CASE BASED DISCUSSIONS

A case of behavioural hyperventilation associated with severe central sleep apnoea and follow-up management

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YL (Junior Doctor): A 36-year-old man was observed by his wife to have irregular breathing with sighs followed by recurrent episodes of prolonged breathing cessation while falling asleep. The longest witnessed pause lasted approximately 3 min and during this time his lips became cyanotic. The patient was unaware of these episodes until his wife informed him. No wheezing, stridor, cough, gurgle or vomiting was observed during these episodes. A detailed interview revealed that the patient had a history of obstructive sleep apnoea and inferior turbinate hypertrophy and had undergone an electrocoagulation operation on the inferior right turbinate 2 years prior. Around 6 months after the operation, the patient became chronically congested and acquired a habit of laboured respiration through his nose. He also reported bloating and eructation linked to the severity of choking while falling asleep. Fiberoptic nasopharyngolaryngoscopy showed deviation of the nasal septum and mild inferior turbinate hypertrophy, and without evidence of reflux or laryngeal dysfunction.

RR, YS and KZ (Junior Doctors): Two consecutive overnight diagnostic polysomnograms followed by a standard multiple sleep latency test (MSLT) on the third day, as well as simultaneous transcutaneous pCO_2 ($TcpCO_2$) monitoring showed that the patient's respiratory rate increased to 27–35 breaths/min resulting in a decrease of $TcpCO_2$ to 25–27 mm Hg during resting wakefulness (table 1) and subsequent transitions to non-rapid eye movement (NREM) sleep were associated with multiple central sleep apnoea (CSA) events (see online supplement figure S1A). The longest duration of CSA during the initial sleep period was 3 min. However, respiratory rate returned to 14–17 breaths/min and $TcpCO_2$ was 41–43 mm Hg during stabilised stage 2 NREM sleep, during which times no CSA episodes were observed. Other sleep values were shown in table 1. Arterial blood gas assessment during daytime wakefulness revealed pH of 7.47, pO_2 of 93 mm Hg and pCO_2 of 28.1 mm Hg, with alveolar–arterial O_2 gradient (A–a O_2 gradient) was 22 mm Hg.

A pulmonary function test showed that FEV_1/FVC was 80%, maximal voluntary ventilation was 154.0 L/min, minute volume was 13.3 L/min and ventilation reserve (VR) % was 91.4%, which indicated a marginal reduction in ventilatory reserve and hyperventilation. Methacholine challenge test was negative. A further chest X-ray scan did not show evidence of COPD, emphysema or cystic fibrosis. In this case, we speculated that the patient's marginal reduction in ventilatory reserve was associated with hyperventilation. Physical examination, laboratory tests (including complete blood cell count, electrocardiography, and head CT scan) did not show evidence of organic cardiovascular or brain diseases. Mental examination by two senior psychiatrists did not find anxiety, depression or panic disorder. The patient had a temperature of 36.8°C, pulse of 68 bpm and BMI of 21.11 kg/m^2. In addition, the patient lived at an altitude of 200 m, and with no history of head trauma or substance abuse or dependence.

YL: Based on systematic interview and examinations, irregular breathing with sighs followed by episodes of breathing cessation while falling asleep was associated with multiple CSA events which were due to behavioural hyperventilation.

Given a diagnosis of behavioural hyperventilation-related CSA, four different treatments were administrated successively (table 1). During the therapeutic process, each follow-up consisted of two consecutive overnight polysomnography followed by third day MSLT and pCO_2 assessments in the sleep laboratory.

Respiratory dead space therapy[1] was first administrated 15 min before light-off and until the first 45 min after sleep onset. Though respiratory dead space therapy has been shown to have a significant effect on decreasing apnoea/hypopnoea index compared with room air, there was no significant improvement of breathing irregularity while falling asleep or the severity of CSA in our patient (table 1). The ineffectiveness may have been due to insufficiency of the dead space apparatus used (mask: 5×3.6 cm and tube: diameter 2 cm, length 80 cm) considering that hypocapnia persisted.

The patient was then prescribed zolpidem[1] at a maximum dose of 10 mg before sleep for 32 days. At the 2nd, 22nd and 32nd day of therapy, follow-up testing was performed (table 1). Episodes of sigh followed by breathing cessation reduced while falling asleep and the severity of CSA improved, however, the therapeutic effect was unstable and severe paradoxical breathing was observed.

Oral lorazepam 0.5 mg for three times per day was then administrated for 30 days. At the 2nd, 12th and 30th day, follow-up testing was performed (table 1). Episodes of sigh followed by breathing cessation were infrequently observed

Table 1 Sleep and respiratory-related physiological variables

Intervention	Diagnostic		Dead space	Zolpidem			Lorazepam			Washout	Duloxetine		Duloxetine and CPAP		
Timeline (day within intervention)	1	2	1	2	22	32	2	12	30	14	22	35	2	40	150
Sleep characteristics															
AHI (h)	30.4	11.1	14.3	8.0	22.2	9.5	10.8	7.5	9.4	14.0	17.7	31.5	4.8	3.0	2.2
CA (n)	23	18	22	3	15	11	8	6	7	17	7	15	13	8	3
Longest CA (s)	171.0	184.0	111.0	71.5	68.0	168.0	82.0	72.0	72.0	120.5	56.0	40.0	98.5	49.0	23.0
OA (n)	85	20	24	19	18	19	20	15	19	45	51	88	1	5	3
Hypopnoea (n)	29	28	27	37	115	47	46	25	41	36	86	131	12	3	4
AI (s)	39.3	45.5	38.3	31.6	30.9	51.6	35.0	31.3	33.6	39.2	25.0	24.7	29.4	17.1	18.2
CL (s)	49.3	54.4	42.2	40.1	44.6	64.0	48.4	39.0	41.5	48.7	33.1	35.2	38.9	24.4	25.4
Min SaO_2 (%)	32	62	69	81	71	43	67	61	61	58	71	80	79	86	88
Snore (% of TST)	30.6	5.0	47.0	18.0	28.2	30.0	33.2	27.3	13.8	21.2	40.0	39.0	0.4	0.1	2.6
TST (min)	272	350	306	435	404	468	411	424	432	424	511	460	353	426	380
SOL (min)	25.0	2.0	68.0	8.5	5.0	27.0	13.5	12.0	12.0	2.5	7.5	8.5	4.0	7.5	5.0
WASO (min)	185.0	50.0	44.0	19.0	73.5	52.5	22.0	43.0	9.5	50.0	40.0	32.5	130.0	10.0	38.0
MSLT (min)	16.6	15.0	13.6	15.5	11.6	18.6	6.3	7.6	6.8	16.6	15.8	11.4	15.5	15.6	15.3
Physiological indexes measured															
Respiratory rate (range, breaths/min)															
Daytime (wake)	29–34	27–35	26–29	22–28	30–31	24–28	28–34	24–26	21–26	27–32	23–27	16–23	16–25	17–21	16–20
SOL	27–35	27–35	22–26	20–25	23–29	22–25	26–28	25–27	22–25	27–31	24–29	21–25	15–25	15–21	15–23
NREM stage 2	15–17	14–17	14–16	14–16	14–15	14–15	14–15	15–16	15–16	14–15	13–15	12–15	15–16	14–15	15–16
$TcpCO_2$ measured (range, mm Hg)															
Daytime (wake)	NA	25–27	26–28	38–42	32–35	37–40	29–35	39–43	40–43	26–29	37–41	44–47	39–46	37–48	34–46
SOL	NA	21–25	25–34	39–43	31–42	31–36	31–34	31–35	37–38	23–28	31–33	43–46	38–51	42–54	39–43
NREM stage 2	NA	41–43	39–43	46–49	43–45	47–49	39–42	41–45	44–46	41–43	47–51	45–49	43–44	40–44	43–44
Arterial blood gas assessment															
pH values	NA	7.47	7.40	7.39	7.44	NA	7.41	7.39	NA	7.42	7.40	NA	NA	7.40	NA
pCO_2 (mm Hg)	NA	28.1	33.7	40.9	33.0	NA	37.2	39.2	NA	31.7	40.7	NA	NA	42.7	NA
pO_2 (mm Hg)	NA	93	94.1	90.0	94.2	NA	93.2	91.1	NA	92.8	90.0	NA	NA	88.7	NA
A–a O_2 gradient (mm Hg)	NA	22	15.3	10.9	16.1	NA	12.0	11.7	NA	19.0	11.0	NA	NA	9.9	NA

A–a O_2 gradient, alveolar–arterial O_2 gradient; AHI, apnoea/hypopnoea index; AI, apnoeic interval; CA, central sleep apnoea; CL, cycle length; MSLT, multiple sleep latency test; NA, not available; NREM, non-rapid eye movement sleep; OA, obstructive sleep apnoea; SOL, sleep onset latency; $TcpCO_2$ transcutaneous pCO_2; TST, total sleep time; WASO, wake after sleep onset.

while falling asleep; furthermore, frequency and duration of CSA events and hyperventilation improved, but the patient began to experience excessive daytime sleepiness (EDS). The mean MSLT values were 6.3, 7.6 and 6.8 min in three follow-up evaluations during lorazepam therapy. Thereafter, the patient stopped taking lorazepam for 14 days and EDS disappeared, but extremely long CSA events relapsed (table 1).

JGW (Medical Student): A literature review revealed that benzodiazepines, such as triazolam and midazolam, have been reportedly used in CSA and hyperventilation therapy.[1] In addition to stabilising sleep, benzodiazepines might act through resetting the central nervous system to regulate control of ventilation. In this case, improvement of breathing control could be reflected by decreased average apnoeic interval (AI) and cycle length (CL) (table 1). Though significant improvements in hyperventilation and CSA episodes, the onset of EDS due to the sedative effect of lorazepam was unacceptable to the patient, prompting investigation for alternative therapeutic approaches.

YL: After a 14-day washout period, duloxetine 60 mg was administrated for 35 days. On the 22nd and 35th day of therapy, follow-up testing was performed (table 1). Almost no episodes of irregular breathing with sigh or breathing cessation during falling asleep were observed, and the frequency and duration of CSA events, hyperventilation, as well as average AI and CL significantly improved (see table 1 and online supplementary figure S1B). However, positional obstructive/hypoapnoeas and loud snoring were observed.

CPAP was then added to the treatment agenda. Under combination therapy of duloxetine and CPAP, the patient's CSA, obstructive/hypoapnoea events and loud snoring successfully resolved when measured at 40 and 150 days, and no significant side effects were observed (see table 1 and online supplement figure S1C, D).

JGW: An A–a O_2 gradient of 22 mm Hg at baseline is abnormal in this patient. Based on systematic examination and testing described above, organic cardiovascular and pulmonary disorders and anaemia which may relate to hypoxia were ruled out. Moreover, after several different treatments which targeted hyperventilation, the patient's A–a O_2 gradient improved as compared with baseline (table 1). Thus, we speculate that the increased level of A–a O_2 gradient was secondary to hyperventilation in this patient.

XT (Professor and Clinician): The mechanism involved in the genesis of CSA primarily relates to a high loop gain and thus an unstable ventilation drive,[2] as well as removal of the wakeful drive to breathe and the unmasking of a pCO_2-sensitive apnoeic threshold below which rhythmic breathing ceases in this patient.

Based on systematic interview and examination, a variety of lower airway and upper airway conditions as well as psychiatric conditions (ie, asthma, pulmonary embolus, intrinsic lung diseases, vocal cord dysfunction, laryngopharyngeal reflux and panic disorder) which may relate to hyperventilation could be ruled out. In our patient, hyperventilation appeared to be a behavioural manifestation of (1) hypersensitive respiratory control and (2) sensation of congestion. Hyperventilation occurred during all his wakefulness and continued through the subsequent transitions to superficial NREM sleep, thereby precipitating sequences of long central apnoea episodes.

LL (Professor and Clinician): Increase chemosensitivity of respiratory control effects is associated with an increase in loop gain, which is associated with CSA. Previous animal and preterm infant studies have shown that stimulation of upper airway receptors may cause central apnoea. Moreover, studies have shown that nasal obstruction could cause central apnoea and are associated with hyperventilation.[3 4] High-frequency low-pressure ventilation and CPAP have been shown to improve CSA which suggests upper airway receptor stimulation may induce central apnoea in human beings. Thus, behavioural hyperventilation appears to be the cause of CSA in this patient.

XT and LL: Duloxetine is a serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressant here used for the first time for hyperventilation or CSA therapy in human beings. In our patient, hyperventilation and CSA were successfully and stably improved under duloxetine therapy.

Both serotonin (5-hydroxytryptophan (5-HT)) and norepinephrine (NE) are involved in the maturation of the respiratory network. It has been reported that reduction in serotonergic neurotransmission leads to hyperventilation and increased CO_2 sensitivity, while the administration of 5-HT agonists depress respiration.[5] Moreover, systemic administration of the noradrenergic tricyclic antidepressant desipramine has been shown to stabilise abnormal breathing patterns in NE deficient mice.[6] A novel study using a non-anxiety/panic mouse model showed that basal respiratory burst frequency was markedly reduced after 28-day SNRI (venlafaxine) administration; this finding suggests drugs capable of simultaneously blocking the 5-HT and NE reuptake transporters have an ability to depress the central respiratory neural network.[7] In sum this evidence suggests that regulation of the respiratory centre by stabilising respiratory control effects, which would be reflected by decreased in average AI and CL as seen in our patient, may be the underlying mechanism of duloxetine for treating hyperventilation-related CSA in this patient.

Limitations of this case should be noted: we did not administer (1) nocturnal oxygen therapy, which may stabilise respiratory control effects in non-hypercapnic CSA and (2) the measure of ventilatory CO_2 sensitivity across different conditions.

In conclusion, this case indicates that (1) behavioural hyperventilation during wakefulness which is independent of emotional disturbance or airway conditions may lead to severe CSA during subsequent sleep; (2) sedative medicine may be partially effective in patients with hyperventilation-related CSA. However, side effects of EDS and an unstable therapeutic effect limit the usefulness and (3) SNRIs, such as duloxetine, may be a novel option to manage CSA related to behavioural hyperventilation during wakefulness, with advantages of a limited side effect profile and a stable therapeutic effect.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The whole study procedure was approved by the University's Institutional Review Board and informed consent was obtained from the patient.

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