

# ACQUIRED ONDINE'S CURSE

## Case report

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**ABSTRACT** - We report and discuss the case of a 55-year old man who presented a history of stroke as well as chronic obstructive pulmonary disease. When admitted into the emergency room, he was diagnosed with a vertebro-basilar syndrome. A brain MRI showed a hyperintense area in the lower right brainstem laterally within the medulla, which corresponds to the area of the pathways descending from the autonomic breathing control center. During hospitalization, the patient had several episodes of prolonged apnea, mainly when asleep, having often to be "reminded" to breath. A tracheostomy was then performed with the patient under mechanical ventilation. Treatment with medroxyprogesterone, fluoxetine and acetazolamide was also started. He was discharged after 64 days breathing environmental air with no apparent episodes of apnea. He returned to the emergency room in the following day with a clinical picture of aspiration bronchopneumonia, followed by septic shock and death. *Conclusion:* the Ondine's curse is one of the posterior stroke's presentation characterized by loss of automatic breathing and for the unpredictability of clinical evolution and prognosis. Such a syndrome has rarely been reported in adults and the diagnostic criteria are not consensual in the reviewed literature. Thus any diagnostic confirmation should be flexible. There are many therapeutic symptomatic options in such cases, ranging from pharmacologic approach, use of bilevel positive airway pressure and implantation of diaphragmatic pacemaker.

**KEY WORDS:** Ondine's curse, posterior stroke, loss of automatic breathing.

### Maldição de Ondina adquirida: relato de caso

**RESUMO** - Relatamos e discutimos o caso de um paciente de 55 anos de idade que apresentara história de acidente vascular cerebral e doença broncopulmonar obstrutiva crônica. Quando admitido no setor de emergência, foi diagnosticado como vítima de síndrome vértebro-basilar. A ressonância magnética mostrou hiperintensidade no tronco inferior à direita ao nível do bulbo, o que corresponde a área das vias descendentes do centro do controle respiratório automático. Durante a hospitalização o paciente teve vários episódios de apnéia prolongada, especialmente durante o sono, tendo sido freqüentemente "lembrado" a respirar pela equipe médica e enfermagem. A traqueostomia foi então realizada, com o paciente inicialmente mantido em ventilação mecânica. Tratamento com medroxiprogesterona, fluoxetina e acetazolamida foram também iniciados de forma escalonada. Foi liberado após 64 dias, respirando ao ar ambiente sem episódios aparentes de apnéia. Retornou à emergência no dia seguinte com quadro clínico compatível com broncopneumonia aspirativa, seguida por choque séptico e morte. *Conclusão:* a Maldição de Ondina é uma das formas de apresentação de um acidente vascular encefálico de circulação posterior, marcada por perda da respiração automática e pela imprevisibilidade da evolução clínica e prognóstico. Tal situação foi raramente descrita em adultos e os critérios diagnósticos não são um consenso na literatura revisada, devendo haver flexibilidade na determinação desta entidade. Existem várias opções terapêuticas sintomáticas no manejo dos pacientes com esta síndrome, indo desde a abordagem farmacológica, uso do BIPAP (bilevel positive airway pressure) até a colocação do marcapasso.

**PALAVRAS-CHAVE:** maldição de Ondina, acidente vascular encefálico de circulação posterior, perda da respiração automática.

Ondine's curse, also known as central alveolar hypoventilation syndrome, is an extremely rare condition characterized by failure of breathing mechanisms during sleep<sup>1</sup>. Affected patients can normally breath when they are awake, but inevitably evolving to prolonged apnea after falling asleep. Congenital

central alveolar hypoventilation is extremely rare, with only 60 cases reported in the literature until 1999<sup>2,4</sup> and it is clearly associated with Hirschprung's disease and gastroesophageal reflux. The acquired form of the disease, meanwhile, can result from medullary tumors<sup>5</sup>, infection (particularly poliomyelitis),

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upper cervical trauma with Duret hemorrhage, some mitochondrial diseases, degenerative diseases (e.g. multiple system atrophy), demyelinating disease (e.g. multiple sclerosis) or non-specific anoxic-ischemic insults<sup>6-8</sup>. Moreover, failure of automatic control of breathing due to brainstem infarction and vertebralbasilar ischemia has rarely been reported<sup>8,9</sup>. Among aberrant ventilatory patterns, which constitute the most important cause of death in the acute phase of stroke, Ondine's curse is the pattern which allows the most accurate localization of the lesion, which typically occurs in the lower brainstem and involves the lateral portion of the medulla. Typically, this lesion causes a selective interruption of the descendent anterolateral medullocervical pathway, which in its turn is responsible for automatic breathing.

The term "Ondine's curse" is more commonly used for cases of congenital central alveolar hypoventilation, but it can also be applied to acquired cases<sup>8</sup>. It arises from Germanic mythology, in which Ondine, an oceanic nymph of incomparable beauty punishes her unfaithful lover with the loss of all movements and functions without not involving his conscious will. Therefore, he was condemned to remain awake forever. A similar situation happens in patients with Ondine's curse, once they cannot sleep without mechanical ventilation aid<sup>8,10</sup>.

#### CASE

A 55 year-old male African descendant patient, with history of hypertension, diabetes mellitus, smoking, alcoholism, chronic obstructive pulmonary disease and a previous stroke 7 months before, presented to an emergency service complaining of vertigo, nausea, vomiting, dysarthria, headache and left hemiparesis which had began right after waking up. His wife mentioned that he had also developed abundant nasal secretions as well as a "stuffed" voice. At physical examination, he had diminished breathing sounds in his left lung and diffuse ronchi. At neurological examination, he manifested left-sided weakness and diminished sensitivity to pain in his right side, sparing the face. Coordination was normal in his right side and it was difficult to evaluate on the left side due to his state of weakness. He also had palmomental, glabellar, mandibular and Myerson reflexes, anisocoria (left pupil larger), right-sided enophthalmos and diminution of corneal reflex. His labial commissure was deviated to the left, and there was bilateral palatine immobility, bilaterally diminished vomiting reflexes and dysphagia were present. No meningoradicular signs were observed. The patient was transferred to the Intensive Care Unit (ICU) after a sudden episode of concomitant apnea with bradycardia, followed by generalized tonic-clonic seizure. He was intubated and submitted to mechanical ventilation. Laboratory exams during the first week after admission showed dyslipidemia, elevated blood glucose, a 1.7 creatinin (BUN/creatinin ratio higher than 40), normocytic anemia and leucocytosis with a shift to the left. Arterial blood samples were obtained during apnea periods and blood gas analysis showed  $pO_2$  of 49 and,  $pCO_2$  of 98, with 80% of hemoglobin saturation.

The patient's baseline  $pCO_2$  was around 50, and the remaining blood gas values were previously normal. His ECG showed left ven-

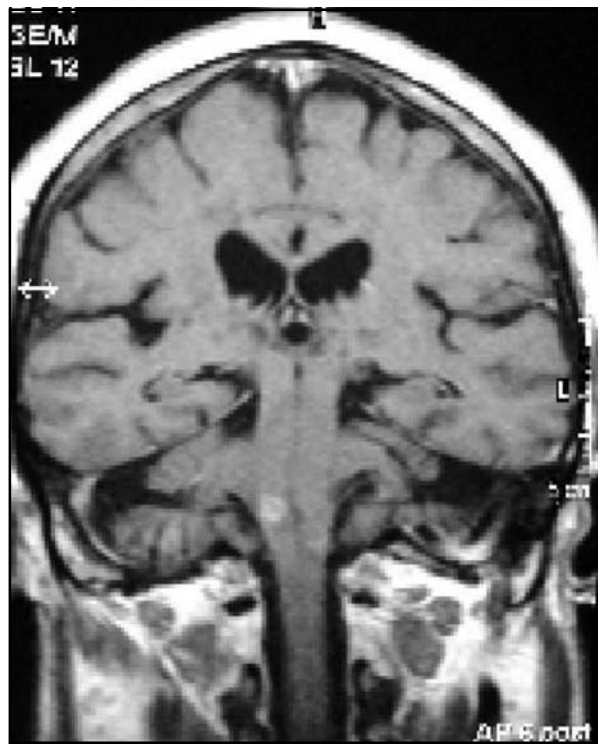


Fig 1. Cranial MRI after de gadolinium infusion.

tricle overload with no acute ischemic changes. CSF examination was unremarkable. The chest X-ray showed hyperexpansion of the lungs and bilateral basal consolidations. Cervical doppler studies showed diminished flow in the right vertebral artery and at the lower limit of normality in the left carotid, while the other vessels were normal. The EEG showed nonspecific diffuse cortical involvement. A head CT with no contrast showed several small, hypodense lesions scattered throughout the white matter, with no evidence of intracranial bleeding or midline shift. Brain MRI showed multiple hyperintense lesions at T2 and FLAIR sequences, located in the periventricular and subcortical white matter, right external capsule, thalami, pons, medulla and at the two cerebellar hemispheres and apparently representing ischemic lesions. After contrast injection, enhancement in a single lesion, located in the inferior cerebellar peduncle and medulla was observed, suggesting a recent lesion. The ventricles and sulci were thought to be slightly prominent for the patient's age. MRI findings are shown in Figure 1.

During his stay at the ICU, the patient had two further episodes of sudden apnea, as well as one episode of transient tetraparesis, which were followed by aspiration pneumonia. Extubation was difficult to perform due to frequent apnea episodes, which required the installation of synchronized intermittent mechanical ventilation to cope with prolonged apnea during sleep or in periods of distraction. The patient was frequently "reminded" by the medical staff and assistant physicians that he had to breathe. After 3 weeks of failing attempts to remove the patient from assisted ventilation, a bilevel positive airway pressure (BIPAP) system was installed, and he was concomitantly medicated with 10 mg medroxyprogesterone 4 times daily, 20 mg fluoxetine once daily and 250 mg acetazolamide twice daily, having responded well to the treatment. He was discharged from

the ICU with recovered strength in the right side of his body but with persistent of some remaining deficits, especially dysphagia and dysphonia.

After leaving the ICU, speech therapy was instituted, recommended to help the patient to control nasal regurgitation of swallowed liquids, as well as to improve his hoarseness. He was discharged from the hospital with nasogastric tube two months after admission, with return medical visits scheduled for both speech therapy and neurology clinics. Polysomnography was also scheduled to confirm the diagnosis. Two days after discharge, however, the patient was back to the emergency room. He had pulled out the nasogastric tube by himself and presented malaise, fever and shortness of breath. A few minutes after his arrival, he had a tonic-clonic seizure followed by cardiorespiratory and distal multifocal myoclonus 6 hours later. After one week he died from sepsis despite broad-spectrum antimicrobial therapy.

## DISCUSSION

Brainstem strokes represent 15-25% of all ischemic events among individuals with risk factors<sup>10</sup>. As the brainstem is an extremely complex structure with several nuclei and pathways, as well as regulatory centers controlling vegetative functions, lesions affecting this area, independently of their etiology, can cause an extremely variable constellation of symptoms. However, despite this diversity, specific syndromes can occur and they will depend on the artery in which the occlusion is placed; the referred syndromes include both the lateral medullary (Wallenberg's) syndrome and the medial medullary syndrome<sup>11</sup>.

In the present clinical case, findings from both medullary syndromes were found with acute involvement of the pontine cranial nerves (V, VII, IX and X) and of the inferior cerebellar

peduncle were found. Anisocoria and enophthalmos can also be attributed to the lesion, due to involvement of sympathetic projections arising from the brainstem. Old ischemic lesions were also found in various subcortical locations, although their significance in this case was uncertain. Another interesting fact was an isolated episode of sudden tetraparesis which resolved in less than 24 hours, and that was thought to be caused by a basilar artery transient ischemic attack. The myoclonic seizures shortly before death could also have been caused to a new ischemic event; however, due to their multifocal (non-generalized) and distal pattern, they were judged more likely to be due to anoxic injury secondary to cardiorespiratory arrest (cortical reflex myoclonus<sup>12</sup>).

The clinical presentation of this patient, therefore, points out to a serious compromise of vertebrobasilar circulation. The vertebral arteries are the main blood supply to the medulla, reaching not only the lower three fourths of the pyramids, but also the medial lemnisci and the most of the retroolivary region (lateral medullary region), the restiform body and the inferior and posterior portions of the cerebellar hemisphere. If an occlusion of the vertebral artery occurs in the branches supplying the lateral portion of the medulla, vertigo can be a prominent symptom in Wallenberg's syndrome. Meanwhile, a smaller lesion arising caused by the occlusion of one of the spinal arteries branching off from the vertebral artery usually causes a form of contralateral hemiplegia which spares the face. It is known as medial medullary syndrome. This kind of lesions can rarely result in quadriplegia. Meanwhile, the obstruction of the basilar artery can result in a combination of several brainstem syndromes, which can also occur in combination with other syndromes due to the occlusion of

Table 1. Patient's signs and symptoms comparing with known neurovascular syndromes.

	Patient's signs/symptoms	Affected structure
Medial medullary syndrome	Hemiplegia sparing the face	Pyramidal tract
	Loss of tactile and proprioceptive sensitivity	Medial lemniscus
	Ataxia with a tendency to fall towards the lesion (ipsilateral)	Uncertain: can involve restiform body, cerebellar hemispheres, olivocerebellar fibers and spinocerebellar tracts
Lateral medullary syndrome	Vertigo, nausea and vomiting	Vestibular nucleus and its connections
	Dysphagia, hoarseness, loss of vomiting reflex, bradycardia	Cranial nerves IX and X
	Ipsilateral loss of pain and temperature sensitivity, sometimes involving the face	Spinothalamic tract
Basilar artery syndrome	A combination of various brainstem syndromes combined with those related to occlusion of posterior cerebral artery branches. Intact sensitivity in the presence of near-complete paralysis (as in the TIA) presented by the patient.	Same as above + thalamic nuclei,

the posterior cerebral artery or its branches<sup>10</sup>. In the case of this patients, it is somewhat difficult to precise which artery of the posterior circulation was affected, as angiographic studies were not performed due to the patient's unstable conditions, both during and after the acute event. However, the occlusion probably occurred in one of the branches of the vertebral artery, with the posterior inferior cerebellar and superior cerebellar arteries being likely candidates.

The signs and symptoms presented by the patient, as well as their relation to recognized medullary syndromes, are summarized in Table 1. In addition to the deficits associated with medullary syndromes, the patient also had evidence of dysfunction of cranial nerves V and VII, probably due to pontine involvement.

Imaging studies demonstrated generalized vascular compromise, with an acute lesion in the lower brainstem visible on MRI. The discrepancy between CT and MRI findings illustrate the lower yield of the former in the diagnosis of posterior fossa lesions. When MRI is not readily available, therefore, physical examination findings are of extreme importance to localize the lesion, as well as for inferring its prognosis. In this case, for example, the involvement of medullary respiratory centers was initially suggested by the loss of automatic breathing after the ischemic event. The recovery of this dysfunction probably occurred due to the resolution of the edema surrounding the ischemic lesion observed through the MRI. Bullemer et al. reported only 2 of 10 patients that showed central defects visible in magnetic resonance like the present case<sup>4</sup>. Bogousslavsky et al.<sup>13</sup>, in their clinicopathological correlation of brainstem strokes with loss of automatic breathing, have detected unilateral ischemia in most of the cases, what suggests that bilateral lesions are not required for the occurrence of significant hypoventilation.

Laboratory criteria for the diagnosis of Ondine's curse are not well established<sup>1-3,14</sup>. Some authors propose that prolonged and persistent periods of apnea associated with desaturation and hypercapnia during non-REM sleep should be demonstrated for diagnosis, while other ones mention some criteria such as: (a) normal pulmonary and mediastinal anatomy, (b) pO<sub>2</sub> normalization through voluntary breathing when awake and (c) precipitation of alveolar hypoventilation with diminished voluntary control (i.e. sleep). Our patient did not fit these criteria, as he was not able to undergo polysomnography and because he had a preexisting pulmonary disease. Nevertheless, the clinical picture and the localization of the lesion suggest that Ondine's curse was indeed the syndromic diagnosis, and that the criteria for diagnosing such syndrome should be flexible in some situations.

Both pharmacological and supportive treatment are available for Ondine's curse. The goal of the former treatment is to activate the remaining respiratory nuclei through the induc-

tion of metabolic acidosis. Drugs such as trazodone, acetazolamide, medroxyprogesteron, protyptilin, clomipramine, tiroxine and caffeine have been used for this purpose<sup>11,15</sup>. As for supportive treatment, the main options are the use of bilevel positive airway pressure and the placement of a diaphragmatic pacemaker, being this latter alternative responsible for a 50-70% success rate in some series<sup>2</sup>.

In patients with acquired Ondine's curse, however, spontaneous recovery is the norm and pacemaker is rarely required. These patients usually respond well to tracheostomy and nocturnal assisted ventilation until spontaneous recovery occurs. Deaths usually occur during sleep, however, presumably due to complete apnea. Therefore, the prognosis of the disease is variable, depending on the specific location of the lesion, and recovery, although frequent, is usually unpredictable.

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