

Pearls & Oysters:

Reversible Ondine's curse in a case of lateral medullary infarction

Michael Mendoza, MD
Julius Gene Latorre, MD,
MPH

Correspondence to
Dr. Mendoza:
mendozam@upstate.edu

PEARLS Ondine's curse is an eponym that refers to central alveolar apnea/hypopnea observed among patients with acquired or congenital brainstem disorders. This condition results in loss of automatic and/or voluntary respiration with characteristic polysomnographic finding of impaired ventilator responses to hypercapnia and sleep apnea, which are more pronounced during non-REM sleep, less in REM sleep, and least during wakefulness.

Brainstem infarction affecting the respiratory medullary neurons may result in Ondine's curse. High index of suspicion with overnight oximetry monitoring and/or polysomnography is necessary to diagnose this condition. Failure to intervene may be catastrophic, resulting in death during sleep.

Initial therapeutic options include mechanical ventilator support with gradual weaning and, in some cases, diaphragmatic pacing.

OY-STERS Patients with brainstem infarction should be closely monitored for apnea/hypopnea especially during sleep. Early diagnosis of this condition during the acute or subacute phase of stroke may prevent serious cardiorespiratory complications with ventilator support and promote functional recovery.

CASE REPORT A 60-year-old man with history of hypertension and dyslipidemia presented with sudden-onset dizziness, headache, nausea, and vomiting. At the emergency room, his neurologic examination revealed left Horner syndrome, dysarthria, dysphonia, multidirectional torsional nystagmus, left appendicular dysmetria, ataxia, and left facial and right body hemianesthesia. Cerebrovascular imaging showed acute infarction in the left lateral medulla due to left vertebral artery dissection (figure 1). The patient required gastrostomy insertion after 10 days of persistent dysphagia. During the procedure, the patient became apneic after receiving midazolam and required emergency intubation. Repeat imaging showed no change in the infarct size. The patient was immediately extubated after waking, but was reintubated emergently during sleep because of complete respiratory arrest. His 24-hour respiratory pattern showed complete apnea during

sleep and absence of respiratory drive to hypercapnia (pH = 7.22, PCO₂ = 60, PO₂ = 89), with immediate return of spontaneous breathing on awakening. The patient underwent tracheostomy and was discharged to a ventilator rehabilitation facility where he was weaned off nighttime ventilator after 4 months.

DISCUSSION Ondine is a mythologic sea nymph based on a German fairy tale written by Fouqué in 1811. It tells about love, betrayal, and demise of Ondine's mortal lover brought upon by the laws of the sea. This eponym was first used by Severinghaus and Mitchell in 1962 to describe a 63-year-old man who developed long periods of apnea after high cervical cord and brainstem surgery.¹ Since then, Ondine became known as the sea nymph who cursed his unfaithful lover to lose breathing during sleep.

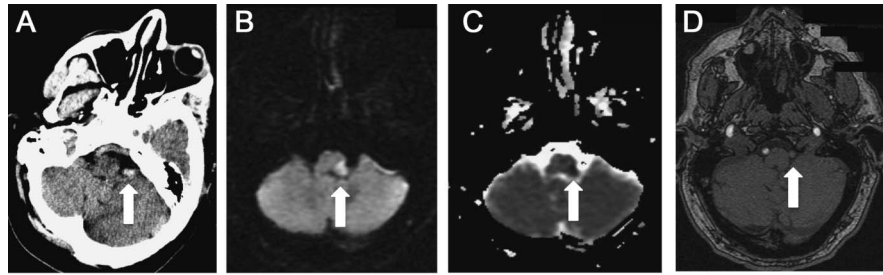
Respiration is centrally governed by 3 interconnected nuclear groups^{2,3} (figure 2). The pontine respiratory group, which consists of the parabrachial/Kölliker-Fuse complex in the rostral dorsolateral pons, is the pneumotaxic center that integrates pulmo-mechanoreceptor reflexes and carries information to suprapontine structures such as the amygdala and hypothalamus. The dorsal respiratory group located in the nucleus tractus receives afferent signals from peripheral respiratory chemoreceptors and mechanoreceptors and integrates respiration and cardiovascular reflexes. The ventral respiratory group (VRG) is a long column of neurons extending from cervical cord C1 to just below the facial nucleus. It is divided into 4 distinct nuclear complexes. Beginning rostrally, the Böttinger complex carries expiratory neurons and can inhibit inspiratory neurons of the nucleus retroambigualis. The pre-Böttinger complex functions as the respiratory rhythm pattern generator. The rostral VRG located ventral to the nucleus ambiguus carries inspiratory bulbospinal neurons. The most caudal nuclear complex, nucleus retroambigualis has bulbospinal expiratory neurons.

Automatic breathing, which is important in sleep, is controlled by feedback mechanisms dependent on changes in oxygen, carbon dioxide, and pH in the

From SUNY Upstate Medical University Hospital, Syracuse, NY.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 Nonenhanced CT of the head showing left vertebral artery clot (A), diffusion-weighted imaging and apparent diffusion coefficient (B, C), and magnetic resonance angiography (D)

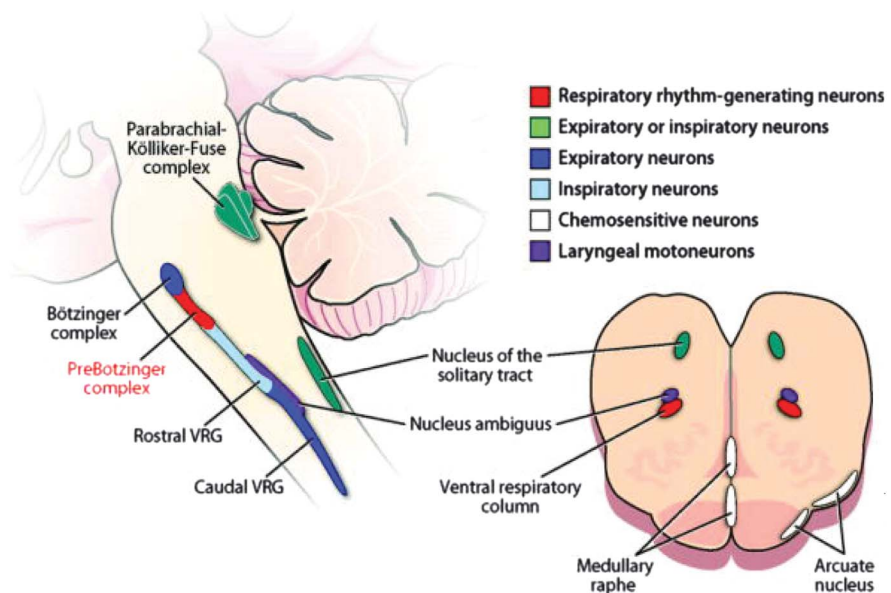


blood and CSF.² Peripheral oxygen-sensitive receptors located in the carotid bodies and chemosensitive neurons such as the serotonergic and glutaminergic neurons in the medullary raphe and medullary surface send afferent signals to the nucleus tractus and VRG. Previous clinicopathologic studies showed that critically placed lesions in the brainstem can selectively affect either automatic or voluntary respiration.⁴ Complete loss of automatic and voluntary breathing was observed in lesions in the pontomedullary reticular formation, nucleus tractus solitarius, nucleus ambiguus, and nucleus retroambiguus. Smaller lesions involving a limited part of the lateral medulla encompassing the medullary reticular formation and nucleus ambiguus and sparing the dorsal medulla and nucleus tractus solitarius on one side result in loss of automatic respiration. Studies also found that bilateral pontomedullary

or medullary lesions are not necessary to cause hypoventilation. Interestingly, loss of voluntary respiration with intact automatic breathing was previously reported in a patient with discrete infarction of the ventral basis pontis.⁵ These support that there are at least 2 separate neural pathways controlling respiration.

The gold standard for evaluation of sleep-related breathing disorders is polysomnography with blood gas analysis and hypercapnia challenge. Central apnea is defined as >10 seconds of cessation of airflow with no thoracic/diaphragmatic excursion as seen in plethysmography. In a case of anterior spinal artery syndrome complicated with Ondine's curse, a polysomnography study was done and showed continuous central apnea appearing immediately after falling asleep accompanied by 10 to 30 seconds of mild oxygen desaturation (3%–6%) and absence of slow-wave

Figure 2 Brainstem area for respiration



Control of respiration is governed by 3 interconnected nuclear groups: pontine respiratory group (parabrachial/Kölliker-Fuse complex), dorsal respiratory group (nucleus tractus solitarius), and the large column of the dorsal respiratory group (Bötzing complex, pre-Bötzing complex, rostral ventral respiratory group [VRG], and caudal VRG). Originally published in *Neurology*[®]: Benarroch E. Brainstem respiratory chemo-sensitivity: new insights and clinical implications. *Neurology* 2007;68:2140–2143. Reprinted with permission, © 2007, American Academy of Neurology.

Table Proposed classification of central ventilation disorder after brainstem infarction			
Classification	Description	Suspected localization	Potential management option(s)
Type I	Incomplete central apnea	Brainstem respiratory center receptor resistance/insensitivity	Acetazolamide, medroxyprogesterone, clomipramine, trazodone, caffeine BiPAP/CPAP
Type II	Complete central apnea, loss of automatic breathing control only	Ventral respiratory nuclei near nucleus ambiguus (pre-Bötzinger region)	Nocturnal mechanical ventilation Phrenic nerve stimulation
Type III	Complete central apnea, loss of voluntary breathing control only	Dorsal respiratory nuclei near nucleus tractus solitarius Lateral pontine tegmentum, corticospinal tract	Phrenic nerve stimulation
Type IV	Complete central apnea, loss of voluntary and automatic breathing control	Dorsal and ventral respiratory centers	Phrenic nerve stimulation Long-term mechanical ventilation

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

and REM sleep.⁶ We did not perform polysomnography in our patient. His recurrent apneic spells during the sleep state (nocturnal or daytime) with immediate return of spontaneous breathing on awakening and absence of ventilator response to hypercapnia documented by blood gas analysis confirmed our diagnosis of central apnea. Fifty to seventy percent of stroke patients have a sleep-related breathing disorder; however, the exact prevalence of central hypoventilation syndrome in brainstem stroke is still not known. In addition, onset of these events has been variably reported in case reports ranging from within 24 hours to as late as 3 months after the brainstem stroke.⁷ In one prospective study that examined the difference of apnea-hypopnea index and central apnea index at the acute phase of stroke (48–72 hours) and stable phase (3 months), the proponents found that central apnea index was significantly lower after 3 months.⁸ Monitoring patients in the acute phase of stroke for central apnea using continuous pulse oximetry is recommended and patients with persistent severe bulbar dysfunction warrant longer monitoring and polysomnography. However, the duration of monitoring is currently unclear; nevertheless, episodes of desaturation need active investigation. Currently, long-term use of mechanical ventilator support or diaphragmatic pacing is the only form of management.

Our patient demonstrated acute medullary dysfunction followed by selective loss of automatic respiration. It was unclear why central apnea occurred 10 days after the stroke. Clinical worsening after lacunar infarction has been extensively reported and may result from thrombi propagation, flow limiting arterial lesion supplying the ischemic zone, and perilesional edema.^{9,10} We suspect that secondary neuronal degeneration, apoptosis, or abnormal plasticity involving local synaptic interconnections may explain the delay in the development of Ondine's curse after lateral medullary infarction, ranging several days to several months postinfarct. Likewise,

hypoxemia secondary to altered automatic breathing in brainstem infarctions with hypercapnia-induced cerebral vasoconstriction can increase ischemia. Because multiple respiratory centers may be differentially affected after acute brainstem infarction, we propose a classification of central ventilation disorder after acute ischemic stroke to guide in localization and in future management series (table).

This condition may be reversible and patients should be supported aggressively with full mechanical ventilation. Neurologic rehabilitation is possible and should be initiated early to promote functional recovery. The patient had tracheostomy and was discharged to a ventilation rehabilitation facility with positive end-expiratory pressure +5 and fraction of inspired oxygen of 30% during night and room air tracheostomy while awake. Subsequent outpatient records showed that the patient was eventually weaned off nighttime ventilation with no resultant nocturnal desaturations in the following 4 months. Ondine's curse is a potentially fatal complication after lateral medullary infarction and must be recognized early to avoid preventable cardiorespiratory failure. Brainstem involvement with stroke warrants closer monitoring of breathing and oxygen saturation because they contribute to the extent of the injury and the patient's functional prognosis.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Nannapaneni R, Behari S, Todd NV, Mendelow AD. Retracing "Ondine's curse." *Neurosurgery* 2005;57:354–363.
2. Nogues MA, Benarroch E. Abnormalities of respiratory control and respiratory motor unit. *Neurologist* 2008;14:273–288.
3. Benarroch E. Brainstem respiratory chemo-sensitivity: new insights and clinical implications. *Neurology* 2007;68:2140–2143.

4. Bogousslavsky J, Khurana R, Deruaz JP, et al. Respiratory failure and unilateral caudal brainstem infarction. *Ann Neurol* 1990;28:668–673.
5. Munschauer F, Mador MJ, Ahuja A, Jacobs L. Selective paralysis of voluntary but not limbically influenced automatic respiration. *Arch Neurol* 1991;48:1190–1193.
6. Manconi M, Mondini S, Fabiana A, Rossi P, Ambrosetto P, Cirignotta F. Anterior spinal artery syndrome complicated by the Ondine's curse. *Arch Neurol* 2003;60:1787–1790.
7. Bassetti C, Aldrich M, Chervin R, Quint D. Sleep apnea in patients with transient ischemic attack and stroke. *Neurology* 1996;47:1167–1173.
8. Parra O, Arboix A, Bechich S, et al. Time course of sleep related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med* 2000;161:375–380.
9. Caplan LR. Worsening in ischemic stroke patients: is it time for a new strategy? *Stroke* 2002;33:1443–1445.
10. Yamamoto H, Bogousslavsky J, van Melle G. Different predictors of neurological worsening in different causes of stroke. *Arch Neurol* 1998;55:481–486.

Neurology®

Pearls & Oy-sters: Reversible Ondine's curse in a case of lateral medullary infarction

Michael Mendoza and Julius Gene Latorre

Neurology 2013;80:e13-e16

DOI 10.1212/WNL.0b013e31827b9096

This information is current as of January 7, 2013

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/80/2/e13.full
References	This article cites 10 articles, 3 of which you can access for free at: http://n.neurology.org/content/80/2/e13.full#ref-list-1
Citations	This article has been cited by 2 HighWire-hosted articles: http://n.neurology.org/content/80/2/e13.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Cerebrovascular disease/Stroke http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke Natural history studies (prognosis) http://n.neurology.org/cgi/collection/natural_history_studies_prognosis Plasticity http://n.neurology.org/cgi/collection/plasticity Sleep apnea http://n.neurology.org/cgi/collection/sleep_apnea
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2013 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

