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PRACTICAL PEARL

Ondine's Curse with Accompanying Trigeminal and Glossopharyngeal Neuralgia Secondary to Medullary Telangiectasia

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Abstract
Background Central hypoventilation syndrome ("Ondine's Curse") is an infrequent disorder that can lead to serious acute or chronic health consequences. This syndrome, especially in adults, is rare, and even less frequent in the absence of clear pathogenic lesions on MRI. In addition, we are not aware of any previously reported cases with associated cranial nerve neuralgias.
Methods We describe a patient with baseline trigeminal and glossopharyngeal neuralgia, admitted with episodes of severe hypoventilatory failure of central origin, consistent with "Ondine's Curse". After evaluation, she was found to have a medullary capillary telangiectasia, thought to be the causative lesion, and which could explain her complete neurologic and hypoventilatory syndrome. The patient was treated with placement of a diaphragmatic pacing system, which has been effective thus far.
Results This case illustrates the need for investigation of centrally mediated apnea, especially when co-occurring cranial nerve neuralgia is present and cardiopulmonary evaluation is negative. It provides an example of capillary telangiectasia as the causative lesion, one that to our knowledge has not been reported before.
Conclusions Placement of a diaphragmatic pacing system was warranted and became lifesaving as the patient was deemed to be severely incapacitated by chronic ventilatory insufficiency.

Keywords Ondine's curse · Central apnea · Diaphragmatic pacing · Medullary telangiectasia · Trigeminal neuralgia · Glossopharyngeal neuralgia · Neurovascular medullary compression · Hypoventilation

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Case Report

The case involves a 72-year-old woman, who initially presented after being found unresponsive by her husband, with no obvious inciting events or ingestions. She was taken to the Emergency Room at their local hospital, and found to be in hypercapnic respiratory failure. An arterial blood gas on oxygen showed a pH of 7.11, pCO_2 81, pO_2 of 143, and HCO_3 of 29. Her status quickly improved with non-invasive ventilation, and she remained stable. The patient required a short inpatient stay, where she underwent a negative cardiopulmonary evaluation including spirometry, echocardiogram, and chest radiographs. The patient was discharged with a plan for outpatient follow-up, only to be re-admitted shortly thereafter for a similar episode. This time, the patient was not able to wean from non-invasive ventilation due to continued episodes of hypoventilation, and was transferred to the neurologic ICU at our institution for evaluation and management.

The patient's past medical history included refractory trigeminal neuralgia in V_3 distribution, as well as glossopharyngeal neuralgia, both diagnosed about 5 years prior. She had continued to have attacks of pain involving her left lower face, jaw angle, and posterior pharyngeal wall, which were aggravated by chewing and swallowing, and had required multiple interventions. She was otherwise healthy, had never been a smoker, and had a normal body mass index. She had no history of unusual exposures. She was not on any sedating medications including opioids/benzodiazepines, and had no history of neurologic or cardiopulmonary disease.

Upon arrival at our ICU, the patient was initially stable, with intact mental status and respiratory rate. A baseline arterial blood gas showed a pH of 7.44, pCO_2 40, pO_2 79. However, soon after admission, the patient experienced a spontaneous and prolonged apneic episode. Arterial blood gas at that time showed a decline in pH to 7.07, with an elevation in pCO_2 to 130. The patient was intubated at that time and remained in the ICU for further evaluation.

The patient underwent intensive diagnostics while in the ICU. Electrolytes, blood counts, and thyroid studies were normal. Several serologic studies for neuromuscular, autoimmune, and paraneoplastic disease were sent, including: ANNA, AGNA, PCA, Amphiphysin, CRMP, Calcium channel antibodies, muscle binding antibodies, anti-striated muscle antibody, acetylcholine receptor antibodies, neuronal voltage-gated potassium channel antibody, anti-MUSK antibody; these studies were all negative/unrevealing. EMG and nerve conduction studies were normal. Chest X-ray and CT scan were repeated and were once again normal.

The patient remained intubated, eventually requiring tracheostomy placement. She was maintained on a pressure support setting, with minimal oxygen requirement. At most times, her breathing was spontaneous with adequate ventilation, but she was prone to occasional hypoventilatory episodes triggering a backup rate on the ventilator. Voluntary breathing seemed to be intact, as hypoventilatory episodes responded to verbal reminder for the patient to increase her respiratory rate. Blood gases during these episodes showed continued CO_2 retention with normal A-a gradient. These episodes were more frequent at night, but occurred occasionally even during the day and precluded her extubation. At this time, we began a workup for a central cause for her apneic episodes. An EEG with respiratory effort monitoring was performed (Fig. 1); the results showed periods of central apnea, usually occurring during transition from wakefulness to sleep, and most severe during drowsiness. The EEG findings along with this state-dependent decrease in respiratory drive have been described with the eponym, "Ondine's Curse". An MRI of the brain and C-spine followed, which showed a 1.4 × 0.5 cm lesion in the dorsolateral medulla. The lesion was mildly hyperintense on T2-weighted images, and faintly enhancing on axial T1-weighted post-contrast images, thought to represent a capillary telangiectasia (Fig. 2). No other abnormalities were found. Cerebrospinal fluid evaluation was unremarkable.

The patient remained in the ICU for nearly 1 month, maintained on a pressure support setting, with a backup rate triggered during frequent episodes of hypoventilation. Due to the lack of improvement, we felt that she would be a treatment candidate, with the treatment of choice being diaphragmatic pacing. The patient underwent testing of phrenic nerve function using placement of a Neurally Adjusted Ventilatory Assist (NAVA) probe. With this technology, bipolar electrodes attached to a nasogastric tube were positioned in the esophagus at the level of the crura of the diaphragm. These electrodes were able to detect measurable charges created by the diaphragm muscle when stimulated. Since direct measurement of phrenic nerve function is not possible, this system allowed us to have a surrogate marker for diaphragmatic innervation. When central drive was intact, our patient was seen to have adequate neural stimulation of the diaphragm, with resulting normal minute ventilation. Since phrenic nerve and diaphragm function were intact, she was felt to be a

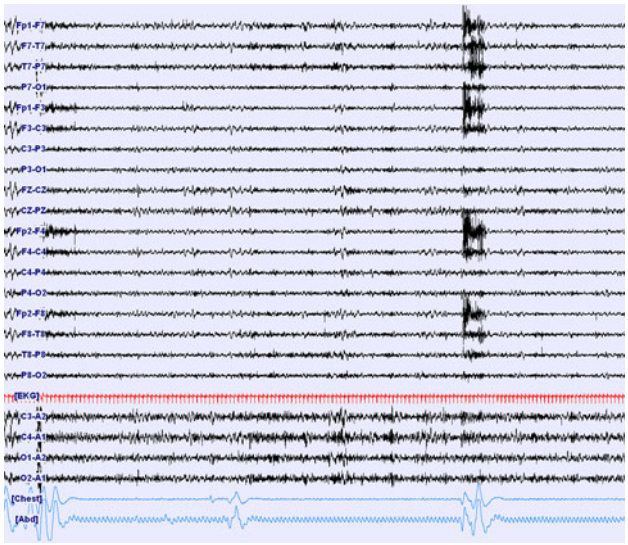

Fig. 1 EEG with supplementary chest and abdomen plethysmography. This study disclosed periods of central apnea usually during transitions from wakefulness to sleep, as marked by theta activities on EEG. Apneic events were most severe during drowsiness

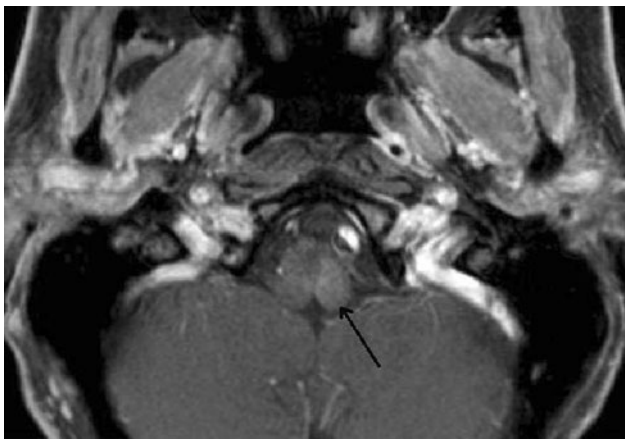

Fig. 2 Axial T1 post-contrast MRI of the brain showing poorly defined and vaguely enhancing lesion (*black arrow*) in the left dorsolateral medulla most closely consistent with capillary telangiectasia

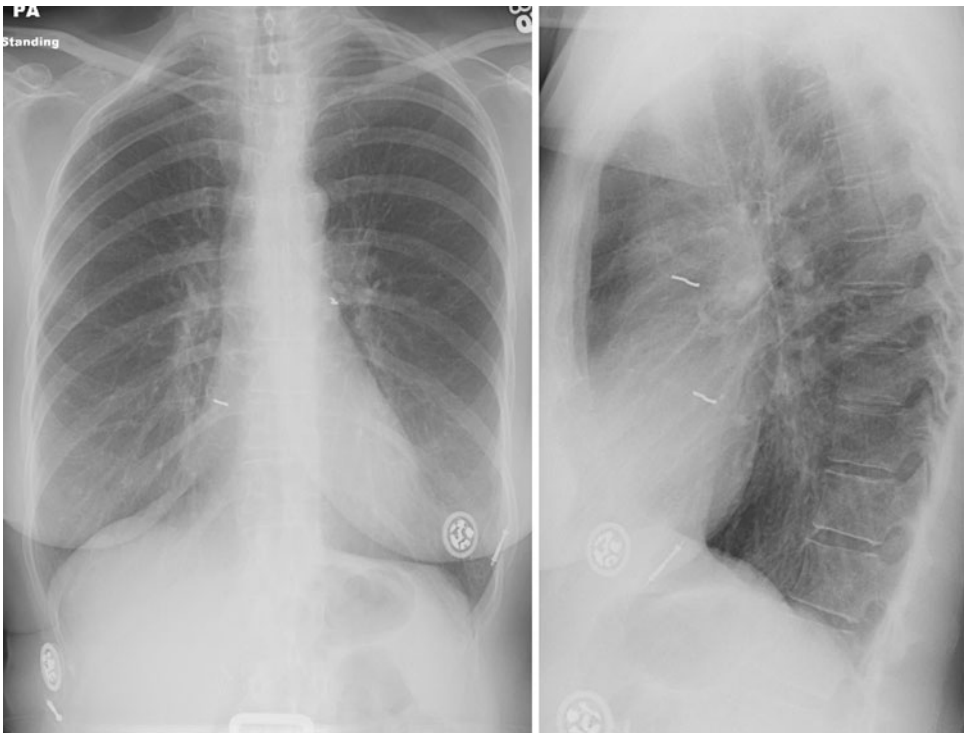

Fig. 3 PA (*left*) and Lateral (*right*) chest radiographs of the patient after diaphragmatic pacemaker placement. Electrodes are seen on both views tethered to the right and left side of the pericardium. Circular device receivers are seen embedded in subcutaneous pockets on each side of the lower chest

good candidate for pacing system placement. The patient subsequently underwent thorascopic placement of an Avery Mark IV diaphragmatic pacing system (Fig. 3), which was tested intraoperatively and found to be functioning adequately. This procedure went well without complication.

The patient was monitored in the intensive care unit for 1 week post-operatively, after which she was discharged home. Initially, she required ventilator support while sleeping; however, with the pacing system functional she has been without any further episodes of hypoventilation. An attempt was made at decannulating the tracheostomy tube, but following this the patient developed obstructive apneas due to upper airway collapse. Therefore, the tracheostomy was again inserted, and remains in place to prevent obstructive apneas. At 1-month follow-up, she remains with tracheostomy in place, but is otherwise doing well and remains without ventilator requirement.

Discussion

Ondine's curse was originally described as an uncommon "primary" alveolar hypoventilation syndrome occurring after bilateral ventrolateral high cervical cordotomy [1]. Patients exhibit long periods of apnea even when awake, but can breathe voluntarily when commanded to do so, suggesting problems with the involuntary pathways lying anywhere between the respiratory center in the medulla to the phrenic nerves. Due to normal loss of voluntary breathing control, patients are usually affected more severely during sleep, often leading to profound hypoxia and/or hypercarbia [1]. Acutely, the hypoventilation can be fatal, while chronic hypoventilation can lead to problems including secondary polycythemia, systemic hypertension, pulmonary hypertension, and cor pulmonale [2].

The name Ondine's curse comes from Germanic mythology, in which Ondine, an oceanic nymph, punishes her unfaithful lover with the loss of involuntary control of breathing; he is left with normal voluntary breathing, but is thus forced to remain awake forever for fear of cessation of breathing while sleeping [3]. This disorder is very uncommon, with most case reports in the pediatric literature. In children, the idiopathic form, known as congenital central hypoventilation syndrome (CCHS) is felt to be genetically acquired and usually presents in early infancy [4]. The PHOX2B gene is felt by some to be responsible, and may have a role in neural crest cell migration [4, 5]. Supporting this idea is the association between CCHS and other neural crest cell disorders including: Hirschsprung disease, ganglioneuroma, neuroblastoma, ganglioneuroblastoma, and abnormalities of the autonomic nervous system. In addition to the idiopathic form, other causes reported in children include structural lesions in the medulla or medullocervical pathway [2, 4].

Uncommon in children, Ondine's curse is extremely infrequent in adults, with only rare case reports in the literature. Few cases have been reported of patients with

medullary tumors, acute vertebrobasilar strokes, as well as other structural lesions presenting with hypoventilation [1, 2, 6–8]. Most, but not all cases in adults do have corresponding bulbar lesions on MRI. Antic et al. [5] described a series of five adults with central hypoventilation syndrome presenting in adulthood, none of whom had corresponding brainstem abnormalities All of these patients were screened for and found to have abnormalities in the PHOX2B gene, suggesting genetic disease similar to CCHS in children. All of these presented as young adults (mean age 34), and all had history of mild respiratory/ventilatory abnormalities as children.

Our case represents a very unusual presentation for different reasons. Her symptoms of coexisting, chronic, trigeminal, and glossopharyngeal neuralgia are likely related. These symptoms, as our patient had, typically include facial pain with trigeminal neuralgia. Glossopharyngeal neuralgia presents as recurrent tongue, tonsil, throat, and ear pain with a comparable time course to trigeminal neuralgia and also with detectable triggers including swallowing and talking [9]. Simultaneous symptoms of trigeminal and glossopharyngeal neuralgia suggest the possibility of a structural lesion in an area that could capture both trigeminal and glossopharyngeal nerve pathways. From an anatomic perspective, this would include the spinotrigeminal nucleus and tract (CN V), the solitary nucleus (CNVII, IX, and X), and the nucleus ambiguous (CNIX and X), all of which are in close proximity in the medulla. In this patient, her lesion was located in a region of the medulla that could explain both her central apnea as well as her cranial nerve neuralgias. We are not aware of any previous association between Ondine's Curse and trigeminal or glossopharyngeal neuralgia.

In addition, already an extremely rare syndrome in adults, it is even more unusual to see forms of Ondine's Curse without clear corresponding MRI abnormalities (such as stroke, hemorrhage, vascular malformations, or tumor). There are case reports of unruptured capillary telangiectasia causing mild symptoms including headache, vertigo, tinnitus, cranial nerve, and nuclei palsies, but overall they rarely cause symptoms especially without rupture [10]. Review of the literature found only one report of a bulbar hemangioma causing Ondine's curse, but to our knowledge capillary telangiectasias have never been associated as a cause [7].

Some reports of Ondine's curse in adults describe improvement in ventilation with treatment of the underlying disorder [5–7]. There are descriptions of tumor-related central apnea improving with radiation, and post-CVA apnea improving with time. For our patient, from the time of symptom onset to discharge was nearly 1 month, and she had no signs of improvement. Testing was done which confirmed intact phrenic nerve and diaphragm muscle function. Studies were done which ruled out a treatable cause such as neuromuscular disease or hypothyroidism. We therefore felt that placement of a diaphragmatic pacing system would be warranted.

Diaphragmatic pacing has been described in series', with reported success rates between 50 and 70% [11, 12]. Candidates for diaphragmatic pacing must be severely incapacitated by chronic ventilatory insufficiency and are usually receiving ventilatory support before pacing is instituted. It is imperative to confirm adequate neural/neuromuscular function distal to the pacing site, which was done in this case. Our patient underwent pacing system placement, which has thus far worked to remedy the central apneas. Of note, one problem encountered in her case was the development of obstructive apneas. This is a common problem in this scenario, thought to be due to a lack of coordination between the diaphragm, pharyngeal dilator muscles, and accessory respiratory muscles. As in this case, especially when pharyngeal muscle denervation has occurred due to brainstem lesions, long-term tracheostomy is often required [11].

Conclusion

This case describes a woman with past history of trigeminal and glossopharyngeal neuralgia who presented with new onset of severe hypoventilation. There are several causes of hypoventilatory respiratory failure with pathologic lesions potentially located anywhere from the respiratory center in the medulla to the lungs themselves. Our patient was worked up extensively, and we felt that this constellation of symptoms was likely due to medullary capillary telangiectasia found on MRI and afflicting lower brain stem nuclei.

The points illustrated in this case are the need for investigation for centrally mediated apnea, especially when cardiopulmonary evaluation is negative and history suggests other processes affecting the brainstem. In addition, although spontaneous recovery of central apnea is possible, diaphragmatic pacing should be considered as a potential treatment option.

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