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Ondine's Curse: A Patient with Medullary Dorsolateral Infarction

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Abstract

A 67-year-old female developed breathing difficulty due to medullary dorsolateral infarction without lung disease, and used a ventilator to assist breathing. However, she suffered sleep apnea after stopping the ventilator and eventually died in sleep. We have considered this type of central sleep apnea Ondine's curse syndrome. Acquired Ondine's curse is rare and often secondary to the lesions of medulla oblongata and pontine brain, such as inflammation, tumor, stroke, trauma, surgery, demyelinating disease, angioma, Leigh's disease, Arnold-Chiari malformation, syringobulbia, multisystem degeneration, and cervical cord infarction due to anterior spinal artery occlusion. The medullary infarction affects the brainstem chemoreceptors, causing the body to reduce the sensitivity to carbon dioxide during sleep and resulting in hypoxia during sleep and apnea. At present, there is no definite diagnostic standard for Ondine's curse. Although being a rare clinical syndrome, Ondine's curse should be identified by clinicians as soon as possible, because it is almost invariably fatal without prompt treatment. The therapeutic approaches include tracheotomy, ventilator support, and phrenic nerve pacing. The aim of the report is to provide clinicians with emphasis on medullary dorsolateral infarction.

Keywords: Ondine's curse, Medullary dorsolateral, Sleep apnea, Ventilator

Introduction

Ondine, a mythological figure of European tradition, was invented by Paracelsus in the 16th century to describe the spirit residing in the element of water. Jean Giraudoux, the French play writer, introduced the concept of the loss of automaticity of all functions as the "curse of Ondine" [1]. Severinghaus and Mitchell first used “Ondine's” to define central sleep apnea in 1962 [1,2], since then “Ondine's curse” has been a term to describe autonomic respiratory dysfunction caused by neurological diseases, characterized by carbon dioxide retention, hypoxemia and apnea during sleep.

Ondine's curse syndrome primarily refers to the cases of congenital or acquired brainstem disorders that result in central alveolar apnea. Congenital Ondine's curse is also called congenital central hypoventilation syndrome (CCHS), which is classified inherited disease and tends to occur to infants [3]. Acquired Ondine's curse is rare and often secondary to medulla oblongata and pontine brain injury caused by various factors. Ondine's curse syndrome is seldom documented, mainly due to the imperfect establishment of its diagnostic criteria. The proposed criteria include hypercapnia during non- rapid eye movement (REM) sleep, normal PO_2 (arterial blood gas, (ABG)) during voluntary breathing when awake, alveolar hypoventilation during sleep and exclusion of pulmonary diseases [4]. As a complication or manifestation of dorsolateral medullary lesion, Ondine's curse syndrome may cause central sleep apnea and even the weakness or loss of automatic respiration, resulting in fatal outcome [5, 6].

Here, we report a rare case of lateral medullary dorsolateral infarction complicated Ondine's curse.

Case report

A 67-year-old female was admitted to our hospital for dizziness, slurred speech and unsteady walk. Neurological examination revealed right Horner's syndrome, hoarseness, dysarthria, dysphonia, drooping right eyelid, smaller eye fissure of the right eye with normal extraocular movements, anhidrosis on the right side of the face, and left facial and right body hypoalgesia. The right side of the body ataxia movement was unstable, round bilateral pupils (right pupil 3. 0 mm; left pupil 3. 5 mm) were sensitive to light reflex, and large horizontal nystagmus was seen in left vision. The right nasolabial sulcus became shallow, and the bilateral Babinski's sign was positive (+). The result of internal examination was not remarkable. Auxiliary examination with brain CT scan (October 20th, 2018) demonstrated multiple ischemic foci. The patient received anti-platelet aggregation and anti-lipid plaques treatment to improve the circulation, scavenging oxygen free radicals, etc.

At 21:42 on October 20th, 2018, the patient exhibited sputum cough, irritability and decreased pulse oxygen. An electrocardiogram (ECG) monitoring unveiled the SPO_2 of 85%. The patient was congested with phlegm, so an oropharyngeal airway was inserted. Respiratory and cardiac arrest occurred at 21:48, and the patient was given extracoracic cardiac compression immediately, with intravenous injection of adrenaline, simple respirator assisted breathing, and then endotracheal intubation and ventilator-assisted breathing. At 22:05, spontaneous respiratory was recovered (SPO_2 of 95%) and the rescue concluded. Still restless, the patient was administrated with intravenous pump infusion of midazolam. Blood gas analysis showed that: pO_2 of 77 mmHg, pCO_2 of 44 mmHg, Na^+ of 132 mmol/L, K^+ of 3. 0 mmol/L, Glu of 14. 0 mmol/L, and Lac of 5. 2 mmol/L.

Brain magnetic resonance diffusion weighted imaging (DWI) (November 2nd, 2018) showed diffusion-limited signal in right medullary (Figure. 1). The brain vascular magnetic failed due to the patient's own reasons. Tried offline ventilator multiple times, but all failed. On the third day of tring offline ventilator, the patient suffered a second rescue on November 5th, 2018 due to her uncooperative, and then apnea during sleep occured, and blood gas analysis revealed hypoxemia and blood carbon dioxide retention without a ventilator. After the patient’s condition was stable, her family purchased a ventilator, which was not regularly used after discharge. Her death in sleep occurred on the 58th day after discharge.

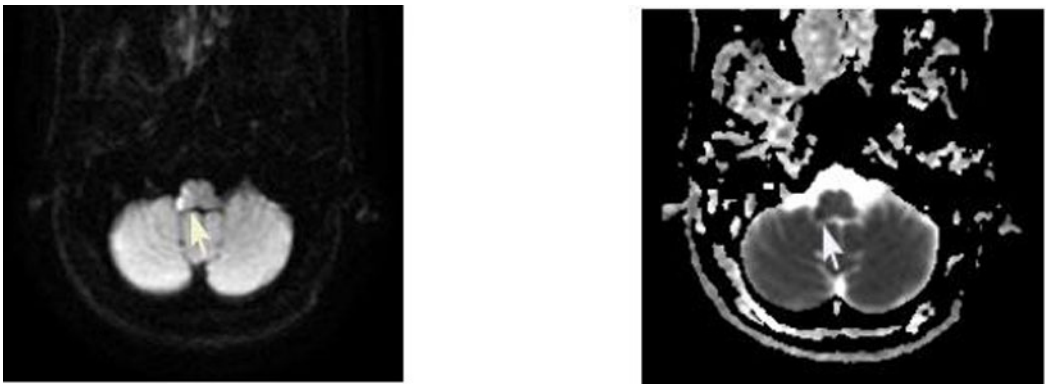

Figure. 1 A and B(Patient's brain MRI) : A: Image of craniocerebral DWI cross-sectional scan revealed a signal at the right side of the medulla oblongata(white arrows); B: the corresponding ADC showing a low signal involving pyramidal tracts and reticular structures (white arrows).

Discussion

Acquired medullary infarction was first reported by Severinghavs. Subsequent reports were almost caused by bilateral medullary infarcts [7]. In 1977, Levine et al reported a case of left medullary infarction leading to Ondine's curse, but autopsy found pathological changes of bilateral medulla [8]. However, unilateral medullary infarction also led to Ondine's curse. In 1990, Bogosslavsky et al reported two cases of respiratory failure caused by dorsolateral infarction of the medulla oblongata [9]. Terao reported a case of right medullary dorsolateral and bilateral cerebellar infarction with Ondine's curse and rapid respiratory failure [10]. In 2018, Yusuke Mon reported a case of lateral medullary infarction with severe dysphagia and worsening of respiratory failure in the chronic phase of recovery, but without ondine's curse syndrome [11]. Some Japanese researchers reported that medullary infarction can cause respiratory failure or central respiratory dysfunction [12, 13, 14]. In any case, these reports indicate that in the medulla, there are neurons that affect respiratory movement.

In the central system, the groups of nerve cells generating and regulating the rhythm of respiratory are called the respiratory centers, which distribute in the cerebral cortex, diencephalon, pons, medulla oblongata and spinal cord. In 1923, Lumen's experimental study of cats with transverse brainstem sections confirmed that the basic respiratory rhythm in mammals originated from the lower brainstem. The human respiratory center consists of random respiratory system and autonomic respiratory system. The nerve impulses of random respiratory system originates from the cerebral cortex and conducts along the corticospinal tract [15]. Autonomic respiratory system originates from the lower brainstem, modulating breathing movement according to the concentration of oxygen and carbon dioxide of blood. The central autonomic respiratory center is divided into three major groups, dorsal respiratory group (DRG), ventral respiratory group (VRG) and pontine respiratory group (PRG), which distribute in three symmetrical regions [16] (Figure. 2). DRG is located in dorsal medial medulla, the ventrolateral part of the nucleus, tractus solitarius, which mainly contains inspiratory neurons. Its function is to contract the inspiratory muscles and to cause inspiration. VRG is located in ventrolateral medulla oblongata, including nucleus doubtful and nucleus posterior facial nerve and their adjacent areas. Its function is to cause the contraction of the expiratory muscles, to produce active expiration, and to regulate the activities of laryngopharyngeal assisted ventilator and respiratory neurons in the medulla oblongata and spinal cord. PRG is located in the dorsal part of the pontine head, which is considered as the respiratory adjustment center, mainly containing expiratory neurons, and its function is to restrict inspiration and to promote the transformation from inspiration to expiration [15, 16]. The dorsal respiratory center refers to the solitary tract and nucleus of solitary tract in the dorsal medial part of the medulla oblongata. The ventral center includes the nucleus ambiguus, the dorsal vagal nucleus and the reticular structure of the medulla oblongata. The automatic breathing during sleep depends on the activity of chemoreceptor neurons that respond to hypoxia, hypercapnia, or both. They are provided by the brainstem reticular structure, controlling respiratory rhythm and respiratory motion, whose impaired manifestations include sleep apnea and rhythmic respiratory abnormalities. Studies have shown that serotonin and glutamatergic neurons located near the medullary surface of the medulla may play a key role in maintaining automatic respiration in the human body. Unilateral medullary lesions reduce the sensitivity of chemoreceptors

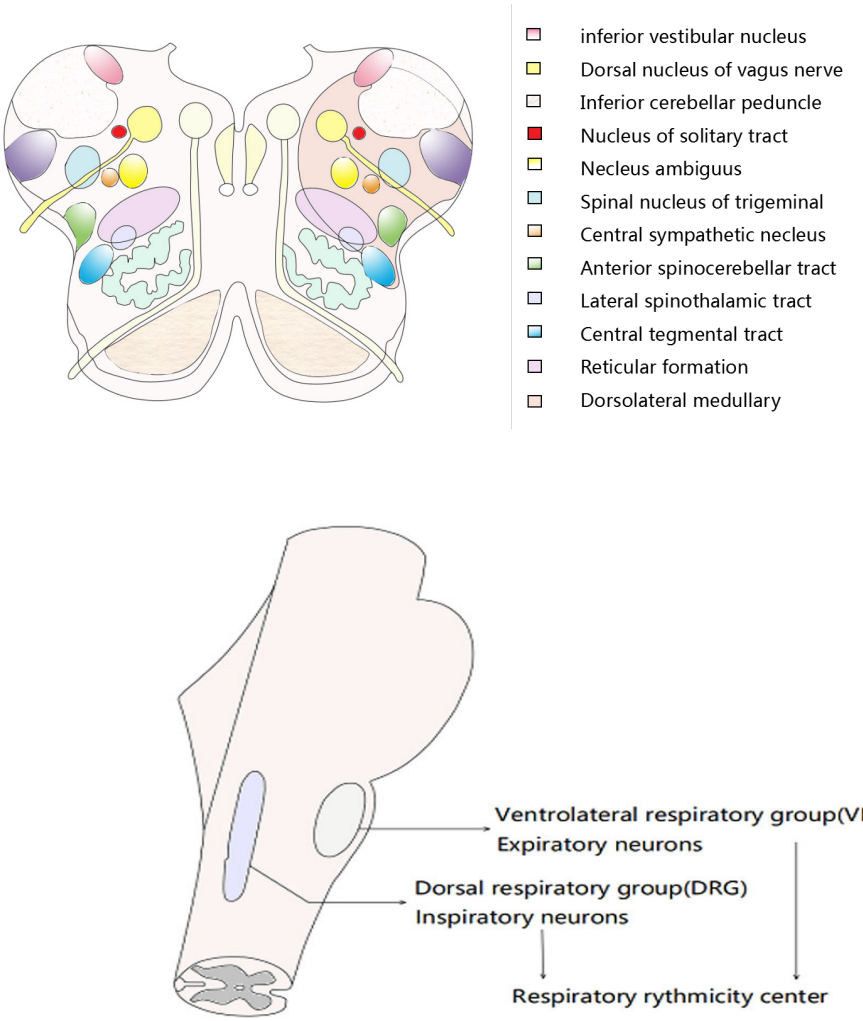

Figure. 2 [21] A and B (Pattern diagram of Medulla): A: Neurons and fiber bundles involved in dorsolateral medullary injury; B: The distribution of respiratory neurons in the medulla.

to CO_2, while chemosensitivity exerts minimum effect on respiration during waking [16, 17]. When the automatic respiratory system is damaged, the respiratory afferent input of medullary neurons and solitary tract nucleus is reduced, and the automatic component of breath-driven is also reduced. Patients cannot effectively cope with carbon dioxide retention during sleep, which may be involved in central sleep apnea [15, 18]. It has been reported that animals with chemically induced unilateral lesions in the retrotrapezoid and subretrofacial nuclear areas exhibit absent or decreased phrenic nerve output during inhalation of CO_2 [19]. Some researchers have assumed that the unilateral dominance of the medulla oblongata was controlled [15]. Some scholars believed that the reticular structure first crossed to the contralateral side before it was sent to the descending fibers to the spinal cord, so unilateral medullary infarction damaged both sides of the controlled respiratory fibers [20]. The infarction of the medulla oblongata is the leading cause of secondary central alveolar hypoventilation syndrome in adults, most common in unilateral or bilateral posterior inferior cerebellar arteries. It is well known that Wallenberg syndrome can be induced by infarction of the dorsolateral medulla oblongata due to either thrombotic occlusion of the ipsilateral posterior inferior cerebellar artery (PICA) or stenosis/occlusion in the proximal vertebral artery or its branch [19].

This patient was unilateral medullary infarction without major respiratory dysfunction, manifested by recurrent dyspnea during sleep, apnea and decreased oxygen. Blood gas analysis unveiled hypoxemia and blood carbon dioxide retention. Her clinical symptoms were rapidly improved after waking up or application of mechanical ventilation, and there was no significant change in neurological symptoms. The above symptoms were in line with the charateristics of Ondine's curse syndrome.

During the later follow-up, the patient still needed a ventilator to maintain breathing at night and intermittent oxygen inhalation in the daytime. The ventilator was gradually detached, but the patient died in sleep on the 58th day after discharge. Therefore, we consider that the sleep apnea may be caused by the cerebral infarction damage to the brainstem reticular structure of the medulla oblongata, or the occlusion of the posterior cerebellar artery, which may result in the loss of spontaneous respiratory control function. Unfortunately the patient did not complete the process of brain MR. In addition, it may be that the long-term using of the ventilator causes respiratory muscle fatigue and does not adapt to spontaneous breathing.

Because of the extremely high mortality rate of Ondine's curse syndrome, patients with suspected medullary infarction should be vigilant, and doctors and families should also pay close attention to it. There is no definite standard for the diagnosis of secondary Ondine's curse syndrome. Take effective measures to help patients avoid death. Application of mechanical ventilation is the primary therapeutic approach. If the ventilator is applied in time and taken offline as soon as possible according to the patient's condition, the patient may be prevented from fatigue due to ventilator, and it may be possible to leave the ventilator and avoid death. The treatment of aminophylline, salicylic acid, caffeine, thyroxine and other drugs can enhance the sensitivity of central chemoreceptors to CO_2, but further investigations are still needed.

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