

ALS

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NARRATIVE REVIEW

PAIN MANAGEMENT

Pathogenesis and management of pain in amyotrophic lateral sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease is characterised by deadly progressive motor neuron disease and other neuronal cells death, which is featured by progressive paralysis and leads to advanced disability and mortality due to respiratory failure. By the year of 2040, ALS is estimated to nearly double due to global population ageing.

Pain is one of the overlooked symptoms but widely complained about by patients with ALS. It can arise at any stage of the disease; the intensity of pain may increase with the course of the disease. The pain characteristic depends upon its pathogenesis in inducing pain such as nociceptive, neuropathic, or painful cramps. Pain intensity can be severe at an advanced stage of ALS, thereby increasing the use of pain relievers and sedatives. It has been related to a declined functional status leading to a decreased quality of life and escalating the rate of depression. Management in ALS patients with complaints of pain differs according to the multifactorial character of pain.

The different aspects of pain in ALS has not been much discussed. Therefore, this article will provide an overview of it.

Key word: Pain; Amyotrophic lateral sclerosis; ALS; Pathogenesis; Pain management

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease that implicates central and peripheral motor neurons. The patients succumb to the disease within 2–4 years from the onset. Clinically, ALS manifests as progressive loss of general muscle strength and dystrophy, which leads to respiratory muscle paralysis due to the onset of the bulbar or spinal level.^{1,2}

Pain is one of the indirect secondary conditions of ALS that can be as debilitating as those symptoms associated with the disease directly. It develops in almost 70% of ALS patient during the progression of the disease. The pain frequency is thought to increase with the disease progression.³

The identification of pain in patients with ALS should not be underestimated. It should be evaluated to prevent its adverse effects on the patients' quality of life. It is essential for adequate pain management

to understand the pathophysiology of the condition in each individual suffering from ALS.¹

2. Neurodegenerative mechanism of ALS

The most common adult-onset, primarily motor neuron disease, is ALS. It²² was depicted by unalterable progressive loss of motor neurons at the level of the motor cortex, bulbar and spinal cord, which leads to death. This process results in weakness, spasticity and muscles atrophy, proceeding to paralysis.⁴⁻⁶ The onset is insidious, and although it can occur in people in their 20s and 30s, most occur between the age of 40 and 70 y (the average age of diagnosis is 50 y); men are more affected than women.⁵ The etiology of ALS is largely unknown.⁷ The disease development is significantly influenced by the interaction of genetic, lifestyle and environment, promote to critical environmental and epigenetic factors dysfunction.^{8,9}

There are two types of ALS that cannot be discerned clinically, sporadic and familial-type. Sporadic ALS (sALS) is an ALS type without a family history (90–95% of all cases), while the familial type ALS (fALS), an ALS type with a history of familial genetic mutations, reflects 5–10% of all cases.^{4,10} To explain ALS pathogenesis,

understanding the relation between dysfunction of upper motor neurons (UMN and lower motor neurons (LMN), notably the onset site is crucial. There have been three hypotheses of how ALS occurs: dying forward, dying back and independent degeneration hypothesis.⁹

The dying forward hypothesis states that ALS is preceded by hyperexcitability in corticomotoneuron, which induces degeneration of the anterior horn cells. This process is mediated by the degeneration of anterograde motor neurons through the process of glutamate excitotoxicity.^{9,11,12} Meanwhile, the dying back hypothesis proposed that ALS begins due to a disorder of neuromuscular junction (NMJ) or muscle cells, in which motor neurotrophic hormone deficiency was present and perilous factors transported retrogradely to the cell body from NMJ.^{12,13} The independent degeneration hypothesis proposed degeneration of upper and lower motor neuron occurs independently.^{9,12}

Molecular and genetic complex interaction pathway seems to be mediating ALS. Astrocytic excitatory amino acid transporter-2 (EAAT2) dysfunction mediates glutamate excitotoxicity by reducing glutamate uptake from the synaptic cleft. Translation abnormalities and intracellular neuronal aggregates formation caused by TDP-43, c9orf72 and fused

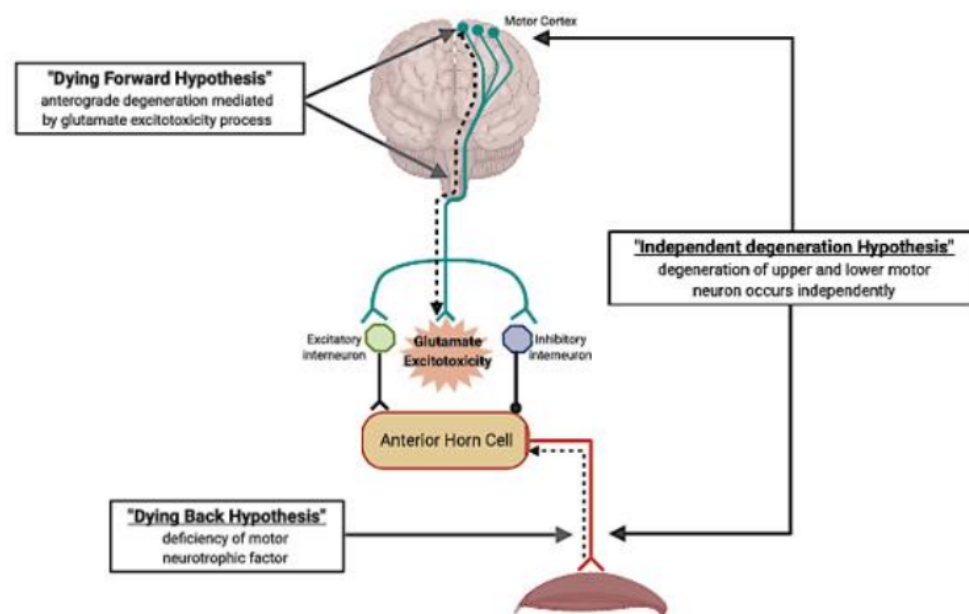


Figure 1: The illustration of three hypothesis for ALS

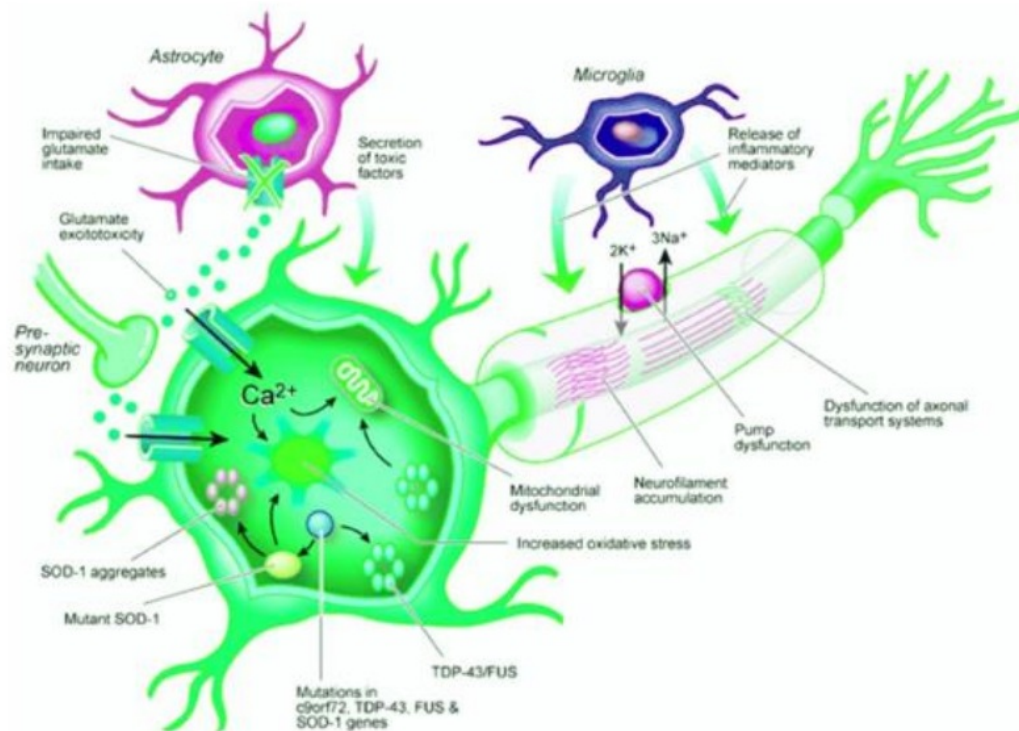


Figure 2: Molecular and genetic interaction in ALS pathogenesis

in sarcoma (FUS) genes mutations through dysregulation in RNA metabolism. Increased oxidative stress due to superoxide dismutases-1 (SOD-1) gene mutations, leading to intracellular aggregates and defective axonal transportation. Proinflammatory cytokines and neurotoxicity secretion are the results of microglia activation separately.⁹

ALS has a focal onset, unrelentingly progressive. A patient who has developed ALS can have several symptoms, mostly sorted as bulbar, spinal or respiratory, behavioural and/or cognitive alteration and pain.^{1,7,14,15} The general bulbar symptoms such as facial weakness, words slurred, impaired tongue movements, sialorrhea, dysphagia are considered as a consequence of UMN breakdown.^{14,15} Respiratory symptoms can appear individually or simultaneously, patients frequently showing orthopnea, dyspnea, hypoventilation and weakness on respiratory muscle.¹⁴ The main cause of weakness in ALS is LMN breakdown.⁷ Fine motor disruption, arms and legs paralyse, weakness and/or

wasting and fasciculation in the muscles of arm and leg are part of spinal onset symptoms.¹⁵ It is now recognised that ALS implicates non-motor symptoms, such as cognitive and/or behavioural alteration and pain. The involvement of frontotemporal circuits occurs between 30%–50% of patients who have cognitive alteration detected on a formal test.⁷ Pain in ALS could manifest 2 years or more in advance of motor alteration. At the onset of the disease, aching cramps in the hands or legs often occur.¹

The recognition of coexisting UMN and LMN signs remain subservient to diagnose ALS, as well as a sign of disease progressivity and neuromuscular mimicking disorder has excluded.^{13,16} The great clinical variability presentation in the early stage of ALS has become burdensome to diagnose. The finding of UMN and LMN signs within distinct body regions described as bulbar, cervical, thoracic and lumbar was necessary to diagnose ALS.¹⁷ Compelling diagnostic delays have been reported due to the absence of a pathognomonic test and clinical

phenotype variance. Numerous ALS staging have been suggested using fast, functional assessment, rehabilitation, distinct treatment models comparative, biomarker analysis, and health economics.¹⁸

The World Federation of Neurology Research Group on Motor Neuron Diseases established clinical-based criteria called El Escorial criteria.^{13,17} These criteria were first established in the year 1991.¹⁹ The exclusion of different etiologies of signs and symptoms is the base of ALS diagnosis, as described in the initial diagnostic criteria.²⁰ This criterion presents a set of guidelines to diagnose ALS, rest on disease spread pattern but are not in themselves a staging system.¹⁸

The diagnostic criteria of ALS confide in the finding of UMN and LMN signs within distinct regions described as bulbar, cervical, thoracic and lumbar regions.¹⁷ Diagnosis of ALS was based on the revised El Escorial Criteria. It requires the existence of LMN degeneration signs (clinical, electrophysiological or neuropathologic examination), UMN degeneration signs (clinical examination), progressive expansion of signs within a region or to other regions, following nonappearance of electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations; and neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.²¹

The most extensively studied proposals have been the Milano-Torino (MiToS) functional staging and King's clinical staging systems.¹⁸ The MiToS staging system relies on the functional ability of four domains: movements, swallowing, communication and breathing, as appraised by the ALS Functional Rating Scale-Revised (ALSFRS-R), where stage 0 is a normal function, and stage 5 is death.^{18,22} The King's system is based on two domains: neurological regions (bulbar, cervical, thoracic, lumbar) and further prognostic criteria. It uses five stages, with stage 1 being the symptom onset and 5 being the death.^{18,22}

Afterwards, the neurophysiology-based Awaji criteria were established as an addition to the El Escorial criteria to intensify the ALS diagnosis sensitivity.^{13,23} Based on the revised Awaji Criteria (2008), there is clinically definite, or probable or

possible ALS. The clinically definite ALS is defined as UMN and LMN signs clinical or electrophysiological evidence in the bulbar region and at least two spinal regions, or UMN and LMN signs in three spinal regions. The clinically probable ALS is defined as UMN and LMN signs clinical or electrophysiological evidence in at least two regions, with some UMN sign rostral to LMN signs. The clinically possible ALS is defined as UMN and LMN signs clinical or electrophysiological evidence of alone in two or more regions, or LMN signs rostral to UMN signs.¹⁷

No cure for ALS has been found yet. The average ALS survival is around 2–5 y, but some patients with more passive disease progression are able to get through for over a decade. Individual clinical management in ALS patients can be optimised by multidisciplinary treatment. The fundamental management is symptomatic, supportive and neuroprotective treatment; likewise, some vague disease-modifying treatment, e.g., gene therapy and stem cell transplantation, have also been tried.^{17,24} Two treatments have been identified as a disease-modifying therapy: riluzole and edavarone. Excitotoxicity has been thought to play a role in ALS pathophysiology. Riluzole targets excitotoxicity by act as an anti-glutamatergic agent. Although the definite mechanism of riluzole in ALS is not well established yet, it slows the disease progressivity. Edavarone is a strong antioxidant agent that works by eliminating hydroxyl radicals and lipid peroxides. The mechanism of action in ALS is also unclear.²⁴ The use of riluzole has strong evidence according to the American Association of Neurology (AAN) guideline for the care of the patient in ALS (Level A), it is also recommended by the European Federation of the Neurological Societies (EFNS) to initiate the treatment as soon as possible with dose 50 mg q12h (Level A).^{25,26} A variety of other drugs, including anti-apoptotic agent, anti-inflammatory, anti-excitotoxicity, antioxidant, anti-aggregation, neuroprotection and neurotrophic growth factor, glial-restricted precursor, cell-based therapy, neural gene therapy and progenitor stem cells, are still being studied and under-researched.²⁴

3. Pathogenesis of pain in ALS

The current definition of pain as endorsed by the International Association for the Study of Pain (IASP), is “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.^{27,28} pain is a response to tissue injury, noxious stimuli, or trauma. Nociceptive pain transmissions to the brain are affected by duration, functional abnormality and /or structural change of nerve.³ Actual or threatened damage to non-neural tissue causing Nociceptive pain arose and is due to nociceptors' activation. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system.²⁸ Disease or lesion in the somatosensory nervous system can cause neuropathic pain, which originated by either central or peripheral nervous system or both.²⁹ Patient's quality of life can be disrupted due to pain in terms of work, social relationships, sleep, daily activities, mood and cognitive process.²⁷

ALS cause pain in many patients, although it is not considered to be a primary consequence of ALS. However, there is a lack of research regarding the pathogenesis of pain in ALS and the effective means to achieve nociceptive control.³ Pain incidence ranges from 15% to 85% in ALS patients.¹ It has been suggested a dorsal root ganglia neuropathy followed by progressive sensory axonal atrophy, secondary demyelination–remyelination and eventual axonal loss generated by the first disturbance of the sensory system in ALS.^{30,31}

Although it has been said that neuropathic pain, as well as spontaneous (tingling, paroxysmal shooting, burning sensation) and provoked (hyperalgesia, aftersensation, allodynia) manifestation, are the primary matters of pain in ALS, but some studies showed different results. As the disease progresses, secondary matters (mostly nociceptive) of ALS pain begin to emerge. Prolonged immobility, muscle weakness and atrophy leads to degenerative changes in bones, joints and connective tissue, causing a musculoskeletal pain. In the terminal phase of the disease, several patients also have general and unexplained pain.¹

²³ A study of pain characteristics in ALS carried out by Hanisch et al. showed that 53% of patients with ALS informed pain in several sites. The most frequent sites are; the back (50%), the extremities (47%), and the joints (42%). It was proposed that the pain is caused by bone and joint stress due to muscular atrophy. The disease duration and pain severity were not related, according to this study.³²

A different study by Moisset et al. assessed a large population of ALS patients with neuropathic pain to determine the characteristics and the prevalence. It showed that 65.6% of ALS patients reported pain, out of which 9% exhibited neuropathic characteristic. The pain was frequently described as spontaneous (rarely evoked), numbness, electric shock-like, burning, tingling and pins-and needle. In this study, there were no relations to patients age or gender, disease duration, the onset of bulbar or spinal disease, respiratory or nutritional status.³³

Spinal MRI studies using diffusion tensor imaging (DTI), magnetisation transfer (MT) imaging, and inhomogeneous magnetisation transfer (ihMT) imaging showed progressive degeneration of sensory tract and dorsal column over time. Pathology of the dorsal column was able to be detected soon after symptoms onset. It suggests sensory involvement is fairly an initial ALS feature.³⁴ Study combining spinal DTI⁵ and neurophysiology ascertained significant sensory pathway degeneration in ALS patient lacking sensory symptoms, it disclosed subclinical sensory deficits in 85% of ALS patients.^{34,35}

4. Pain management in ALS

Since pain is an adequately manageable condition, it is quite disturbing that inadequate pain management had a significant impact on ALS patients' social well-being and emotional health. There are several factors, which contribute to inadequate pain management in ALS since it is not a principal consequence of the disease. Regular pain screening is infrequently done in a patient with ALS.³ The good clinical practice must be the basis to manage pain in ALS since there is still no particular pain management guideline for ALS. Treatment may

follow the pattern of non-malignant chronic pain guideline, which are readily available.^{26,36}

Pharmacological therapy for primary and secondary pain in ALS can be classified according to the drug's mechanism of action. It includes medications for neuropathic pain, cramps, spasticity, and analgesics for pain relief from immobilisation.¹ Neuropathic pain medication is chosen based on the guideline for the management of neuropathic pain for any cause. Therapies chosen as the first line include gabapentin (900–3600 mg/day), pregabalin (150–600 mg/day) and tricyclic antidepressants (50–100 mg/day).^{1,37}

Levetiracetam can be given as first-line therapy at a dose of 1500–3000 mg/day to manage spasticity.³⁸ Intrathecal baclofen can be used as a second-line antispasticity drug.¹ Combined oral therapy and administration of intrathecal route baclofen can be used if severe spasticity is not resolved with single oral therapy or physical therapy.³⁹ A case series in 8 ALS patients used intrathecal baclofen at a dose of 25–50 µg/day and was able to reduce pain intensity by 54%.⁴⁰ Co-administration of levetiracetam and baclofen intrathecal should be avoided. Other drugs that can be given include baclofen oral twice or thrice a day in 10 mg dose, tizanidine 6–24 mg/day, dantrolene 25–100 mg/day, and benzodiazepines such as diazepam 10–30 mg/day.^{1,3,26,41} Intramuscular botulinum toxin (BoNT) injections also utilised as a treatment to reduce ALS spasticity.³ Spasticity might be safe and effectively prevented with routine stretching, passive or active range-of-motion exercise. Painful and function-limiting contractures, especially at the ankle and shoulder joints, can be prevented with regular, proactive stretching plans. These methods are beneficial for maintaining physical mobility and muscle length as well.⁴²

Stretching and massaging is clinically effective for treating cramps in the superior and inferior extremities, the abdomen. Cramp therapy in ALS is largely based on empirical data and not supported by systematic data. Levetiracetam is the therapy recommended as a first-line therapy (level A) by EFNS to treat cramps in ALS.³⁹ Quinine sulphate at a dose of 250–500 mg/day can be given, which is known to reduce the number and intensity of cramps at any cause. The superior efficacy of quinine sulphate compared to other placebo or other interventions has been reviewed in Cochrane review,

but it is not specific for cramp due to ALS.³⁹ Other therapies that can be given are gabapentin, mexiletine, dronabinol and levetiracetam.^{1,38,42,43}

Nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, and opioids are some analgesics that can be used to treat pain due to immobilisation.^{1,3} NSAIDs and paracetamol were chosen to be the first-line therapy.¹ To treat acute nociceptive and neuropathic pain, a combination of paracetamol and codeine can be used.¹ Opioids are a second-line therapy option for pain that is not treated with first-line therapy.¹ Daily assistive ROM exercises based on clinical experience can also help reduce pain due to mobilisation.⁴² Avoid strenuous exercise; choose exercises with a low risk of falling. This approach is also useful for maintaining muscle strength and physical mobility. Other therapeutic modalities include acupuncture, transcutaneous electrical nerve stimulation, cold and warm compresses, and intraarticular steroid injection with or without lidocaine.^{1,42}

Medication treatment given in the early course of the disease aims to control muscle cramps and fasciculations. Vitamin E or magnesium are often utilised to treat mild muscle twitches.³ Higher doses might cause fatigue, sedation and weakness, which may aggravate the progression of the disease.³

5. Conclusion

People with ALS can encounter pain due to spasticity, cramps and decreased mobility. A study of ALS pain is less well documented. It is potentially overlooked and undertreated by physicians. It can arise along the course of the disease and requires treatment. Multidisciplinary management should be opted to treat pain related to ALS to achieve a better quality of life in patients who have ALS.

6. Conflict of interest

None declared by the authors

7. Authors' contribution

All authors contributed in the concept and drafting and editing the manuscript

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