

Medullary Infarction with Central Hypoventilation (Ondine's Curse): A Case Report

Hong-Nan Shih, Chi-Tzong Hong, and Hsing-Yu Wong

Abstract- Ondine's curse, also termed central alveolar hypoventilation, presents as hypoventilation or total loss of automatic ventilation with progressive hypercapnia and hypoxia during sleep. This syndrome is often associated with large medullary infarction, Hirschsprung disease and ganglioneuroblastoma. We report a 75-year-old man with right lateral medullary infarction who presented with apnea and cyanosis suddenly during sleep on the third day of admission. Due to bradycardia (HR: 22) and decreased SaO₂ (22%) he was intubated with ventilator support. Two and half months later, the patient could finally breathe without ventilator support, although his neurological deficit was just as that before intubation. Ondine's curse as a result of acute medullary dysfunction was the most likely etiology causing sudden cyanosis and apnea of this patient. Close monitoring and adequate ventilation support are important for patients at risk of developing Ondine's curse.

Key Words: Central hypoventilation syndrome, Ondine's curse, Brainstem infarction

Acta Neurol Taiwan 2003;12:201-204

INTRODUCTION

Ondine's curse, also termed central alveolar hypoventilation, presents as hypoventilation or total loss of automatic ventilation with progressive hypercapnia and hypoxia during sleep. The name, Ondine's curse, derives from a German story of a sea nymph whose husband jilted her for another woman, and the man was cursed for his unfaithfulness with loss of automatic breathing, requiring him to remember to breathe continuously. Eventually, he died because he could not help falling asleep⁽¹⁾. "Ondine's curse" was applied for the

first time in the medical literature to three patients who were thought to suffer from damage to medullary carbon dioxide chemoreceptors as a result of surgery on the high cervical cord and brainstem^(1,2). It may be present in cases with low brainstem lesions caused by encephalitis⁽³⁾, hypoxia-ischemia⁽⁴⁾, ganglioneuroblastoma, Hirschsprung disease, glioma⁽⁵⁾, or surgical trauma.

Ondine's curse is considered in any patient who has hypoventilation resulting in progressive hypercapnia and hypoxia during quiet sleep, due to impaired sensitivity to these changes and in the absence of any primary cardiothoracic or neuromuscular pathology⁽⁶⁾.

From the Department of Neurology, Wan-Fang Hospital, Taipei Medical University, Taipei, Taiwan.

Received June 3, 2003. Revised July 16, 2003.

Accepted August 27, 2003.

Reprint requests and correspondence to: Hsing-Yu Wong, MD. Department of Neurology, Wan-Fang Hospital, Taipei Medical University, No.111, Sec. 3, Sing-Long Road, Taipei, Taiwan. E-mail: why1968@giga.net.tw

The hypercapnia and hypoxia may be reversible if assisted ventilation is initiated. There may be significant differences between blood gas data in awake state and those obtained during sleep.

We report a patient with medullary infarction whose hospital course was complicated by a cyanotic episode from Ondine's curse. Relevant literature is reviewed.

CASE REPORT

A 75-year-old man was brought to our ER due to acute onset of dizziness, vertigo and deviation of mouth angle to the left side. He had history of hypertension and a brainstem infarction with mild right hemiparesis. At ER, neurological examination showed newly-developed dysarthria, and mild right peripheral type facial weakness. After admission, the patient complained of poor sleep due to cough with copious sputum. Brain MRI revealed new lesion over right upper medulla and MRA disclosed right vertebral artery occlusion (Figs. 1-3). On the third day of admission, about five minutes after a short conversation with the nursing staff, he finally fell asleep but was found comatose and cyanotic soon. The monitor showed bradycardia (HR: 22) and decreased SaO2 (22%). After emergent endotracheal intubation and

brief resuscitation, his heart rate and SaO2 returned to normal. Neurological examination showed quadriplegia with equal pupils and preserved light reflex.

The patient awakened two days later and his muscle power improved gradually. Aspiration pneumonia was noticed and treated appropriately. After pneumonia had subsided, it was noticed that the patient could not main-



Figure 2. The brain MR revealed high signal in DWI image over right medulla, suggesting an acute lesion (black arrow).

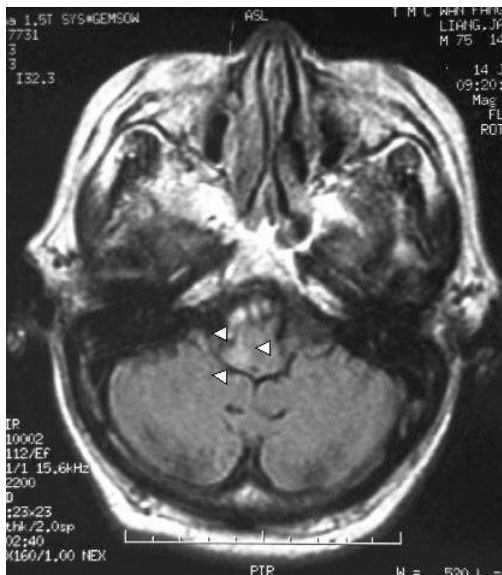


Figure 1. The brain MR of the patient showed high signal in FLAIR image over right upper medulla (white arrow head), which was larger than the previous lesion half a year ago.



Figure 3. The brain MRA showed poor visualization of right vertebral artery, suggesting total occlusion of right vertebral artery (white arrow head).

tain oxygen saturation during sleep ($\text{SaO}_2 < 70\%$, $\text{RR} < 6/\text{min}$). In awake state, he could maintain good saturation and ventilation (SaO_2 : 100%, RR : 20-30/min) without ventilator. However, on continuous positive airway pressure (CPAP) mode, his oxygen saturation could be maintained better. Therefore, he was dependent on ventilator, especially during sleep, and his condition improved slowly. Two and a half months later, the patient could finally sleep without ventilator and monitor. Moreover, several days later, tracheostomy tube was removed and he could breathe smoothly. Besides, his neurological deficits recovered back to the state before he became cyanotic and comatose.

DISCUSSION

Ondine's curse is a rare neurogenic respiratory disorder characterized by normal ventilation when the patient is awake but has insufficient response to hypoxia and hypercapnia during sleep, in the absence of pulmonary or neuromuscular diseases. The probable cause of this condition is alveolar hypoventilation resulting from failure of autonomous ventilation. Automatic respiration is stimulated by rhythmic discharges of the respiratory center neurons in the ventrolateral area of the medulla⁽⁷⁾; and regulated by chemical stimuli through both central and peripheral chemoreceptors as well as nonchemical stimuli such as pulmonary baroreceptors. In normal individuals cortical stimuli and appropriate chemoreceptor responses provide afferent inputs to the brainstem respiratory center for the regulation of respiration. During non-REM sleep, the chemoreceptors alone may be responsible for providing afferent inputs to the respiratory center; whereas in REM sleep, cortical stimuli may be more dominant. Central chemoreceptors respond to changes in the cerebrospinal fluid hydrogen ion, determined predominantly by changes in PaCO_2 . On the contrary, peripheral receptors are mainly influenced by changes in PaO_2 and pH ^(8,9).

Many drugs have been used in the management of Ondine's curse, with limited or no success⁽¹⁰⁾. Acetazolamide and theophylline are the most frequently discussed ones. Acetazolamide induces a metabolic acidosis which may stimulate respiratory drive. The benefi-

cial effects are well documented. However, its clinical use is limited because of potential adverse effects, such as electrolyte imbalance, precipitation of calcium phosphate salts in alkaline urine and paraesthesias. The effect of theophylline is to increase respiratory drive and cardiac output in central apnea associated with congestive heart failure. Long-term assisted mechanical ventilation (CPAP) or diaphragmatic pacing is currently the preferred method of treatment for Ondine's curse. Diaphragmatic pacing appears to be effective in reducing pulmonary vascular resistance and pulmonary hypertension, but its long-term use can lead to loss of phrenic nerve conductivity⁽¹¹⁾.

Our patient presented with acute medullary dysfunction and severe hypoventilation accompanied by a marked disturbance in respiration during sleep. We did not perform polysomnographic study because the equipment was not available. Before the initial apneic attack, the patient had disturbed sleep for days because of choking and coughing. After suction, the patient felt better and fell asleep. It might be the first true sleep after admission. This perhaps could explain why this hypoventilation event happened on the third day after admission. Ondine's curse as a result of acute medullary dysfunction was the most possible cause of sudden apnea and cyanosis of the patient. The symptom might be transient and reversible in stroke cases. Close monitoring and intubation with mechanical ventilatory support were the most important managements if dyspnea or cyanosis occurred from hypoxia. Short-term ventilator support was effective in our patient; and CPAP might be beneficial for treatment of Ondine's curse.

It has been reported that unilateral involvement of pontomedullary reticular formation and nucleus ambiguus is sufficient for the loss of automatic respiration, while associated lesion of the nucleus tractus solitarius may lead to more severe respiratory failure involving both automatic and voluntary responses⁽¹²⁾. In our case, the lesion was near lateral part of medulla, indicating more involvement of nucleus tractus solitarius. However, the automatic respiration of our patient seemed to more impaired, and his voluntary response was relatively spared.

Ondine's curse may be one reason for a higher mor-

tality seen in cases of medullary infarction without close monitoring. Patients with medullary lesion may develop Ondine's curse in a few days though their clinical conditions become stabilized temporary. Therefore, close monitoring of respiratory function and the use of ventilation support when needed are of great importance in the care of patients with strokes involving medullary region.

REFERENCES

1. Severinghaus JW, Mitchell RA. Ondine's curse- failure of respiratory center automaticity while awake. *Clin Res* 1962;10:122.
2. Krieger AJ, Rosomoff HL. Sleep induced apnea. 1. A respiratory and automatic dysfunction syndrome following bilateral cervical cordotomy. *J Neurosurg* 1974;40:168.
3. Giangaspero F, Schiavina M, Sturani C, et al. Failure of automatic control of ventilation (Ondine's curse) associated with viral encephalitis of the brainstem: a clinicopathologic study of one case. *Clin Neuropathol* 1988;7:234-7.
4. Beal MF, Richardson EP, Brandstetter R, et al. Localized brainstem ischemic damage and Ondine's curse after near-drowning. *Neurology* 1983;33:717-21.
5. Roshkow JE, Haller JO, Berdon WE, et al. Hirschsprung disease, Ondine's curse, and neuroblastoma manifestation of neurocristopathy. *Pediatr Radiol* 1988;19:45-9.
6. Commare MC, François B, Estournet B, et al. Ondine's curse: a discussion of five cases. *Neuropediatrics* 1993;24:313-8.
7. Plum F. Neurological integration of behavioural and metabolic control of breathing. In: Porter R, ed. *Ciba Foundation Hering Breuer Centenary Symposium: Breathing*. London: J & A Churchill, 1970:159.
8. Wells HH, Kattwinkel J, Morrow JD. Control of ventilation in Ondine's curse. *J Pediatr* 1980;96:865-7.
9. Yasuma F, Nomura H, Sotobata I, et al. Congenital central hypoventilation (Ondine's curse): a case report and review of the literature. *Eur J Pediatr* 1987;146:81-3.
10. Grunstein RR, Hedner J, Grote L. Treatment options for sleep apnea. *Drugs*. 2001;61:237-51.
11. Manning HL, Leiter JC. Respiratory control and respiratory sensation in a patient with a ganglioglioma within the dorso-caudal brainstem. *Am J Resp Crit Care Med* 2000;161:2100-6.
12. Bogousslavsky J, Khurana R, Deruaz P, et al. Respiratory failure and unilateral caudal brainstem infarction. *Ann Neurol* 1990;28:668-73.