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Locked-in Syndrome: Insights into Etiology, Diagnosis, Management, and Quality of Life

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Abstract

Locked-in Syndrome (LIS) is a rare and severe neurological condition resulting from damage to the ventral pons, leading to complete paralysis of voluntary muscles while preserving consciousness and cognitive function. This review consolidates current knowledge on the etiology, diagnosis, management, and quality of life in LIS, emphasizing its complexity and the need for a multidisciplinary approach.The condition's etiological spectrum includes vascular events, trauma, infections, and demyelinating disorders, necessitating a comprehensive diagnostic approach integrating advanced neuroimaging and electrophysiological tools.

Therapeutic strategies emphasize multidisciplinary care to address acute stabilization and long-term rehabilitation. Early interventions, such as thrombolysis and respiratory support,

combined with advanced neurorehabilitation techniques, have shown promise in improving outcomes. Notably, patients with LIS often report a higher-than-expected quality of life, attributed to strong social support, emotional resilience, and access to assistive technologies, highlighting the resilience of patients in adapting to extreme physical limitations.

This review underscores the importance of individualized care that aligns with patient values and emphasizes the necessity of further research. Future studies should focus on refining diagnostic methods, advancing communication technologies, and exploring the psychological dynamics affecting both patients and caregivers. By fostering a collaborative, patient-centered approach, the quality of life and care for individuals with LIS can be significantly improved.

Key words: Locked-in syndrome, brainstem injury, management, quality of life

Introduction

Locked-in Syndrome (LIS) is a rare but devastating neurological disorder primarily caused by damage to the ventral pons, often following ischemic events such as basilar artery occlusion. This condition exemplifies the profound impact of neurological injuries on motor functions and communication, making it a critical area of study in neurorehabilitation. The syndrome is characterized by complete paralysis of voluntary muscles in all four limbs and the inability to speak (aphasia), with preserved consciousness and cognitive function. Vertical eye movements and blinking, which remain intact in most cases, are crucial for minimal communication [1].

LIS can be classified into classical, incomplete, and complete subtypes, each with distinct clinical features [1,5]. First described by Plum and Posner in 1972 [2], LIS represents one of the most disabling neurological disorders due to the profound loss of voluntary motor control, severely impairing communication and quality of life.

The epidemiology of Locked-in Syndrome (LIS) reveals that the mean age of onset typically ranges between 30 and 50 years. Research shows a slight male predominance, with studies reporting that 51.2% of cases occur in men compared to 48.1% in women [3]. The age of onset has been documented to range from 22 to 77 years, with a mean age of approximately 46.79 years [3]. Patients with LIS of vascular origin frequently exhibit comorbid conditions such as hypertension, atherosclerosis of major arteries and diabetes, emphasizing the role of

systemic vascular risk factors in the syndrome's pathogenesis [3]. Understanding the epidemiology of LIS, including its vascular risk factors and demographic trends, is critical for guiding diagnostic and therapeutic strategies.

This review aims to synthesize current evidence on LIS, focusing on its etiology, clinical presentation, diagnostic challenges, therapeutic strategies, and quality of life considerations.

A comprehensive literature review was conducted using PubMed, Google Scholar, and ScienceDirect databases to gather current and rebeliant information. The search covered publications up to 2024 without a lower time limit to ensure the inclusion of foundational studies. Search terms included "Locked-in Syndrome," "etiology," "diagnosis," "management," "prognosis," "quality of life," and "brainstem injury", combined in various ways to ensure a broad retrieval of relevant articles.

The review included peer-reviewed scientific publications written in English, with a particular focus on original research, systematic reviews, and case reports addressing key aspects of LIS. Studies that did not contribute significantly to the understanding of LIS, such as those focusing solely on pediatric cases, were excluded. By applying these criteria, the literature search aimed to synthesize high-quality evidence, providing a thorough and objective overview of the current understanding of Locked-in Syndrome.

By consolidating findings from a wide range of studies, this review aims to provide a clear and up-to-date understanding of the challenges associated with LIS and the potential avenues for future research. This synthesis will serve as a resource for clinicians, researchers, and healthcare providers working to enhance outcomes for patients affected by this condition.

Clinical features

Locked-in syndrome (LIS) presents with a distinct and severe clinical profile primarily characterized by tetraplegia and anarthria, resulting from extensive motor impairments. Patients lose voluntary control of all four limbs due to the involvement of the corticospinal tracts, and the inability to produce speech stems from paralysis of the facial, glossopharyngeal, and laryngeal muscles [1,4]. Despite these profound motor deficits, patients with LIS retain their consciousness and limited ability to communicate. This communication is usually possible through eye movements, particularly vertical gaze and blinking, which are controlled

by midbrain structures that remain unaffected in most cases. However, horizontal eye movements can be impaired when pontine structures are involved, depending on the extent of the lesions.

Locked-in syndrome (LIS) can be categorized into three main subtypes based on the extent of motor and communication impairments. Classical LIS is characterized by complete paralysis of voluntary muscles, with preserved vertical eye movements and blinking, which serve as the primary means of communication. Incomplete LIS involves partial preservation of motor function, such as slight movements of a finger or toe, allowing for limited interaction and communication. Complete LIS represents the most severe form, marked by total loss of voluntary motor function, including the inability to perform vertical eye movements or blinking, which eliminates any overt form of communication [2,4,6].

Some individuals may experience diplopia (double vision) or blurred vision. Emotional lability, such as inappropriate laughter or crying, is another frequent feature of LIS. Sensory pathways are typically preserved, maintaining normal or slightly altered sensation. In some cases, sensory deficits ranging from mild to complete absence may occur. Respiratory dysfunction can also arise from lesions extending to the pontine respiratory centers, causing abnormal breathing patterns, such as Cheyne-Stokes respiration or ataxic respiration, necessitating vigilant monitoring and support [1,4].

Other associated symptoms include insomnia and vertigo, contributing to the complexity of the condition. Internuclear ophthalmoplegia (impaired coordination between the eyes) may also occur. While cognition and consciousness are usually preserved, some patients in early stages of LIS may experience mild impairments in attention, memory, or executive functioning, though these are far less severe than the motor deficits [1,4].

Pathophysiology

The pathophysiology of Locked-in Syndrome (LIS) arises from lesions in the ventral pons or caudal ventral midbrain, disrupting the corticospinal and corticobulbar tracts while sparing the reticular activating system, thereby preserving consciousness [2,3]. Quadriplegia results from damage to the corticospinal tract, which controls voluntary movements of the limbs and trunk.

Injury to the corticobulbar tract leads to loss of speech and facial expressions, as it controls cranial nerve-mediated motor functions [2].

Eye movements provide a crucial insight into the pathophysiology. Horizontal gaze is coordinated by the paramedian pontine reticular formation (PPRF), which interacts with the ipsilateral abducens nucleus and contralateral oculomotor nucleus via the medial longitudinal fasciculus (MLF) [2]. Lesions affecting this region impair horizontal gaze. Vertical gaze, on the other hand, is controlled by mesencephalic structures, including the rostral interstitial nucleus of the MLF (riMLF) and the interstitial nucleus of Cajal. These structures are often spared in LIS, allowing vertical eye movements and blinking to persist. However, more extensive lesions can compromise these centers, resulting in vertical gaze palsy or, in severe cases, complete ophthalmoplegia.

Large lesions may also impact the pontine respiratory centers, leading to disruptions in the regulation of breathing. This can result in irregular respiratory patterns caused by impaired coordination of signals necessary for maintaining rhythmic and effective ventilation [3].

This selective disruption of motor pathways, with preservation of consciousness and partial eye movement control, highlights the unique pathophysiological mechanisms underlying LIS. Accurate localization of lesions through advanced imaging techniques is crucial for diagnosis and targeted management [3].

Etiology

Locked-in Syndrome (LIS) is caused by lesions or damage to the ventral pons or caudal ventral midbrain, arising from various etiologies, including vascular events, trauma, masses, infections, demyelinating disorders, and iatrogenic complications [2,3]. The most common cause is vascular in origin, predominantly ischemic or hemorrhagic stroke [3,4,5]. Other vascular causes include aneurysms or malformations of the basilar artery, arterial dissection (e.g., cervical manipulation), basilar artery vasospasm, and basilar migraines [2].

Traumatic brain injury, both blunt and penetrating, is the second most frequent cause [3], often leading to direct damage to the ventral pons or secondary infarctions. Other traumatic causes include supratentorial lesions resulting in brainstem herniation.

Nonvascular causes include masses, such as primary or metastatic tumors (e.g., pontine astrocytomas or metastases from adenocarcinomas), exerting pressure on the brainstem. Rarely, infections like pontine abscesses or meningitis may cause LIS through increased intracranial pressure or direct brainstem involvement [3].

Demyelinating disorders such as multiple sclerosis, central pontine myelinolysis (commonly due to rapid correction of hyponatremia) [3], and Guillain-Barré syndrome [3,4] are rare but significant causes. Central nervous system infections, including those associated with SARS-CoV-2, have also been reported to cause LIS-like presentations [2].

Certain iatrogenic complications, such as coronary bypass surgery, lumbar puncture, shunt procedures, and stellate ganglion or brachial plexus blocks, have been linked to LIS. Adverse medication effects or post-cardiac arrest reactions may also contribute to its development [2].

Other less common etiologies include poisoning (e.g., neurotoxic bites like those from a krait snake) [4], exposure to toxins affecting neuromuscular function, and neurodegenerative conditions like amyotrophic lateral sclerosis (ALS) [3]. Additionally, metabolic conditions such as severe hyperhomocysteinemia, prolonged hypoglycemia, and certain CNS infections have been implicated in rare presentations of LIS [3].

Diagnosis

The diagnosis of Locked-in Syndrome (LIS) requires a comprehensive approach combining physical examination, neuroimaging, and functional diagnostic tools. Key clinical features include quadriplegia, anarthria, and preserved vertical eye movements or blinking, which enable assessment of cognitive function through responses to visual stimuli or eye-based communication [1]. Eye-tracking technology can further confirm preserved cognition in patients with limited motor output [15].

Neuroimaging, particularly magnetic resonance imaging (MRI), is essential for identifying brainstem lesions, often in the ventral pons. Techniques like diffusion tensor imaging (DTI) provide insights into white matter integrity, while functional MRI (fMRI) and electroencephalography (EEG), including event-related potentials (ERPs), are valuable when behavioral assessments are inconclusive [13,14]. Recent EEG advancements, such as alpha and theta band oscillations, offer improved detection of cortical activity and covert awareness

in LIS patients [10,11,15]. Combining these tools with structured scales like the Coma Recovery Scale-Revised (CRS-R) enhances diagnostic precision, particularly in cases with minimal or inconsistent responses [15].

Differentiating LIS from conditions with overlapping symptoms, such as unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), and cognitive motor dissociation (CMD), remains challenging [2,3,12]. UWS presents with spontaneous eye-opening but no behavioral evidence of awareness, while MCS shows fluctuating responses to stimuli. CMD involves preserved cognition without external motor output and requires advanced diagnostics like fMRI and ERP for confirmation [2]. Other conditions, such as akinetic mutism (linked to frontal-subcortical damage) and catatonia (a psychogenic state with mutism and rigidity), further complicate the differential diagnosis [3].

Brain death and coma must also be excluded; brain death is characterized by the absence of brainstem reflexes and respiration, whereas coma involves impaired consciousness with varying brainstem reflex preservation. Cervical spinal cord injury may mimic LIS with quadriplegia but sparing of facial motor function [3]. Lesion localization is critical, as LIS typically stems from brainstem damage, whereas UWS, MCS, and CMD are associated with supratentorial lesions [2].

A thorough clinical history, toxicological analysis, and structured, repeated assessments are essential to rule out reversible causes, such as drug-induced states or neurotoxic poisoning, which can mimic LIS [3]. This multimodal diagnostic strategy establishes the foundation for timely and tailored therapeutic interventions.

Communication

Communication in Locked-in Syndrome (LIS) is a critical issue, as it serves as the primary means for patients to express their needs, emotions, and thoughts despite their profound motor impairments. Effective communication strategies not only improve patient quality of life but also play a pivotal role in facilitating medical care and psychosocial support.

Voluntary eye movements, such as blinking or directional gaze (e.g., upward, downward, or lateral), are central to communication in LIS, as they often remain the only available means for patients to connect with their environment. Advances in assistive technologies and

augmentative and alternative communication (AAC) systems have significantly expanded these possibilities, providing innovative solutions that enable non-verbal patients to express their needs. Furthermore, the growing accessibility of computers and internet connectivity has enhanced the implementation of such technologies, especially for individuals with severe motor impairments [5,6].

Communication methods for LIS patients are diverse, encompassing a range of non-invasive and advanced technologies tailored to the patient's abilities. Non-invasive approaches include simple tools, such as letter boards, communication grid systems, and more sophisticated eye-tracking systems that interpret gaze movements [5,9]. For more advanced needs, brain-computer interfaces (BCIs) enable communication through neural signals, with options ranging from non-invasive EEG-based systems to invasive approaches like electrocorticography (ECoG). Additionally, advanced imaging techniques, including functional MRI (fMRI) and magnetoencephalography (MEG), provide opportunities to analyze brain activity and enhance communication strategies. While promising, these methods require further refinement to improve usability and accessibility. Collectively, these technologies underscore the critical role of innovation in overcoming communication barriers in LIS patients [5].

One promising innovation is Blink-To-Live, an eye-based communication system specifically designed for patients with motor neuron disorders who experience severe speech impairments [7]. This system uses eye gestures, such as upward or downward gaze and blinking, to encode phrases and commands, which are processed in real-time using smartphone-based computer vision algorithms. The encoded gestures are translated into text and synthesized speech, providing a low-cost and accessible alternative to traditional eye-tracking systems. By leveraging readily available smartphones, Blink-To-Live is particularly suited for low-income settings. Initial testing has shown its effectiveness in facilitating communication, although further optimization is needed to enhance processing speed and accuracy [7].

Important evidence of the effectiveness of assistive technologies in LIS comes from a survey conducted with the French Association of Locked-in Syndrome (ALIS). This study evaluated communication and recovery in LIS patients, finding that 62% of respondents used assistive technologies, 49% regained verbal communication, and 73% recovered some motor function.

These results emphasize the potential for recovery and the importance of advanced communication tools and rehabilitation in improving outcomes for LIS patients [8].

Emerging technologies, such as neural implant-based communication systems, hold promise for further improving communication capabilities in LIS patients. These innovations, though still experimental, represent a crucial direction for future research.

Management and rehabilitation

The treatment of Locked-in Syndrome (LIS) requires a comprehensive, multidisciplinary approach that addresses both the acute stabilization of the patient and long-term care to manage complications and improve quality of life. In the acute phase, immediate priorities include maintaining vital functions and preventing secondary complications. Respiratory support is often necessary, as brainstem lesions can compromise respiratory centers, leading to hypoventilation or respiratory failure [16]. Mechanical ventilation is frequently employed in these cases, alongside close monitoring of blood gases. Nutritional support via enteral feeding, typically through a nasogastric or percutaneous endoscopic gastrostomy (PEG) tube, is essential to meet caloric and hydration needs while minimizing the risk of aspiration pneumonia.

In cases where LIS is caused by ischemic stroke, the prompt administration of thrombolytic therapy has shown potential to significantly improve outcomes, as demonstrated in a case report of a 66-year-old woman with acute LIS. Thrombolysis was administered within the therapeutic window, resulting in the successful recanalization of the basilar artery. The patient experienced a rapid neurological recovery and, after six months of rehabilitation, regained full independence, highlighting the importance of an early intervention [17]. Additionally, early anticoagulation or antiplatelet therapy may be initiated to prevent further thrombotic events, provided there are no contraindications. Hemorrhagic stroke-related LIS may require surgical interventions, such as hematoma evacuation or decompressive craniectomy, to manage intracranial pressure and reduce the extent of brainstem damage [16]. Furthermore, infection control is critical during this phase, as patients are at high risk of respiratory infections, particularly ventilator-associated pneumonia. Antibiotic therapy tailored to the causative pathogen is a key component of managing these infections. Additional interventions, such as

managing electrolyte imbalances, controlling blood pressure to prevent further vascular damage, and addressing hyperglycemia or hypoglycemia, are crucial in the acute setting.

In the chronic phase, rehabilitation should focus on tailored care plans developed by a multidisciplinary team, ensuring that therapy addresses the patient's specific needs and goals. According to recent recommendations, integrating physical therapy, occupational therapy, and speech therapy into a comprehensive rehabilitation program can significantly improve outcomes. Evidence from systematic reviews highlights that tailored physical activity and rehabilitation interventions not only prevent complications like muscle atrophy and joint contractures but also improve motor function and quality of life for individuals with LIS. Structured exercise programs that include active-assisted and resistance training have been shown to enhance strength and reduce long-term disability in patients recovering from LIS caused by stroke [20]. Innovative neurorehabilitation techniques, including robotic-assisted therapy and functional electrical stimulation, have shown promise in enhancing motor recovery and promoting greater independence in LIS patients [18].

In a Swedish cohort study, patients who underwent comprehensive rehabilitation for LIS highlighted the importance of long-term, multidisciplinary care tailored to the individual needs of each patient. The study emphasized strategies such as targeted physical and occupational therapy to improve mobility and independence, along with specialized interventions to manage respiratory and nutritional needs during the recovery process. The findings underscored the importance of addressing comorbidities such as muscle atrophy, pressure ulcers, and thromboembolic events through early and consistent rehabilitation measures [19].

Psychological support for both patients and their families is a critical component of the rehabilitation process, as the psychological burden of LIS is immense. Counseling and psychiatric care aim to address issues such as depression and anxiety, which are commonly observed in these patients. While the prognosis of LIS varies depending on the underlying etiology and the extent of the brainstem damage, a coordinated approach in both the acute and chronic phases can improve survival rates and enhance the quality of life for patients.

Quality of life and care

Quality of life (QoL) in patients with Locked-in Syndrome (LIS) is a complex concept influenced by the profound physical limitations of the condition. However, studies suggest that individuals with LIS often report a satisfactory QoL, challenging societal assumptions about severe disability. This phenomenon, known as the "disability paradox," highlights a disparity between external assessments by healthcare providers and the subjective experiences of patients. For example, a 57-year-old male with LIS following a brainstem stroke resisted recommendations to withdraw care, emphasizing his perceived QoL and strong desire to live. These findings underline the importance of understanding QoL from the patient's perspective and call for further qualitative and longitudinal studies [21].

A study involving 65 individuals with LIS revealed that 72% of participants reported positive QoL despite their physical limitations. Emotional resilience, autonomy, and social support were consistently identified as key factors in preserving QoL in LIS patients. Studies highlight that patients who develop effective coping strategies and receive strong family support often report higher QoL, even in the context of severe physical limitations. Additionally, patients who had lived with LIS longer reported higher QoL, emphasizing the importance of psychological adaptation and early intervention [22, 23].

Studies also highlight a notable discrepancy between the perceptions of QoL reported by LIS patients and their caregivers. While patients often report higher QoL and lower levels of anxiety, caregivers experience significant psychological distress, emphasizing the importance of dedicated psychological support systems for caregivers. Strong social support networks and effective coping mechanisms are critical in preserving QoL among LIS patients, extending beyond physical impairments to include relational and emotional factors [24].

Comprehensive care for LIS patients must extend beyond physical needs, addressing psychological, social, and emotional well-being to ensure a holistic approach to improving life satisfaction.

Implications for Practice and Conclusions

Locked-in Syndrome (LIS) is one of the most profound neurological conditions, presenting unique challenges in diagnosis, management, and rehabilitation. Despite advancements in

medical technologies and care strategies, significant gaps remain, underscoring the need for targeted research and innovation to improve patient outcomes and quality of life (QoL).

Accurate and early diagnosis remains a critical challenge. Misdiagnosis of LIS as other disorders of consciousness often delays appropriate care. Future research should focus on refining diagnostic protocols by integrating advanced neuroimaging tools, such as functional MRI and diffusion tensor imaging, with standardized clinical assessments. Developing automated tools that combine behavioral, neurophysiological, and imaging data could further enhance diagnostic precision, reducing the risk of delays and errors in identifying LIS.

Innovative communication tools are vital to addressing the profound isolation experienced by LIS patients. While assistive technologies such as eye-tracking systems and brain-computer interfaces (BCIs) have improved autonomy, many remain inaccessible due to high costs or technical limitations. Research should prioritize the development of low-cost, scalable solutions that can be widely implemented across diverse healthcare settings. Moreover, exploring hybrid systems that integrate multiple inputs, such as neural signals and eye movements, could enhance the efficiency and usability of these tools, especially for patients with varying levels of motor function.

Rehabilitation strategies require further refinement to address the long-term needs of LIS patients. While personalized physical, occupational, and speech therapies have shown promise, their long-term efficacy in improving functional recovery and QoL is not well-documented. Longitudinal studies are needed to assess the impact of different rehabilitation approaches, including emerging techniques like robotic-assisted therapy and functional electrical stimulation. Additionally, research should explore how to optimize rehabilitation programs for specific LIS subtypes or underlying etiologies, such as vascular versus traumatic causes.

Psychological support remains a critical yet underexplored area in LIS care. Patients often report higher QoL than caregivers, who experience significant psychological distress. This discrepancy highlights the need for structured psychological support programs not only for patients but also for their families and caregivers. Future studies should evaluate the effectiveness of such interventions, particularly in reducing caregiver burden and improving the overall caregiving environment. Understanding the interplay between caregiver well-being and patient outcomes could lead to more holistic care models.

Another key research priority is exploring the long-term trajectories of LIS patients. Comparative analyses across diverse populations and etiologies are essential to identifying factors that contribute to better outcomes. For instance, understanding why some patients adapt better to their condition than others could inform the design of more effective psychological and rehabilitative interventions. Investigating the role of socioeconomic factors, access to healthcare, and technological disparities could also provide valuable insights into improving care delivery.

Finally, collaboration between disciplines, including neuroscience, engineering, psychology, and social sciences, is critical to advancing care for LIS patients. Bridging these fields can drive innovation in assistive technologies, refine neurorehabilitation techniques, and address the broader social and psychological challenges faced by patients and caregivers. Policymakers and healthcare systems should prioritize funding for interdisciplinary research and ensure equitable access to emerging interventions.

In summary, the future of LIS research should focus on three key areas: improving diagnostic accuracy and speed, developing accessible and effective assistive technologies, and optimizing long-term care strategies. By addressing these gaps, the field can better support LIS patients in achieving greater autonomy and QoL, while reducing the burden on caregivers and healthcare systems.

Author Contributions

Conceptualization, UZ and MP; Supervision, UZ and JŚ; Methodology, UZ and WF; Software, UZ and KD; Formal analysis, UZ and GT; Investigation, UZ and WD; Resources, UZ and JW; Writing—original draft preparation, JD and KD; Writing—review and editing, UZ and KS; Visualization UZ; Project administration, UZ and SA; All authors have read and agreed to the published version of the manuscript.

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