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CASE REPORT

Sleep-related breathing disorder (central sleep apnoea) improved coincidentally by medical therapy with fumarates (dimethyl fumarate)

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Abstract

Central sleep apnoea (CSA) is a sleep disorder characterized by the repeated cessation or reduction of both airflow and ventilatory effort when sleeping. Individuals with central breathing disorders have difficulty in receiving appropriate medical treatment. In this article, we describe a case study of a 31-year-old woman known to have multiple sclerosis and concomitant severe CSA. She received the medication dimethyl fumarate for the treatment of multiple sclerosis, and her CSA significantly improved to mild CSA after the treatment.

Keywords: central sleep apnoea, hypoventilation, multiple sclerosis, sleep.

Citation

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Introduction

Central sleep apnoea (CSA) is a sleep disorder characterized by the repeated cessation or reduction of both airflow and ventilatory effort when sleeping. It is less common than obstructive sleep apnoea and is frequently interlinked with other health issues.[1] The most prevalent causes of CSA include central nervous system illnesses, congestive heart failure and other pathological alterations in the breathing muscles.[1]

In an attempt to uncover the aetiology of CSA, different types of CSA have been identified. The two primary CSA types are hypercapnic and hypocapnic CSA.[1] Hypercapnia is linked to sleep-related hypoxaemia. Hypoventilation-related CSA develops whenever alveolar hypoventilation is sufficiently severe to force central apnoea to develop whenever the patient sleeps because the awake cue to breathe is lost. Nervous system suppressive medication or nervous system disorders, including multiple sclerosis (MS) and significant anomalies in respiratory mechanics, can all cause hypoventilation-related CSA.[2]

Several research initiatives have been undertaken to treat CSA, including the administration of acetazolamide to curb the effects of the ailment,[3] positive airway pressure or supplemental oxygen.[4]

Herein, we present the case of a 31-year-old woman with MS and treated for this with dimethyl fumarate (DMF); her general health condition significantly improved following treatment. Concomitantly, the patient had severe CSA, which was remarkably improved to mild CSA following DMF treatment. The study details her condition before DMF administration and compares it with that post-treatment.

Case study

The patient was a 31-year-old woman with bronchial asthma, MS and seizure disorder who was using Tegretol. She was seen on July 2, 2019, and had been referred from another healthcare facility to the sleep clinic, having a history of gasping at night with uncontrolled sleepiness during the day. Her Epworth Sleepiness Scale score was 7. She went to bed at ~12 am and woke at ~5 am. The patient reported that, under normal circumstances, she required ~2 hours to fall asleep, and woke up once every night being awake for 10 minutes before going back to sleep. The patient reported rarely taking a nap, and her

family observed loud snoring and breathing pauses. The mentioned symptoms lasted for 2 years and worsened as time progressed, leading up to her visit to the clinic. She had a history of coffee consumption of three cups per day and denied any urge to move her limbs. The patient also denied a history of alcohol or tobacco consumption. Notably, her MS diagnosis was given in 2016 and was started on teriflunomide with no significant finding in the brain MRIs conducted. The patient had no history of heart diseases, thyroid disease, diabetes, stroke, sinusitis or nasal congestion, allergies, or anxiety. At the time of presentation, the patient had been on carbamazepine and teriflunomide for 6 years.

Statement of ethics

This study protocol was reviewed and approved by The Institutional Review Board at King Fahad Medical City, IRB Registration Number with KACST, KSA: H-01-R-012, IRB Registration Number with OHRP/NIH, USA: IRB00010471 Approval Number Federal Wide Assurance NIH FWA00018774 and approval number [IRB log number 23-160]. Written informed consent was obtained from the patient for publication of medical case details and any accompanying images.

Physical examination

The patient's vitals were taken and were stable. She had a BMI of 24.17 kg/m^2. The patient had a neck circumference of 34 cm and a Mallampati score of class 1. There was no major clinical abnormality discovered throughout the physical examination. ENT examinations were conducted, and she has found to have a deviated nasal septum to the left side. Cardiovascular examination and oxygen saturation were normal, and laboratory tests revealed normal blood gas.

The patient underwent full-night polysomnography according to symptoms mentioned by the patient as well as the overall clinical picture, which showed the following: total recording time: 485.4 minutes; total sleep time: 142.5 minutes; sleep efficiency: 29.4%; total Apnea–Hypopnea Index (AHI) score: 48; time in non-rapid eye movement (NREM): 45 minutes and no rapid eye movement (REM) sleep was recorded, with significant desaturation; minimal oxygen saturation of 45%; and end-tidal carbon dioxide ($ETCO_2$): 45 mmHg.

Bilevel positive airway pressure (BiPAP) titration study was performed on 19 October 2019, where the optimal BIPAP pressure was at 16/8 cm H_2O with a backup rate of 14, which showed improvement in her sleep efficiency. Total AHI was 8.7, and NREM was 9.4. She maintained a regular follow-up in sleep medicine.

During her regular follow-up on 6 August 2021, she complained of an MS attack 2 months prior and was treated with a pulse steroid. Later on, her neurologist changed her treatment from teriflunomide to DMF 120 mg twice daily for 7 days then increased to the maintenance dose of 240 mg twice daily as she had relapsing disease. Because that time, she started to complain of sleep apnoea; through a more detailed history, it was ascertained that these were more likely a panic attack rather than apnoea and continued despite being awake, with generalized fatigability not improving with BiPAP. There was no loss of consciousness or any new symptoms. Polysomnography and pulmonary function tests were performed for reassessment. Polysomnography showed improvement: total recording time: 506.9 minutes; total sleep time: 287 minutes; sleep efficiency: 56.6%; total AHI was 7.1; time in NREM was 6.7 minutes and REM 10.9 minutes, with no significant desaturation; minimal oxygen saturation was 88%. The hypnogram showed mild CSA; the sleep study is summarized in Table 1.

Performance of a pulmonary function test was not possible due to poor effort. With significant improvement in her polysomnography, she was advised to stop BIPAP. She was also administered a regular follow-up in the sleep medicine clinic.

Discussion

CSA is not due to a single aetiology. Rather, it is a symptom of central breathing instability in a variety of clinical disorders. There are several current therapy options for CSA derived from approaches used for the treatment of obstructive sleep apnoea.[5] CSA is a disease that causes a periodic pause or decrease in both airflow and ventilatory effort whilst sleeping, where temporary suppression of respiration motor activity causes central apnoea. Transient hypocapnia, an inconsistent respiration control system, upper airway impulses, and a reduction of brain tissue rhythmic synthesis may all play a role in trying to switch off motor functions of respiratory muscles and the formation of central apnoea.[6] Respiratory depression or post-hyperventilation may be the primary processes of central apnoea. When the wakefulness desire to breathe is removed, the respiratory motor rate is reduced.[1] This may be insignificant in healthy people but, in individuals with insufficient respiratory capacity, such as individuals suffering from neuromuscular diseases, it can lead to respiratory distress and even apnoea. Hypoventilation may also be caused by the prescription of opioids and other central nervous system suppressants.[5] For example, hypoventilation-related core events can occur preceding diurnal hypercapnia. In addition, central apnoea is more likely during NREM sleep.[2] This demonstrates that central apnoea can manifest itself in a variety of ways, all of which result in trouble breathing when a person falls asleep.

Table 1. Summary of polysomnography.

Sleep variable	Sleep study A*	Sleep study B**	Sleep study C***
Sleep latency	82.8 min	30.8 min	139.1 min
REM latency	N/A	68 min	245 min
Total time in bed	485.4 min	465.6 min	506.9 min
Total sleep time	142.5 min	336.5 min	287 min
Sleep efficiency	29.40%	72.30%	56.60%
N1	32 min	35.5 min	60.5 min
N2	67 min	204.5 min	188 min
N3	43.5 min	53 min	22 min
REM	NA	43.5 min	16.5 min
AHI total	48	8.7	7.1
AHI in NREM	45.1	9.4	6.7
AHI in REM	NA	1.4	10.9
Central apnoea index	37.1	1.6	2.5
Obstructive apnoea index	0	0	0
Mixed apnoea index	0	0	0
Hypopnoeas index	10.9	7.1	4.6
Desaturation index (#/hour)	8	0.2	0.4
Time under 90% oxygen saturation	56.3 min	3.1 min	0.8 min
Time under 95% oxygen saturation	97.5 min	23.4 min	33.1 min
Minimum SpO_2 value during sleep	45%	82%	88%
Average SpO_2 whilst awake	99%	97%	96%
Average SpO_2 whilst in REM	N/A	96%	96%
Average O_2 whilst in non-REM	90%	96%	97%
Arousal index	40.8	24.4	33.7
Limb movement index	2.1	0.4	0.4
Highest $ETCO_2$ during TIB	45 mmHg	43 mmHg	45 mmHg

*Full-night diagnostic study conducted Oct/11/2019; **Therapeutic sleep study on BIPAP conducted on Oct/17/2019; ***Full-night diagnostic study conducted on Aug/8/2021.

AHI, Apnea–Hypopnea Index; $ETCO_2$, end-tidal carbon dioxide; N1, N2 and N3, non-rapid eye movement stages of sleep; REM, rapid eye movement stage of sleep; TIB, total time in bed.

Because the waking "urge to breathe" is absent during NREM sleep, respiratory processes are highly reliant on chemical factors, particularly the partial pressure of CO_2 (PCO_2). As a result, NREM sleep reveals the apnoeic limit, a sleeping state-dependent occurrence.[7] If arterial PCO_2 falls below an extremely sensitive apnoeic level, CSA develops. Transient hypocapnia (a reduction in PCO_2 below the stable state of NREM PCO_2) is a common cause of diminished respiratory motor activity in the NREM sleeping state. However, various aspects modify and may counteract the inhibitory effects of hypocapnia on respiratory muscle output. A personalized management plan for central apnoea integrates clinical features, comorbid diseases and polysomnographic data. Positive pressure therapy, phrenic nerve stimulation and pharmacological therapy, including low-flow supplemental O_2 administration, are all available options for treatment. The therapeutic effect of pharmacological therapy in the treatment of central apnoea is limited, and there are no long-term controlled clinical trials to define the limits of effectiveness. There is evidence from small studies to support the use of acetazolamide and theophylline in the treatment of central apnoea but no large clinical trials. Several studies have demonstrated that acetazolamide, a

weak diuretic that generates modest metabolic acidosis, can reduce the severity of central apnoea. Theophylline treatment improved central apnoea and Cheyne–Stokes respiration in patients with congestive heart failure whilst having no negative effects on sleep architecture.[1]

Many studies have attempted to investigate the relationship between inflammation reduction and the severity of sleep apnoeas. A previous study aimed to assess the repercussions of DMF on obstructive sleep apnoea, with findings indicating that DMF partially improves the severity of obstructive sleep apnoea.[8] The mean difference in Respiratory Disturbance Index between groups was 13.3 respiratory events/hour of sleep: -3.1±12.9 *versus* 10.2±13.1 in the DMF and placebo groups, respectively, achieved when DMF suppressed inflammation throughout the body by reducing NF-κB signalling.[8] NF-κB signalling increases the production of molecules that cause inflammation in the airways and blood stream and may aggravate sleep apnoea. In addition to inflammation, pharmacodynamic studies of fumaric acid showed that the metabolic pathway involved esterases is likely to enter into tricarboxylic acid cycle, leading to the generation of CO_2.[9] It is possible that increased CO_2 production may contribute to improved CSA.[10]

Given that the patient demonstrated near resolution of her sleep disturbance (from severe to mild) after starting DMF, resulting in complete recovery of her symptoms, and we managed to stop positive airway pressure therapy, pharmacological therapy remains a potential future opportunity awaiting definitive clinical trials.

Conclusion

CSA is a sleep disorder that reduces breathing efforts on a regular basis when patients fall asleep. Causes of the ailment have been clinically researched, and existing health conditions, such as central nervous system illnesses, congestive heart failure and other pathological alterations in the breathing muscles, have been identified. Likewise, for central apnoea, there are numerous treatment options available such as supplementing oxygen and minimizing opioid medication. The patient of the case study improved from severe CSA to mild CSA after being treated for MS with DMF. For this reason, DMF was deemed to be a successful treatment for CSA. Nevertheless, placebo-controlled studies are needed to determine the long-term efficacy of fumarate medication, which is a promising option for the treatment of sleep-related respiratory illness in patients intolerant to positive airway pressure therapy.

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References

1. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep*. 2012;35(1):17–40. https://doi.org/10.5665/sleep.1580
2. Marrie RA, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of sleep disorders and seizure disorders in multiple sclerosis. *Mult Scler*. 2015;21(3):342–349. https://doi.org/10.1177/1352458514564486
3. Ni YN, Yang H, Thomas RJ. The role of acetazolamide in sleep apnea at sea level: a systematic review and meta-analysis. *J Clin Sleep Med*. 2021;17(6):1295–1304. https://doi.org/10.5664/JCSM.9116
4. Bordier P, Lataste A, Hofmann P, Robert F, Bourenane G. Nocturnal oxygen therapy in patients with chronic heart failure and sleep apnea: a systematic review. *Sleep Med*. 2016;17:149–157. https://doi.org/10.1016/J.SLEEP.2015.10.017
5. Badr MS, Javaheri S. Central sleep apnea: a brief review. *Curr Pulmonol Rep*. 2019;8(1):14–21. https://doi.org/10.1007/S13665-019-0221-Z
6. Donovan LM, Kapur VK. Prevalence and characteristics of central compared to obstructive sleep apnea: analyses from the Sleep Heart Health Study Cohort. *Sleep*. 2016;39(7):1353–1359. https://doi.org/10.5665/SLEEP.5962
7. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. *Chest*. 2007;131(2):595–607. https://doi.org/10.1378/CHEST.06.2287
8. Braley TJ, Huber AK, Segal BM, et al. A randomized, subject and rater-blinded, placebo-controlled trial of dimethyl fumarate for obstructive sleep apnea. *Sleep*. 2018;41(8):zsy109. https://doi.org/10.1093/SLEEP/ZSY109
9. Lategan TW, Wang L, Sprague TN, Rousseau FS. Pharmacokinetics and bioavailability of monomethyl fumarate following a single oral dose of bafiertamTM (monomethyl fumarate) or tecfidera® (dimethyl fumarate). *CNS Drugs*. 2021;35(5):567. https://doi.org/10.1007/S40263-021-00799-9
10. Javaheri S, Badr MS. Central sleep apnea: pathophysiologic classification. *Sleep*. 2023;46(3):zsac113. https://doi.org/10.1093/SLEEP/ZSAC113