# Analysis of Ondine's Curse Syndrome

L Liu, K Pu, Z Shi

***ABSTRACT***

*Ondine's curse Syndrome is a central sleep apnoea syndrome caused by medulla respiratory centre dysfunction, with clinical manifestations such as respiratory dysfunction during wake, difficulty breathing, increased partial pressure of carbon dioxide ($PCO_2$), sleep apnoea or death during sleep. This paper presents a case of a patient, who was confirmed with the diagnosis after clinical analysis, $PCO_2$ comparison and tracking two similar cases in the family. Ondine's curse syndrome is rare and easily missed, and there is no specific drug treatment. The disease prognosis is poor. The treatment of this disease is difficult and the use of mechanical ventilation and diaphragm pacing therapy might exhibit some short-term efficacy. Drug treatment still needs further study; the long-term effect was still not good.*

**Keywords:** Genetics, Ondine's curse syndrome, partial pressure of carbon dioxide

# Análisis del Síndrome de la Maldición de Ondina

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***RESUMEN***

*El síndrome de la maldición de Ondina es un síndrome de apnea del sueño central causado por disfunción del centro respiratorio de la médula oblonga, con manifestaciones clínicas tales como disfunción respiratoria durante el despertar, dificultad para respirar, aumento de la presión parcial del dióxido de carbono ($PCO_2$), apnea del sueño, o muerte durante el sueño. Este trabajo presenta el caso de un paciente que fue confirmado con el diagnóstico después de análisis clínicos, comparación de $PCO_2$, y el seguimiento de dos casos similares en la familia. El síndrome de la maldición de Ondina es raro y fácilmente escapa al diagnóstico. No hay medicamento específico para el tratamiento. El pronóstico de la enfermedad es pobre. El tratamiento de esta enfermedad es difícil, pero el uso de la ventilación mecánica y la terapia de estimulación del diafragma pueden tener cierta eficacia a corto plazo. El tratamiento medicamentoso requiere todavía de más estudio; su efecto a largo plazo todavía no es bueno.*

**Palabras claves:** Genética, síndrome de la maldición de Ondina, presión parcial del dióxido de carbono

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## INTRODUCTION

Ondine's curse syndrome is a kind of central sleep apnoea syndrome caused by medulla respiratory centre dysfunction with clinical manifestations such as: no respiratory dysfunction during wake, difficulty breathing, increased $PCO_2$, sleep apnoea or death during sleep. Ondine's curse syndrome is divided into primary type and secondary type (1, 2), which is rare in clinical practice, and to contrast the $PCO_2$ during the day-wake and night-sleep is useful in diagnoses. The treatment of the disease is more difficult. The cases reported in this research was of the constitutional type (CCHS), and mechanical ventilation therapy was used [Puritan-Bennett 840 Ventilator system, Manufactured in Idrelan for Puritan-Puritan-Bennett Corporation, a subsidiary of Mallinckrodt

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inc, Carlsbad, CA, United States of America [USA] (3), which exhibited a certain short-term effect, while the medication treatment had no effects (4). But the long-term efficacy is not so good, thus the treatment of this disease still needed further research.

**CASE REPORTS**

The patient was male, 13 years old, who was sent to the intensive care unit (ICU) of the Fifth Affiliated Hospital of Zhengzhou University, because of cough and expectoration for more than 10 days and who deteriorated with dyspnoea for two hours. The patient had the previous history of ventilation dysfunction occurring during sleep at night, and often has to be awaked by his parents' with stimulation in the early morning. Admission examination finding were: temperature was 36.4 °C, BP–100/60 mmHg, $SpO_2$–90%, in light coma, being pushed into the ward by flat car, bilaterally pupil's size and shape was equal, about 3 mm in diameter, and light reflex was not present, lips were cyanosed; the breath sounds were harsh, and rhonchi could be heard, the heart rate was 87 beats/minute, the rhythm was regular and no pathological cardiac murmur was heard and P2 > A2. The abdomen was soft, with no tenderness or rebound tenderness; bilateral Babinski responses were negative. Cardiac colour ultrasound showed pulmonary arterial hypertension and ECG showed no abnormalities.

Preliminary diagnosis was as follows: pneumonia and respiratory failure and pulmonary hypertension. After admission, the arterial blood gas analysis was performed with GEM premier3500 blood gas analyzer (Instrumentation Laboratary Company, 180 Hartwell Road Bedford, MA 01730−2443, USA), the results showed pH: 7.18, $PaO_2$: 58 mmHg, $PaCO_2$: 89 mmHg, $HCO_3$: 37.4 mmol/L, BE: 9.0 mmol/L; the bedside chest film showed pulmonary infection; the routine blood studies showed: white blood cell (WBC) 18.3 × $10^9$/L, neutrophils: 90%. The patient received endotracheal intubation, mechanically ventilated, (PB-840 respirator, USA), piperacillin tazobactam (piperacillin/tazobactam, produced by Zhongshan Branch, United Laboratories Co, Ltd, Zhongshan, China) and given phentolamine (produced by Shanghai Xudong Haipu Pharmaceutical Co, Ltd, Shanghai, China) intravenous infusion for reducing pulmonary artery pressure, eliminating phlegm, relieving asthma, nutritional support and symptomatic treatment.

The next day after admission, the patient recovered consciousness, the sputum culture grew Bauman Acinetobacter, which was sensitive to piperacillin, after antibiotic treatment for five days, the haemogram reverted to normal, the pulmonary infection was improved, and the patient was extubated. Echocardiography review results suggested that the structure and function of the heart was normal. After extubation, $PCO_2$ was daily checked for six hours: 65−82 mmHg at night, 48−60 mmHg during the day. Two hours after night-sleep at the third-day after extubation, patient could not be awakened and was found to have an scultatory rhonchi not significantly increased than before. An urgent check of arterial blood gas analysis showed pH: 7.28, $PaO_2$: 68 mmHg, $PaCO_2$: 82 mmHg, $HCO_3$-: 27.4 mmol/L, BE: 6.1 mmol/L; blood routine examination showed that the WBC was 12.3 × $10/^9$L. The patient was once again intubated and mechanically ventilated and imipenem cilastatin sodium (produced by United Laboratories Co, Ltd, Sanzhao Science and Technology Industrial area, National High Tech District, Zhuhai, Guangdong, China) was added for strengthening anti-infection treatment. On the following day, the patient was awake, and was extubated on the third-day after the second intubation, and then was given antibiotic centinned anti-infection treatment, at the fifth day after the second extubation, the patient had no cough, no expectoration, and no dyspnoea, with normal routine blood results.

After the second extubation, the night-sleep breathing became shallow and slow with irregular respiratory rhythm and amplitude and the both lung fields were clear and the patient could open his eyes after strong stimulation, then be gradually awoke, and could answer questions correctly with normal respiration by the next morning, although the patient was awaken by stimulation. The arterial blood gas analysis indicated $PaCO_2$ during waking hours was lower than during sleep. During the daytime, the patient could undergo normal activities, without muscle weakness and could eat with normal breathing. After the second extubation, the patient had no further coma. The medical history, revealed that a brother and a cousin had the same symptoms, and the brother of the patient was found unconscious an early morning three years ago, and died. The clinical symptoms and patient and family history, suggested the diagnosis of Ondine's curse (CCHS) syndrome. Thirty days after discharge from hospital, when the parents went to wake him up in the morning, the patient was found death.

## DISCUSSION

Ondine's curse syndrome is a kind of central sleep apnoea caused by medulla respiratory centre dysfunction, namely active breathing control failure. The clinical manifestations are no respiratory dysfunction during the waking state. The brain cortex gives breathing instruction and the respiratory system undergoes ventilation. During sleep, the brain cortex is inhibited, whereas the bulbar centre respiratory centre in the Ondine's patient also dysfunction experience, and cannot give breathing instruction, so the patient may manifest severe respiratory dysfunction. Ondine's curse syndrome is divided into primary type and secondary type (1, 2): the former may be associated with genetic defects (5, 6), which is most common in infants and young children, and can also occur in adults; the latter is mainly caused by factors such as intracranial operation, trauma, infection, particularly the brainstem lesions (leading to respiratory dysfunction).

Primary Ondine's curse is also called congenital central hypoventilation syndrome (congenital central hypoventilation syndrome, CCHS), which was first reported under the name of CCHS by Melins in 1970, and now has more than 300 cases reported. The aetiology and pathogenesis of CCHS is not clear, and it has the characteristics of familial aggregation and genetic involvement evidence. It has been proven that CCHS is an autosomal incomplete dominant genetic disease, and PHOX2B (similar with pairing homologous gene 2B) is the main pathogenic gene, located in 4p12 (7, 8). There were three persons in the patient's family who had a similar history, which indicates obvious genetic features. Partial pressure of carbon dioxide which is persistently higher than 60 mmHg during sleep is a recognized indicator.

In 1999, the USA Thoracic Society (ATS) put forward criteria for the diagnosis of Ondine's curse syndrome: 1) lack of ventilatory response in hypercapnia and hypoxaemia; 2) in general, the patient has enough ventilation during wake, while during sleep, although the patient has the normal respiration rate, the patient may have inadequate ventilation, because of reduced tidal volume; 3) some cases may have inadequate ventilation during wake and sleep 4) the primary nerve muscle, lung, cardiovascular and brain stem disease that can explain the inadequate ventilation must be excluded (9). Partial pressure of carbon dioxide of this patient during sleep was significantly higher than that during the day, indicating that the patient had an obvious respiratory disorder during sleep, which is in accordance with the characteristics of CCHS.

Ondine's curse syndrome as a central sleep apnoea syndrome, needs early diagnosis. Treatment of Ondine's curse syndrome is mainly to improve the ventilatory disorder by mechanical ventilatory support (3) and diaphragm pacing (10), while there is no specific medication (11, 12). The patient had been admitted to hospital for pneumonia, and had been in coma during admission, but the patient did not previously appear to have pneumonia, also did not appear to be in coma. From the progression of the disease, it can be considered that pneumonia might induce exacerbation of Ondine's curse syndrome. The results of this case report were consistent with that reported by Trang (5), while the effects of medication still needed further study. The long-term prognosis effect of this disease is poor.

## CONCLUSIONS

The Ondine's curse syndrome is a central sleep apnoea syndrome, caused by functional disorder of the medullary respiratory centre, the clinical manifestations exhibited no respiratory dysfunction in the waking status, while breathing difficulties would occur during the sleep. The disease is very rare and the comparison of $PCO_2$ between the awake status during the day and sleep at night could help the diagnosis. The disease is difficult to treat and the use of mechanical ventilation and diaphragm pacing therapy might exhibit some short-term efficacy. The results of this observation were consistent with Trang (5) and drug treatment still needs further study, while the long-term prognosis is still not good.

## AUTHORS' NOTE

All authors have no conflict of interest regarding this paper.

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