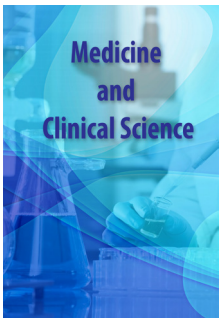
Medicine & Clinical Science

Case Report




# Locked In Syndrome: Looking Inside It, A Case Report

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## Abstract

Locked-in syndrome (LIS) is well known to the public, since the masterful description of Alexandre Dumas. Additionally, Émile Zola reflected this condition in one of his characters, and later, others did as well [1]. In medical practice it is considered a rare neurological disease, with an incidence and a prevalence that is difficult to determine. It affects both sexes and is more common in adults, basically as a complication of cerebrovascular diseases (CVD). Patients with classic LIS develop quadriplegia, but normally remain conscious and can communicate by blinking, constituting the most dramatic presentation of brain stem involvement. To diagnose it is challenging because of its similarity to conditions such as akinetic mutism, coma, persistent vegetative state, psychogenic pseudocoma, or brain death. There have been cases reported that have taken months and even years to establish a definitive diagnosis. The CVD incidence rate in Africa is among the highest incidence in the world, with West Africa (WA) being the largest. Paradoxically, no reports of LIS associated with CVD have been found in the subregion. Our goal is to document the first case in WA of a patient with classic-type locked-in syndrome, secondary to acute pontine ischemic infarction, associated to severe vitamin B deficiency, and accompanying with acute osmotic demyelination syndrome. Which was a result of the intensive correction of severe hyponatremia. A case that is difficult to manage and complex to diagnose, which makes it especially interesting for our professionals. Recognizing the disease will avoid delays in diagnosis and facilitate early intervention, reducing associated complications and mortality, which remains high in the initial phases. Then, together with a multidisciplinary team, achieve the best possible social reintegration of patients, knowing in advance the serious limitations they will face in their future.

## Introduction

A 57-year-old patient, previously healthy and strictly vegetarian, was found in her bed, in a stupor. Family members reported having lost contact with her in the last 48 hours, so it cannot be confirmed that she ingested water or food during that period. She arrived at hospital with moderate dehydration, severe hyponatremia (Na = 100 mmol/L), and pneumonia as working diagnosis. The hydromineral imbalance was corrected, sodium reached 135 mmol/L, then vital signs normalized; nonetheless, a progressive deterioration of consciousness was observed. After two weeks of admission, severe progressive CNS dysfunction established. The patient was transferred to our clinic, at the request of her family. Upon arrival, she was admitted to the critical care unit. General physical examination: The patient was in bed, inert, in a 30° supine position, dependent on oxygen (7 liters x min), with a high-flow mask and enteral nutrition via NGT. Skin with normal coloring. Marked respiratory arrhythmia is observed, which presents with paroxysms of superficial polypnea, despite maintaining an oxygen saturation level greater than 95%, which drops sharply to 82–83%, again requiring supplemental oxygen, with evident exhaustion and profuse sweating.

Temperature: 36.7 °C. Chest examination revealed apneustic respiratory pattern, with fine bilateral crackles. Cardiovascular examination, with sinus rhythm that is frequently interrupted by paroxysmal tachycardia, which does not exceed 150 beats per minute, and coincides with the respiratory arrhythmias described above. BP: 130/70 mmHg. The abdomen is motionless, and unremarkable exam. CNS: Upon admission, it was not possible to establish communication with the patient caused by the impossibility of obeying orders.

Pupils were isochoric and slightly reactive to light, with spontaneous opening of the eyelids and the appearance of vertical eye movements, with inability to make horizontal movements, emitting incomprehensible grunts. Oculocardiac, oculocephalic, cough, and gag reflexes were absent, as well as corneal reflex. Proprioception, light touch, temperature,

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and pain sensation cannot be assessed as a complete lack of communication, which equally affects the complete examination of the cranial nerves. She couldn't chew, swallow, talk, or made any movement, with quadriplegia (power 0/5). Hyperreflexia with bilateral Hoffman and Babinski found. GCS=4(E1, V2, M1). Severe brain stem dysfunction was suspected. After two weeks of treatment in the ICU, and three from the onset of the disease, the patient progressively improved. The respiratory rhythm disorders and cardiac arrhythmias ceased. The GCS score reached 8/15 (E4, V2 and M2). It is during this period, which the medical team observed during the family member's visit, that a response pattern usually appeared characterized by hyperventilation, profuse sweating of the forehead, and sinus tachycardia. At such times, she typically kept her eyes open and blinked, although the anarthria persisted. EEG and computed axial tomography of the brain were requested. The report informed ischemic infarction and pontine myelinolysis. The EEG described normal brain activity, with the presence of predominantly posterior and reactive alpha activity. The peculiarity of her behavior in being able to recognize the family member and capability to generate a limbic/autonomic response pattern, together with the CNS examination described above, the CT scan report and normal EEG allowed us to consider the diagnosis of classical locked-in syndrome (LIS).

## Discussion

Locked-in syndrome (LIS), cerebra-medullary-spinal disconnection, efference state, or pseudo coma; with all these names, a complex, and rare, neurological disorder is described that causes complete paralysis of all voluntary muscles, except those that control eye movements. The condition was first described in one of the sessions of the Société Anatomique of Paris in June 1875 under the presidency of Jean-Martin Charcot, a hospital intern named Camille Darolles presented a clinical pathological case of thrombosis of the trunk of the basilar artery, being considered the first description of the disease. The term locked-in syndrome was coined by1966 by Plum and Posner and the cases reported since remaining to be few [2,3]. Three variants of the LIS are described by Bauer (1979) [4]. The classic form is defined by complete immobility, with preservation of the ability to make vertical eye movements, blink, and maintain a normal level of consciousness. The incomplete variant is like the previous one but with a few additional motor functions. Total immobility is described as complete body paralysis, with loss of eye movement and preservation of cortical function, examined by electroencephalogram (EEG). Our patient, after the initial comatose state, took approximately three weeks to move from coma to locked-in syndrome. In the literature reviewed, there is no harmony in relation to the interval between the beginning of symptoms and diagnosis, with reports of months and even years; but, it is common to observe an average of 3 to 4 weeks. [5-7].

The levels of vitamin B12 in plasma were 150 pg/mL, complemented by moderate macrocytic anemia. Evidencing vitamin B12 deficiency, commonly related to a strict vegetarian habit. The association between low levels of vitamin B12 and homocystenemia is well-documented. Nevertheless, it is still controversial to consider it as a cardiovascular risk factor in entirely vegetarian people, with arguments for and against that explaining the existence of CVD in young people without another risk factor [8,9]. In our case, it is difficult to prove the relationship, so we will limit ourselves to commenting on the association. On the other hand, the link between severe hyponatremia (Na = 100 mmol/l) and cytotoxic cerebral edema explains the comatose state described upon arrival at the hospital. Prompt correction of moderate dehydration, and the severe hyponatremia, explained the pontine myelinolysis secondary to osmotic demyelination syndrome (OSD). Confirmed by computed tomography, with magnetic resonance being the gold standard for the diagnosis [10-12]. This in turn explains the neurological deterioration, despite hemodynamic restoration. Patient brain CT reported low attenuation crossing the midline of the pons, which measured 3.3×2.6×2.7 cm, occupying almost the entire pons, compatible with pontine myelinolysis and acute ischemic infarction (Figure1).

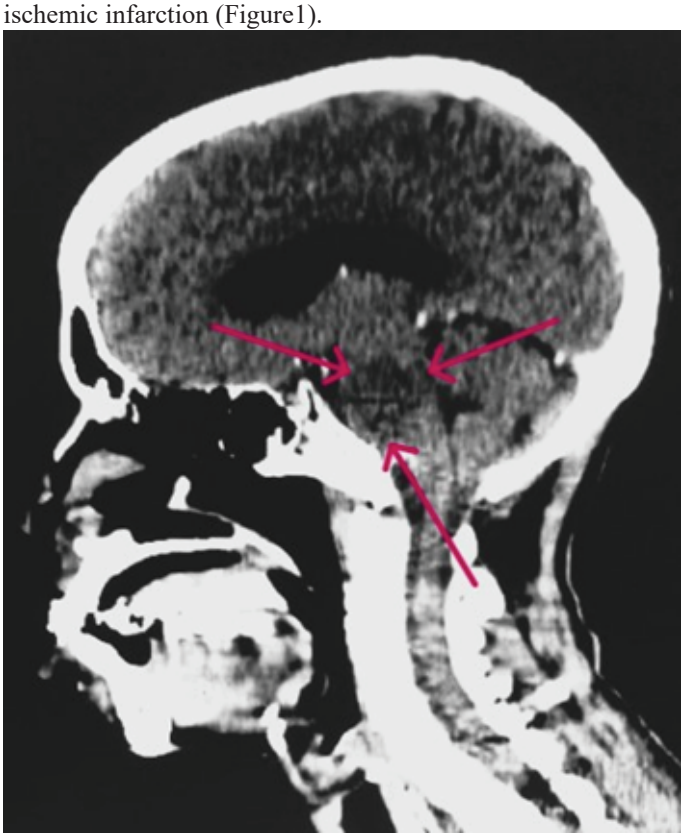

***Figure 1.*** Brain CT Scan

The diagnosis of LIS depends on the physician's ability to identify that the neurological manifestations originate in the brain stem and the posterior circulation that supplies it, requiring a rapid but thorough neurological examination. EEG findings may be useful in differentiating locked-in syndrome from coma.

It usually takes weeks before the patient goes from a coma to a locked-in state [13,14].

Clinical manifestations presented in our patient:

- Quadriplegia
- Apneustic respiratory pattern
- Anarthria.
- Insomnia
- Maintained eye opening and Blinking.
- Emotional lability

Initially, the neurological manifestations were explained as a result of severe dehydration and hyponatremia. Nevertheless, after correction of the hydro electrolyte imbalance, and hemodynamic stability achieved, there was no improvement in the neurological status, and brain stem reflexes remained absent.

It was at the end of the third week that the apneustic respiratory pattern and associated heart rhythm disorders were reverted. During this phase, spontaneous eye-opening is observed and subsequently the autonomic/limbic response pattern described above. In references, it is found that it is usually the family member or the healthcare personnel who assist, who discovers that the patient can establish communication, which occurred in our case. [15,16]. The patient was able to recognize familiar faces among other not familiars, and manifest himself through autonomic/limbic responses, given by tachycardia, increased amplitude, and frequency of the respiratory pattern, as well as profuse sweating on the forehead. A response that was reproduced every time she saw the family member.

Contrasting with the apathy and in expression with health personnel. This behavioral pattern, along with normal electroencephalogram and brain CT results, were key in the diagnosis of LIS. Etiology In principle, locked-in syndrome can be caused by any lesion affecting the ventral pons and midbrain; this includes vascular lesions, mass effects, infections, trauma, and demyelinating disorders. Cerebrovascular diseases are by far the most common etiology, representing more than 70% of cases. LIS is the most dramatic presentation of brain stem CVD. Patterson and Garbois described 139 patients with LIS; 82 (59%) were CVD. The rest included trauma, central pontine myelinolysis, tumors, encephalitis, neuro-Behçet disease, multiple sclerosis, and other less common etiologies [3-6,17]. In our review, we found only two cases reported in West Africa (WA), both in Nigeria and coincidentally secondary to multiple sclerosis [18,19].

## Differential diagnosis

The differential diagnosis includes entities presenting with quadriplegia and acute-onset mutism, such as unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), and akinetic mutism [5,7,15]. UWS (formerly known as vegetative state) is the first stage of coma remission, characterized by spontaneous opening of the eyes and mainly the resumption of autonomic function, the absence of conscious behavior is sinecuanum in its diagnosis. In our patient, we understood by conscious behavior, the patient's ability to recognize a familiar face among other unfamiliar ones and trigger an autonomic/limbic response. Manifested through tachycardia, sweating and hyperventilation, with a recurring pattern, after recognizing the familiar face, recurrently. Which is not repetitive, but discriminative, being able to differentiate between unknown and known people.

This comportment, together with the imaging results and the normality of the EEG, allowed the diagnosis of LIS to be established. In akinetic mutism, patients are conscious, but cannot move or speak, but unlike the LIS, they are not physically paralyzed. On the other hand, there is a psychiatric history, usually depression, and clinical and radiological studies are normal. Catatonia is another condition that can be like LIS and is also related to psychiatric conditions. While people with classic LIS tend to communicate with their eyes, people with catatonia avoid doing so, and radio images studies are also normal. MCS is more challenging; nevertheless, brain stem response reflexes are typically intact in the MCS state. There may also be periods when patients can sporadically respond to commands, making small movements when asked, but they cannot respond or communicate consistently and may only demonstrate very basic cognitive responses, such as reaching for objects, sometimes can answer questions, even if the answer has a repetitive pattern, whether correct or not. In contrast, in classic LIS there is no type of movement, except for blinking, producing a definitive absence of movement in the total variant. Furthermore, differences can be found in the EEG pattern between both, with MCS being like coma, and in LIS, it is typically normal. Additionally, in MCS, the lesion does not necessarily have to be present in the brain stem; it can be attributable to a diffuse brain injury, infection, hypoxemia, toxins, medications, etc.

Organic injury to the brain stem is always present in LIS and is evidenced by computed tomography or magnetic resonance imaging. LIS usually occurs, unlike MCS, related of cerebral vascular diseases, trauma, or demyelinating conditions. PET and SPECT are useful in establishing the diagnosis of MCS. Other differential diagnoses included Guillain-Barré syndrome, myasthenia gravis, and upper cervical spinal cord injury.

## Epidemiology

Cerebro vascular diseases are a major health problem worldwide, and its impact is dramatically brutal in Africa. Over the past five decades, there has been a continuous increase in the number of CVD patients across sub-Saharan Africa. The prevalence has reached 1,460 per 100,000 in some areas, becoming among the highest in the world [20]. The global or regional incidence and prevalence of LIS is still unknown, as it is considered a very rare condition. Fewer than 1,000 people in the U.S. have this disease. In general, there is little data. In 2013, a study estimated a prevalence of 0.7/10,000 patients with classic LIS in Dutch nursing homes, and the ALIS (LIS Association) in France reported that more than 500 people will be living with LIS in 2022 there. The average age of onset for all cases of locked-in syndrome generally ranges between 30 and 50 years. The condition is slightly more prevalent in men in the ALIS study [5,7,17,22,23]. Only two cases found in WA, both were in Nigeria, and associated with multiple sclerosis (MS). It is a curious epidemiological fact, considering that cerebrovascular diseases are overwhelmingly more frequent in the WA than MS, and represent more than 60% of worldwide LIS cases. In addition, MS is a rare entity in Africa, especially in our subregion, determined by the scarcity of epidemiological data, and affected by underreporting and underdiagnosing [24]. Scarce reports of LIS may be associated with the still high mortality from CVD in underdeveloped countries, with up to 80% at three years in some areas [25,26]. Which reduces the possibility of survival of these cases in the acute phase. Still, for those who can survive, the other challenge is getting the correct diagnosis of LIS in the early stages.

## Prognosis

During the chronic phase, respiratory function, the ability to swallow, and consciousness may partially or completely recover. Our patient did not survive the initial stage of the chronic phase and died from bronchopneumonia, which is the most common cause of mortality in these patients. In general, the prognosis of LIS is poor. In countries with low economic development, the data is worse. Conversely, for the lucky ones who manage to overcome the acute phase, LIS is often diagnosed between 2–4 weeks later, after ruling out other similar pathologies. The 5-year survival rate can reach 86% and at 10 years it is around 80% in developed countries. Greater survival has been found in young people who received prompt rehabilitation [27-30]. Still, most people with LIS will remain in the locked-in stage or with permanent limitations for the rest of their lives. Sporadic cases of complete social reintegration have been documented; yet they remain anecdotal.

## Treatment

After the patient is stabilized and the presence of LIS is confirmed, the intervention of a multidisciplinary team is necessary for the management of these patients. Which, depending on the severity of the CNS involvement, the previous health status, and the availability of centers for neurological rehabilitation, have managed to demonstrate sporadic results. Some scores have been developed for the evaluation of these patients and the follow-up. Mortality and recovery are highly variable, depending on the underlying etiology, age, and co morbidity. LIS generally has a high mortality rate in the acute stage. The greatest challenge lies in airway care and achieving enteral nutrition as soon as possible. The vast majority, as in our case, die from respiratory complications. The most reported causes of death are pulmonary complications and further brain stem damage.

## Conclusions

Despite the high incidence of CVD in general, and WA in particular, locked-in syndrome remains an under-reported condition. To date, this is the first LIS report relating to cerebrovascular disease in the WA subregion. It is also the first case associated with vitamin B12 deficiency, and accompanied by pontine myelinolysis, secondary to the correction of severe hyponatremia. Which makes this case much less common and more interesting. In our opinion, if the level of awareness about LIS is increased, more cases could be diagnosed in the sub-region. Allowing early intervention in the acute phase, and after achieving neurological stabilization, starting early rehabilitation. It is essential to perform a thorough and continuous neurological examination, considering that great clinical suspicion is required to consider the diagnosis. It is also important to request neuroimaging studies to confirm or rule out its presence, as well as EEG. We are convinced that it is possible to diagnose more cases if the previous premises are met. The next challenge, once the diagnosis is confirmed, is to create centers where chronic patients can be cared for, improve their quality of life and, if possible, ensure their social reintegration.

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