study showing a sample of central apneas in stage N2 and N3 sleep associated with significant desaturation. LOC and ROC are left and right electro-oculographic tracings, respectively. Chin EMG is the surface chin electromyographic tracing. F4M1, C4M1 and O2M1 are the right frontal, central and occipital electroencephalographic tracings, respectively. ECG is an electrocardiographic tracing. Airflow tracings by nasal pressure and thermistor are depicted as PTAF and THER, respectively; thorax (THOR) and abdominal (ABDM) movements are also shown along with a pulse oximetry (SAO_2) tracing.

(a mu agonist) maintenance treatment (MMT) and compared them with 20 matched control individuals. Thirty percent of the MMT group and none of the controls had central sleep apnea (CSA), defined as an index of 5 or more events per hour (20% had 10 or more). The obstructive sleep AHI was not different between the two groups. Wang *et al.* (2005) hypothesized that the risk for CSA in the MMT patients was due to an imbalance between central and peripheral chemoreceptors, the former being depressed while the latter were relatively enhanced. This "imbalance" favored the development of CSA because the stimulation of breathing by mild hypoxia will periodically drive CO_2 below the apnea threshold.

Reports of opioid-induced sleep-breathing disorders in populations other than MMT patients have also appeared. Farney *et al.* (2003) described different types of sleep-breathing abnormalities in chronic opioid users including CSA, "ataxic

breathing" and sustained hypoxemia. Three patients were symptomatic with fatigue, excessive daytime sleepiness (EDS), sleep disruption and snoring. A larger group of 60 patients who were chronic opioid users was reported retrospectively by Walker *et al.* (2007) and compared with 60 control patients not on opioids. Again, the opioid group had a higher AHI than the controls, almost entirely due to central apneas. The AHI in the opioid subjects was correlated to the morphine equivalent dose and was inversely correlated to the BMI. Of note is that ataxic respiration during sleep was common in the opioid group. Mogri *et al.* (2008) extended the finding of sleep-related CSA to three patients with acute opioid ingestion for relief of non-cancer-related pain. Finally, in a large number of patients attending a pain clinic who had received opioids for 6 months or more, 147 underwent PSG: 24% had CSA, another 8% had CSA together with OSA and 37% had OSA alone. Webster *et al.* (2008) also found a dose–response relationship with CSA, similar to other authors. Thus, these opioid users were similar to MMT patients as far as their sleep-breathing parameters were concerned.

Central sleep apnea is not a common finding in the general population, but nevertheless, several types are recognized besides that induced by opioids. The least common is spontaneous idiopathic CSA, first reported by Guilleminault *et al.* (1973). More common are episodes of CSA that occur at sleep onset in some individuals because of transient fluctuations in the state of consciousness leading to brief arousals accompanied by relative hyperventilation due to CO_2 chemosensitivity. When the subject dozes off, CO_2 levels rise and O_2 levels fall, leading to the arousals that drive the CO_2 levels below the apnea threshold when the subject falls asleep again. The process continues until deeper sleep is attained and no further arousals take place. Finally, there is high-altitude sleep-breathing disturbance characterized by stimulation of overbreathing by hypoxemia and the occurrence of CSA when the apnea threshold is breached. The one factor that these examples of CSA have in common is the importance of the apnea threshold in triggering CSA.

Another form of CSA that has received much attention in recent years is Cheyne–Stokes respiration (CSR). The apnea threshold is also most important in the initiation and persistence of this condition, but it differs from other types of CSA in its phenotypical crescendo–decrescendo manner of breathing following central apneas. Cheyne–Stokes respiration is often associated with congestive heart failure and, when present, there is a higher mortality rate compared with matched heart failure controls with similar ejection fractions. Cheyne–Stokes respiration is also commonly found in patients with supratentorial stroke – in one series, it was present in 50% of patients. However, it is unknown whether it affects the mortality risk in these patients as it does in congestive heart failure.

Several features of our patient are representative of opioid-induced CSA as reported in the literature. One is the patient's BMI (18.8 kg/m^2). The great majority of patients with OSA are overweight or obese; in fact, this is probably the most important risk factor for OSA. On the other hand, several authors have highlighted the opposite trend for opioid-induced CSA (and other forms of CSA); in fact, AHI in CSA seems to be *inversely* proportional to BMI. The reason for this paradoxical association has not been explained in the literature, but one can speculate that there might be an enhancement of peripheral chemosensitivity in thin individuals.

Sleep architecture in opioid users is usually abnormal and, in contrast to patients with OSA, opioid-associated CSA is predominant in NREM sleep whereas obstructive apneas are most often worse during REM sleep. The patient described here had no REM sleep and, consequently, all his respiratory events occurred during NREM sleep. Breathing during NREM sleep (particularly delta sleep, also termed stage N3) is controlled by the metabolic mode of respiration, i.e. blood gases and pH; on the other hand, breathing during REM sleep is largely governed by the "behavioral" mode in which the medullary respiratory centers are under the influence of fibers from higher levels of the brainstem and certain areas of the cerebral cortex. At the same time, the ventilatory responses to CO_2, and to a lesser extent O_2, are depressed in dogs especially, but also in humans, during REM sleep. Other variables, such as those related to the upper airway, are also involved in explaining the dominance of REM sleep in obstructive apneas.

There are no data regarding the outcome of opioid-induced CSA after discontinuation of the offending medication. The patient stopped his morphine 3 months prior to the second PSG study, which was carried out with CPAP, and it can be argued that CPAP was responsible for the improved breathing during sleep.

The management of patients with CSA of whatever cause is uncertain. A number of therapies have been suggested. CPAP was advocated for CSA in the 1980s, only several years following its introduction for the treatment of OSA. The effectiveness of CPAP might be via its role in preventing overbreathing and reduction of CO_2. Another possibility might be stimulation of mechanoreceptors in the upper airway. CPAP has also been investigated as an adjunctive therapy for CSR in congestive heart failure, most notably in the Canadian Positive Airway Pressure study (CANPAP; Bradley *et al.*, 2005).

The trials of pharmacological therapies for CSA have been more variable and less successful. Drugs that have been tried have included theophylline, acetazolamide, serotonergic medications and medroxyprogesterone. The rationale for the use of these drugs differs according to the drug: acetazolamide induces metabolic acidosis, thus stimulating respiratory drive; theophylline inhibits adenosine

receptors; medroxyprogesterone stimulates respiration; and clomipramine, a serotonergic uptake inhibitor, is one of a number of serotonergic agonists and antagonists tested for their effects on sleep-related breathing. With the exception of acetazolamide, studies of these medications on CSA have not been encouraging. There is more positive evidence in favor of the use of O_2 in CSA, however. It probably works by eliminating the hyperventilatory response to hypoxia, thus preventing CO_2 from being driven below the apnea threshold. The addition of CO_2 would act in a similar vein, but its administration is less feasible than that of O_2.

Pearls and gold

Non-obstructive forms of sleep-disordered breathing are less common than the obstructive variety. They include upper-airway resistance syndrome, obesity–hypoventilation syndrome, CSR, high-altitude sleep-breathing disorder and CSA, both idiopathic and opioid-induced.

Opioid-induced CSA has attracted attention in recent years because of the surge in opioid administration to patients with pain.

Contrary to OSA subjects, patients with CSA tend to have a low BMI.

SUGGESTED READING

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Case 2

Fourteen-year-old with sleep-disordered breathing and excessive daytime sleepiness

Leslie H. Boyce

Clinical history

CF was a 14-year-old young woman who, according to her parents, has had problems sleeping for several years. They reported that at night she would periodically stop breathing and then resume with a loud snorting sound. This would occur multiple times at night and the family felt the need to reposition the child on her side to improve her breathing. She had excessive daytime sleepiness (EDS), and several times a week fell asleep in class. She got into bed at 10–10.30 pm, fell asleep immediately and woke at 7 am. She did not complain of fragmented nocturnal sleep. Occasionally she napped during the afternoon. There were no symptoms consistent with cataplexy, no loss of tone with emotional stimuli and no sleep-onset paralysis or hypnagogic or hypnopompic hallucinations. She reported that her legs occasionally hurt and it helped to move about, but this manifestation was not worse in the evening. There was no history of nocturnal stereotypical movements, sleepwalking or sleeptalking.

Past medical history was notable for preterm birth at 28 weeks' gestation with a birthweight of 4 lbs; birth was via cesarean section secondary to premature rupture of the membrane. She required ventilatory support for less than 24 hours and remained in the hospital for 10 days with some initial feeding difficulties, but was discharged home with no further problems. No other significant medical conditions were present, and her motor and language developments were normal. She had been diagnosed with dyslexia and language-based learning disability, but was able to perform well in school with additional time. There were no symptoms suggestive of attentional deficits or hyperactivity.

The family history was notable for an 11-year-old brother with occasional nocturnal enuresis, and both parents snored but neither had been evaluated for sleep apnea. There was no history of parasomnias, restless legs syndrome (RLS) or neurological disorders. Her parents were divorced and she lived with her mother.

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