

## Sleep disorders in Amyotrophic Lateral Sclerosis

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### ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting both the central and peripheral nervous system. The median survival rate for ALS patients after symptom onset is 2.5 to 3.5 years and after diagnosis of ALS is about 1.5 to 2.5 years. Patients with ALS can have a wide spectrum of sleep disorders including but not limited to insomnia, sleep related breathing disorders, parasomnias, obstructive sleep apnea (OSA) and nocturnal hypoventilation (NH). Sleep-related breathing disorders substantially increase both morbidity and mortality in ALS patients. In this review, we have discussed the ALS motor symptoms, sleep-related breathing disorders, behavioral abnormalities and sleep disturbing factors which impair the health-related quality of life.

### Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder which affects both central and peripheral nervous system and often leads to loss of both upper and lower motor neurons (1-3). Symptoms of upper motor neuron involvement include spastic paresis, increased muscle tone and pseudobulbar palsy when corticobulbar tract is involved. Involvement of lower motor neurons leads to atrophy, fasciculations and muscle weakness. Eventually, all skeletal muscles along with extraocular and sphincter externi muscles may get involved in the later stage of the disease. (2, 4).

Spinal-onset ALS subtype results from gradual loss of anterior horn cells which supply the muscles of the trunk and limbs. Bulbar-onset ALS subtype results in dysphagia and dysarthria during the course of the disease (3, 5). The lifetime risk for ALS for men is about 1:300 and about 1:400 for women. (6, 7). Prevalence rate of ALS is about 5-8/100,000 with peak age of onset being 50-70 years. (1, 8, 9).

The median survival rate for ALS patients is about 2.5

to 3.5 years after symptom onset and 1.5 to 2.5 years after diagnosis of ALS (1, 10, 11). Although there is extensive literature available highlighting the genetic role in familial subtypes and molecular pathology of ALS, there is no definite therapy developed till this date. (12).

Riluzole and edaravone are the only two Food and Drug Administration (FDA) approved drugs for management of ALS patients. These medications have disease modifying effects rather than halting the progression of the disease (13, 14). The muscle weakness in ALS eventually leads to swallow dysfunction, dysarthria, chronic hypercapnic respiratory failure and tetraplegia. Chronic respiratory failure and respiratory infections are the most common cause of premature death in ALS patients (1, 2).

ALS not only affects the activities of daily living but also the health-related quality of life for both the patients and caregivers. The impairment of sleep quality in ALS patients significantly affects the physical and mental well-being of the patients (1, 15-17). A holistic multidisciplinary approach is warranted to address disease manifestations (18).

### Methods

#### *Search Strategy and Selection Criteria*

We searched Medline, Google Scholar, and PubMed using keywords; “Amyotrophic Lateral Sclerosis”, “Sleep disorders”, “Breathing disorder”, “Motor disorders”. Search was limited to English language manuscript only. We identified 60 research literature describing sleep related complications of ALS. In this review, we have described the sleep-related breathing disorders, behavioral abnormalities and sleep disturbing factors which impair the health-related quality of life of ALS patients.

#### *Insomnia*

Insomnia is a frequently encountered sleep disorder in ALS patients (19). Sleep disruptions in ALS are caused by various factors which are discussed in table 1 (20).

Sleep is usually non-restorative which impacts both the daytime performance and motor symptoms. Breathing disorder along with muscle cramps, pain and restless leg syndrome (RLS) significantly impair the ability to fall asleep or maintain sleep in patients with ALS. Immobilization impairs the sleep quality. Insomnia might not only be due to the physical symptoms but also because of depression (existential fear) (2, 19, 21, 22).

Figure 1 describes factors disrupting sleep in patients with ALS.

#### *Sleep and Motor Symptoms of ALS*

Motor symptoms of ALS including muscle cramps, fasciculations, RLS and immobilization impairs the sleep

- ❑ Physiological trauma
- ❑ Respiratory problems
- ❑ Increased salivation and swallowing problems
- ❑ Difficulty in changing positions (turning)
- ❑ Myoclonic activity
- ❑ Muscle cramps
- ❑ Pain in neck, shoulders and legs

Figure 1. Most common sleep disrupting factors in amyotrophic lateral sclerosis (ALS) (20)

quality. Swallowing impairment along with sialorrhea and aspiration increases the risk of recurrent choking (1). Muscle fasciculations are caused by lower motor neuron degeneration and may cause sleep disturbance in ALS patients (23).

Muscle cramps commonly affect lower limbs and are often worse at night. Cramps have a prevalence of 45-92% (24, 25). Muscle cramps are often due to spontaneous discharges with higher frequency (> 300 Hz), than essential for voluntary contraction. Though stretching relieves the cramps, it may not be feasible in patients with ALS secondary to substantial leg weakness (2, 26). Management includes symptomatic treatment with adequate fluid intake, correction of electrolyte imbalance and discontinuation of any contributing medications (statins). In a randomized control trial, Mexiletine 150 mg twice daily was reported to be helpful in relieving muscle cramps in patients with ALS (1, 27). Baclofen and other compounds such as Vitamin-E, memantine and L-threonine have not shown any beneficial effects for management of cramps in ALS patients (28). Quinidine has been reported to decrease cramp intensity and frequency, however, given broad side effect profile (cinchonism, thrombocytopenia and myocardial toxicity), extended usage should be considered cautiously (2, 29).

Worsening motor functions can lead to immobilization (difficulty in changing positions) which often causes pain, nocturnal discomfort, risk for skin lesions and increases dependency on caregivers. Although there is sparse literature on effects of immobilization, it is still considered one of the factors that impairs sleep quality in patients with ALS (16, 30).

Diagnostic criteria of RLS includes; an urge to move the legs (unpleasant or painful sensation in legs), onset of symptoms and their exacerbation at rest or during inactivity, worsening of symptoms at night or evening and relief by stretching or walking, and none of other medical or behavioral conditions to explain the symptoms. Prevalence of RLS is about 10% in the general population, and

women are affected more frequently than men (2, 31). The prevalence of RLS in ALS patients is about 14.6% - 25% (32). Small fiber neuropathy and mild sensory neuropathy have been reported in ALS which contributes to the development of RLS like symptoms in these patients (1, 33). Management strategies include iron supplementation (in iron deficiency), dopaminergic agents,  $\alpha 2\delta$  ligands and opioids (for chronic pain) (34).

Periodic limb movements (PLM) in sleep are seldom investigated in ALS patients. Studies on PLM prevalence and its impact on sleep are limited. In ALS patients, PLM is caused by the spinal cord disinhibition through the degeneration of the descending central pathways (35, 36). PLM index is often elevated in many of ALS patients but is not associated with the arousals from the sleep (37).

#### *Nocturnal Pain in ALS*

Pain and sleep quality are interrelated as pain disrupts sleep and disrupted sleep often enhances the occurrence and worsens pain (38). Nocturnal pain in ALS patients arises from immobilization and difficulty to change position in bed. Spasticity or intermittent muscle cramps contribute to pain. Muscle atrophy also increases the pressure load on both bones and joints. ALS patients may suffer from neuropathic pain, often due to small fiber neuropathy which is seen in almost 75% of the ALS patient population. Other ALS patients may suffer from diffuse pain, without any triggers, non-neuropathic, possibly due to central sensitization of the nociceptive pathways (1, 33).

Nocturnal pain is rarely examined in clinical studies. Nociceptive pain treatment should include preventive strategy, non-steroidal anti-inflammatory agents. Opioids should be reserved for refractory pain. Cannabis is often prescribed to ALS patients for its anxiolytic, sedating and appetite-enhancing actions.  $\alpha 2\delta$  ligands and antidepressants should be considered for neuropathic pain. Central muscle relaxants can be used for spasticity. ALS patients often report pain, which disrupts sleep, hence, chronic pain should be addressed appropriately through symptomatic therapy to improve the quality of life (1, 39).

#### *Sleep-related Breathing Disorders in ALS*

Sleep-related breathing disorders in ALS patients includes obstructive sleep apnea (OSA) and nocturnal hypoventilation (NH). Signs and symptoms of the respiratory system involvement in ALS are described below in table 2. OSA is more prevalent in males and often presents with non-bulbar or spinal onset of symptoms. In bulbar-onset ALS, atrophy of tongue hinders pharyngeal collapse and hence OSA is seen less often than in spinal-onset ALS. Shorter survival rates are seen in ALS patients with OSA

before initiation of ventilator therapy (40). Respiratory muscle weakness may contribute to disease progression (37, 41-42).

Sleep-related hypoventilation is caused by phrenic nerve degeneration and diaphragmatic weakness which leads to a rise in carbon dioxide during rapid eye movement (REM) sleep (44). As the disease progresses, hypercapnia can be seen in non-REM sleep. ALS patients with chronic hypercapnic respiratory failure may have diurnal hypercapnia. Clinical features suggesting hypercapnia includes; morning headache, daytime sleepiness, sleep disruption and dyspnea at rest or exertion, during sleep. In late stages of the disease, patients may adopt sitting positions to avoid orthopnea because of diaphragm weakness. Multiple factors including hypopneas, apneas and diminished gas exchange contribute to decrease in sleep efficiency, reduction of REM sleep, increased arousals from sleep and frequent changes in sleep stages (1, 37, 45, 46).

Nocturnal hypoventilation can be detected by pulse oximetry and transcutaneous capnometry. (1, 45, 47). Transcutaneous capnometry is superior to pulse oximeters in identifying nocturnal hypercapnia and is widely used in diagnosing nocturnal hypoventilation, and introduction of non-invasive ventilation. Factors that predict disease progression and survival are respiratory muscle strength measurements including; maximum inspiratory pressure (MIP), forced vital capacity (FVC), and sniff nasal inspiratory pressure (SNIP). SNIP plays an important role in predicting nocturnal hypoventilation and NIV initiation; FVC and MIP are also monitored regularly in neuromuscular patients for NIV initiation (1, 48, 49).

A study by Aekrivo et. al describing prognosticating factors for development of respiratory insufficiency in patients with ALS, reported longer diagnostic delay, advanced age at diagnosis, bulbar onset of symptoms, lower FVC, low body mass index and low dyspnea subscore or ALS functional rating scale (ALSFRRS-R) were associated with development of respiratory failure (50). Another study reported nocturnal oxygen desaturations were associated with development of respiratory failure and worse prognosis (51).

Multiple retrospective studies and randomized trials have validated that early initiation of NIV increases the survival rate in ALS patients (1, 11, 52-55). Long-term usage of NIV enhances both the sleep quality and quality of life, though ventilator dependency increases over time in such patients (1, 56,57).

Treatment adherence is achieved through ideal mask fitting and selection (oronasal masks for mouth leaks),

Symptoms	Signs
Orthopnea Dyspnea with exertion Dyspnea Paroxysmal nocturnal dyspnea Poor sleep Morning headache Daytime somnolence Cognitive change and dysfunction Softer speech Poor cough Difficulty swallowing	Tachypnea Paradoxical abdominal movement Weight loss Use of accessory respiratory muscles Pooling of secretions Increased work of breathing at rest Decreased chest movement

Figure 2. Most commonly reported signs and symptoms of respiratory system involvement in ALS (40, 41).

appropriate titration of respiratory settings, and education of both patients and caregivers. Bulbar-onset ALS with upper motor neuron dysfunction has shown reduced respiratory drive and intermittent glottis closure making NIV ineffective (58, 59).

Volume support ventilation may be helpful with gas exchange and symptom relief. However, it may enhance patient-ventilator dyssynchrony. This can present as flow dyssynchrony, auto-triggering or ineffective triggering. Management strategies include clearance of secretions by manual assisted coughing or mechanical cough assistance (1, 63). A follow up Polysomnography and capnometry should be considered for patients with ALS (1, 60-62). [1]

Figure 2 describes signs and symptoms of respiratory system involvement in ALS.

*Sleep-related Behavioral Abnormalities*

Sleep-related behavioral abnormalities or parasomnias are movements, behaviors, emotions and/ or perceptions which arise on falling asleep, during sleep or waking up. Parasomnias are defined by partial arousals from either REM or NREM sleep (64). There is no strong evidence that NREM parasomnias like confusional arousals or pavor nocturnus and sleepwalking occur in ALS patients. REM behavioral disorder (RBD), is distinguished by either persistent phasic or tonic muscle activation in REM sleep, which is detectable by electromyogram (EMG) and is called REM sleep without atonia (65).

Patients often act out RBD like dream-enacting vocalizations and movements which might cause falls, injuries and aggressive actions on bed partners. RBD are more commonly associated with neurodegenerative disorders like dementia with Lewy bodies, Parkinson’s disease, multisystem atrophy and synucleinopathies. Management of RBD in ALS patients primarily involves injury preventive strategies and reduction in the number of RBD events in sleep. Pharmacological interventions

including melatonin (3-12 mg) or clonazepam (0.25-2 mg) at bedtime may be beneficial, however, the supporting data is sparse (1, 64-68).

Further clinical studies are required to better understand the pathophysiological and clinical role of REM sleep regulatory pathway neurodegeneration in patients with ALS, RBD or REM sleep without atonia (1, 36).

### Conclusion

Sleep disturbances are a frequent cause of increased morbidity in ALS patients. Notable contributory factors including immobilization, sleep-disordered breathing, RLS, muscle cramps, nutritional issues, loss of communication and gradual motor function impairment are associated with increased disease burden on both patients and caregivers. Sleep-related breathing disorders substantially increase both morbidity and mortality in ALS patients. Clinicians should take a thorough history of not only sleep disrupting symptoms but also of depression, fear, despair and grief and these should be addressed accordingly. Future studies are required to undermine the relation between the sleep symptoms and neuronal structural changes in ALS. Further research is warranted to distinguish the effect of sleep on disease progression, prognosis and quality of life (1, 2, 22, 41, 69).

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