*ejpmr, 2017,4(10), 161-173*

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

# AMYOTROPHIC LATERAL SCLEROSIS - A PROGRESSIVE NEURODEGENERATIVE DISEASE: INSIGHTS FOR DISEASE MANAGEMENT

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**Article Received on 21/08/2017** **Article Revised on 11/09/2017** **Article Accepted on 01/10/2017**

## ABSTRACT

Amyotrophic Lateral Sclerosis (ALS), is a progressive, multisystemic and multi factorial neurodegenerative disease that affecting to the motor neurons. The disease affects both the upper and lower motor neurons and it affects the motor functions. As the disease progresses, the patient will be paralyzed and eventually dies due to the respiratory arrest. The exact cause and mechanism for its progression is unknown, hence it is difficult to develop an effective treatment for ALS. Even though the neurologists can able to identify the ALS and its variants, a few percentage of patients were misdiagnosed and delays the actual identification of disease. The drug approved by the Food and drug administration (FDA) for ALS are Riluzole and Edaravone. Riluzole, an inhibitor of glutamate release and noncompetitively inhibits postsynaptic N-methyl-D-aspartate receptor (NMDA) and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and Edaravone is thought to reduce oxidative stress in cells by lowering of free radicals. Also, it is hard to mention that both has a modest effect in prolonging life of the patient. Proper diagnosis, effective communication of the diagnosis, the involvement of patient and their caretakers, and a positive care plan are essential for a better clinical management. As the disease is a multifactorial disease, multiple approaches need to support the patient and their caretakers. In this review, we discussed various diagnostic methods, symptomatic treatments, nutritional and respiratory supports, psychological supports for the patient and their caretakers and the methods to preserve the patient's mobility and communication. Which helps the patient to cope with the impaired function and to improve the quality of life.

**KEYWORDS:** Amyotrophic Lateral Sclerosis; management; diagnosis; treatments; neurodegenerative disease.

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is characterized by a progressive degeneration of upper and lower motor neurons in the cerebral cortex, brainstem, and spinal cord, resulting in muscular atrophy, fasciculation, weakness, and spasticity.[1] The term ALS was first described in 1869 by the French neurobiologist and physician Jean-Martin Charcot, and hence the disease was primarily known as Charcot's disease. He diagnosed the first case of ALS as a specific neurological disease associated with a distinct pathology.[2] ALS also can be called it as motor neurodegeneration disease, due to the gradual degeneration and death of motor neurons. As the disease progresses the muscles of diaphragm and chest wall will fail, and the patient will lose the ability to breath. Eventually the patient leads to paralysis and death due to respiratory arrest within two to five years. The average life expectancy of a ALS patient is about 2-5 years from the onset of symptoms. Also, about ten percentage of people were survived for a longer time. ALS does not affect the person's ability to recognize, see, hear, smell and taste. But several research studies show that the ALS patient may have the alteration in cognitive functions. About 5000 and plus patients were diagnosed each year with ALS. Onset of symptoms usually starts between the ages of 50 and 65.[3,4]

The primary pathogenic process underlying motor neuron disease (MND) are likely to be multifactorial, and the precise mechanisms underlying selective cell death in the disease are at present unknown. Current understanding of the neurodegenerative process in MND suggests that there may be a complex interplay between multiple mechanisms including genetic factors, oxidative stress, excitotoxicity, protein aggregation, and damaging to critical cellular processes, including axonal transport and organelles such as mitochondria.[5] Approximately 10% of ALS patients are familial cases and remaining 90% of ALS cases are sporadic, with no known genetic component.[6] Further-more, Riluzole [6-(trifluoromethoxy)-2-aminobenzothiazole], the only FDA approved compound for ALS in the late 1995. Riluzole was considered as the only one disease modifying drug that prolong the life of the patient. This can inhibit the release of glutamate and noncompetitively inhibit postsynaptic NMDA and AMPA receptors.[7]

Recently, on 5th May 2017 FDA approved Edaravone as a treatment for ALS. It can delay the progression of ALS by reducing oxidative stress in cells by eliminating free radicals. This review attempts to provide an over view of management and supportive treatments for ALS to prolong the life and improve the quality of life of the patients.

## 1. ALS: A debilitating multisystemic neuromuscular disease

During research on ALS, Jean-Martin Charcot observed that lesions within the lateral column of spinal cord resulted in chronic progressive paralysis and contractures, while lesions of the anterior horn of the spinal cord resulted in paralysis without contractures.[8] Per the research findings, he explained that the spinal cord consisted of two-part system, and based on the location of lesion the clinical presentation changes. Later, ALS was defined in two senses. In one sense, it refers to several adult-onset conditions characterized by progressive degeneration of motor neurons. In the second sense, ALS refers to one specific form of motor neuron disease in which there is both upper and lower motor neurons signs.[9]

In early decades, the physicians do the diagnosis but unfortunately, they could not able to give any treatment for ALS patients due to lack of remedy. So, most of the patients were sent back to their home after diagnosis. ALS was paid attention only after the death of famous 37-year old New York baseball player, Lou Gehrig.[2] Until 1969 there was no diagnostic tool for ALS. As the ALS cases increased, researchers developed theories of possible etiology of ALS and formalized electromyography (EMG) as a diagnostic tool. Later several hypotheses developed, likewise involvement of glutamate metabolism abnormality, superoxide dismutase (SOD)-gene, nerve growth factor (NGF). In 1995, first positive clinical trial report announced for ALS. Understanding of prognostic factor is also benefits both physician and patient in scheduling therapeutic interventions and is particularly relevant for the design of clinical trials.[10] Table 1 includes the prognostic factors for ALS. FDA approved Riluzole as the first medication for ALS, and claimed that it influences survival and prolonging the life of patient for several months.[1] The fact that Riluzole does not reverse the damage that happen to the motor neurons. Other designed treatments are only for relieve symptoms and improve the quality of patient. Hence, still researches are going on to find out the exact cause of ALS, to understand mechanisms and to develop effective treatments. Inorder to guide physicians and patients in scheduling therapeutic interventions, a better understanding of factors is necessary.

## 2. Clinical classification of ALS

In 1994, the World Federation of Neurology published the EL Escorial criteria for the diagnosis of ALS. In 1998, in Airlie House (Virginia, USA), an international group of experienced clinics met to discuss optimal management strategies of ALS and to revise the criteria after 4 years of clinical experience and renamed to Airlie House criteria.[29] The revised World Federation of neurology criteria for diagnosis of ALS (EL Escorial revised) defined three categories of certainty based on clinical signs.

a) Clinically definite ALS: Upper and lower motor neuron signs in the bulbar region and in at least two spinal regions, or the presence of upper motor neuron signs in two spinal regions and lower motor neuron signs in three spinal regions.
b) Clinically probable ALS: Upper motor neuron and lower motor neuron signs in at least two regions with some upper motor neuron signs rostral to lower motor neuron signs.
c) Probable, laboratory supported ALS: Upper motor neuron and lower motor neuron signs in only one region, or upper motor neuron signs alone in one region and lower motor neuron signs defined by electromyogram criteria in at least two muscles of different root and nerve origin in two limbs.
d) Clinically possible ALS: Upper motor neuron and lower motor neuron signs in only one region, or upper motor neuron signs alone in two or more regions, or lower motor neuron signs found to rostral to upper motor neuron signs.[30]

## 3. Phenotypes of ALS

Phenotypes mimic ALS but vary in severity and prognosis of the disease. Restricted phenotypes of ALS are;

a) Progressive bulbar palsy (PBP): It is a progressive motor neuron disease that affects only the muscles supplied by bulbar motor nuclei and the corticobulbar pathways.
b) Flail arm (Vulpian Bernhard) syndrome and Flail leg syndrome: This syndrome begins with asymmetric deficits of the arms and legs two body regions.
c) Progressive muscular atrophy (PMA): There will be an evidence of lower motor neuron disease in one limb or region and clinical or electrophysiological evidence of involvement of an adjacent limb or region.
d) Primary lateral sclerosis (PLS): This is a syndrome in which the disease begins with upper motor neuron deficits existing in isolation.

Most of the cases, these restricted phenotypes may develop ALS and hence retention of these phenotypes is desirable. Primarily, we can confirm the diagnosis for ALS by using World Federation of neurology criteria for diagnosis of ALS (EL Escorial revised). Also, the studies show that patient with disease phenotype did not develop respiratory insufficiency or substantial changes in respiratory muscle strength, impairment in the functioning of lungs, or forced vital capacity (FVC).[31] These differences in the clinical condition can provide an accurate information regarding disease and this is necessary for further treatment and management.

## 4. Diagnosis

There is no such definitive test to diagnose ALS. In early stages of ALS, it is difficult to recognize and may go undiagnosed up to one year.[1] The major difficulty to diagnose in the early stages is the similarity between other variety of diseases. So, initially the physician observes complete medical history and status of the patient. Later based on the signs and symptoms, physician conduct tests to exclude other diseases. The diagnosis of ALS is based on the exclusion of alternative causes of signs and symptoms as outlined in the diagnostic criteria.[32] To confirm ALS, neurologic examinations were conducted frequently to assess muscle weakness, muscular atrophy, hyperreflexia, and spasticity.

With respect to specific signs during diagnosis, World Federation of neurology criteria for diagnosis of ALS (EL Escorial revised) proposed and stated that ALS diagnosis should have one of the following:

a) Progressive upper and lower motor neuron deficits in at least one limb or region of the human body; i.e. meeting the revised EL Escorial criteria for possible ALS, or
b) Lower motor neuron deficits as defined by clinical examination (one region) and/or by EMG in two body regions (defined as bulbar, cervical, thoracic, lumbosacral). The EMG findings consist of neurogenic potentials and fibrillation potentials and/or sharp waves.

In 2008, Awaji criteria proposed for the use of electrodiagnostic studies in the diagnosis of ALS and to enable earlier diagnosis of ALS and to make an early entry into clinical trials. It is recommended that neurophysiological data should be used in the context of clinical information, not as a separate, standalone set of data. Later, to promote early diagnosis a new algorithm was proposed based on revised EL Escorial criteria.[33,34,35]

Still most of the physicians misdiagnose ALS due to lack of knowledge and difficulty to differentiate from multifocal motor neuropathy. Several tests are available to confirm ALS and to exclude other diseases. Tests include EMG, nerve conduction studies (NCS), magnetic resonance imaging (MRI) and computed tomography (CT) scan of the spine and brain, identification of biochemical markers in blood and cerebrospinal fluid (CSF), and muscle or nerve and bone marrow biopsy.[29,31,36] EMG and NCS will exclude the possibility of other diseases such as myasthenia gravis or peripheral neuropathy. Imaging techniques also help to exclude spinal cord diseases, such as tumors or multiple sclerosis (MS). Various laboratory tests such as general medical tests, neuromuscular -related tests and cerebrospinal fluid tests are normally conducting for accurate diagnosis (Table 2).[1,37] Genetic testing can identify gene defects in some types of familial ALS and in certain other inherited motor neuron diseases that mimic ALS.[38]

## 5. ALS management

As the disease is a complex multifactorial disease, till to date no curative medicines are available to treat ALS. Hence, per management respective we have supportive and symptomatic treatments to slow down the progression of disease. Still researchers are heading towards improving the quality of life, finding therapies, conducting clinical trials and to finding the exact root cause of the disease.[39] Riluzole and Edaravone are the FDA approved medication to slowdown the progression of ALS. However, symptomatic treatments, respiratory management, nutritional management, and disease modifying medications are also recommended for improving quality of life of the patient.[40,41]

### 5.1. Riluzole and Edaravone

Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is an anti-excitotoxic drug which decrease mortality and slows the course of ALS.[42,43] Riluzole 100 mg/day is found to be safe and help to extent survival about two to three months and decreases tracheostomy in ALS patients.[42,44,45,46] Glutamate excitotoxicity is one of the hypothesis linked to ALS. It reduces excitatory amino acid (glutamate) release from nerve terminals, NMDA mediated effects and partially prevents *in vitro* neuronal degeneration produced by CSF of ALS Patients.[47,48,49] It is reported that riluzole can inhibit the release of acetylcholine, dopamine to a similar extent with similar potency and have a minor inhibition of serotonin release. It weakly inhibits the release of noradrenaline.[50] Riluzole also have a protective action against non-excitotoxic oxidative neuronal injury via protein kinase C (PKC) inhibition.[51] Furthermore, riluzole decreases repetitive firing of action potential in neurons.[48] Also, inhibits persistent $Na^+$ current in in a dose dependent manner and at higher concentrations riluzole inhibits voltage-dependent $K^+$ or $Ca^+$ currents.[52,53,54] Apart from these, riluzole enhances the production of several neuronal growth factors likewise glial cell-derived neurotrophic factor (GDNF), NGF, and brain derived neurotrophic factor (BDNF). Thus, it provides a survival-promoting effect in neurodegeneration.[55,56] Lacomblez *et al* reported a frequent dose related adverse events likewise nausea, asthenia, and elevated liver enzyme levels.[42]

Edaravone, (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one), is a free radical scavenger mainly used for the treatment of acute cerebral infarction. It can able to eliminate lipid peroxides and hydroxyl radicals and can protect from degeneration and oxidative stress. In 2017 May, FDA approved Edaravone to treat ALS in the US. The efficacy of the drug was demonstrated in a six-month clinical trial conducted in Japan. They found that progression of motor dysfunction was slowed in the Edaravone treated patients.[57,58] Most common adverse reactions reported are bruising and gait disturbances.

Also, it is associated with serious effects that require immediate medical care, such as hives, swelling, shortness of breath, and allergic reaction to sodium bisulfite.[59]

### 5.2. Symptomatic treatments

Apart from riluzole there are several symptomatic treatments are available for ALS. For muscle weakness, it is recommended to perform exercise inorder to strengthen the unaffected or mildly affected muscles. Exercise should include stretching, strengthening and aerobic exercises.[60] For spasticity doing moderate intensity, endurance type exercises for the trunk and limps is the better recommended therapy and no other medical surgical and alternative treatments had been evaluated for ALS patients.[1] Dysarthria and dysphagia are other ALS associated symptoms. Most of the ALS patients experience dysarthria prior to dysphagia. It will worsen as the disease progresses.[1] Another commonly reported problem is the sialorrhea. Most often used drugs are anticholinergics, but there is very little evidence for its effectiveness in ALS patients. Botulinum toxin injections and/or radiation therapy in the salivary glands were recommended when anticholinergic drugs are not effective.[61] Loss of mobility in ALS patient results in joint contractures or bed sores. Hence the studies reported that, most of the ALS patients were suffering mild to severe pain. Non-narcotic analgesics, anti-inflammatory drugs, and antispasticity agents were usually recommend for patients those who are in initial treatment of pain. Opioids are the drug of choice when non-narcotics analgesics fail.[62] Another common symptom reported in ALS patients is constipation and improper bowel function due to diet changes, exercises, weak abdominal muscles, and lack of fluid intake. Inorder to improve the bowel function dietitian will recommend making changes in the diet (add adequate fiber in food), drink 6 to 8 glasses of water per day, and more over be active as possible. Use of laxatives also recommended for these patients.[1] Apart from these issues, it is reported that the patients are suffering from depression, anxiety, and other psychological and emotional problems. To maintain the mental stability and emotional issues it is recommend taking anti-anxiety drugs and anti- depressants. If it is not managed by medication, then psychiatric consultation is necessary to improve the quality of the patient. Besides anxiety, insomnia and fatigue are the other symptoms associated with reduced mobility and muscle cramps. Symptomatic medications for ALS patients were tabulated in the Table.3.

### 5.3. Nutritional management

As the disease progresses, the nutritional status of the patient get worsens and it will lead to higher mortality. By proper nutritional management, it is possible to modify the survival of the patient and can improve the quality of life of patient.[64] Most of the ALS patients were reported to be malnourished due to difficulty in swallowing (dysphagia) and it leads to increased risk of weight loss, dehydration, and aspiration. As the patient in hypermetabolic state, they required to take increased calorie and dietary advice.[65,66] Nutritional management mainly involves detection and correction of inadequate nutrient intake, food consistency modification (blending food, adding thickeners to drinks), also advice to change the swallowing posture or head position such as a ‘chin tuck’ maneuver (flexing the neck forward on swallowing to protect the airway.[67,68] As a part of nutritional management parenteral and enteral nutritional therapy, importantly percutaneous endoscopic gastrostomy (PEG) are recommended.[69] If parenteral feeding is established, maintain oral feeding to maintain or enhance the nutritional status as long as there is risk free aspiration and which will improve the quality of life of ALS patient.[67]

#### 5.3.1. Percutaneous endoscopic gastrostomy (PEG)

PEG is the standard procedure by inserting a small tube through the skin directly into stomach for maintaining the nutrition status of ALS patient with dysphagia and nutritional intake inadequate.[62] It is recommended for the patients with minor bulbar symptoms, dysphagia, inadequate nutrition, and without significant respiratory muscle weakness.[67] Studies show that ALS patients those who are not receive PEG, resulted in disease progression. PEG at early stage of ALS give better results than at the late stage of disease.[70] PEG require sedation for the introduction of endoscope tube. It is not recommended to the patients those who have vital capacity less than 50% and sniff nasal insufficiency less than 40%. If the vital capacity (VC) is greater than 50% and sniff nasal pressure (SNP) more than 40%, survival after gastrostomy get increased. Hence, before gastrostomy check for respiratory insufficiency. If there is a respiratory insufficiency reported, it is recommended to offer non-invasive ventilation (NIV) before gastrostomy.[67]

#### 5.3.2. Radiologically inserted gastrostomy (RIG)

The advantages of RIG over PEG is that it avoids sedation and only fine bore nasogastric tube (NGT) is inserted with the help of local analgesics to inflate the stomach with air. The NGT in RIG is an advantage in patients with masseter muscle spasm and who cannot undergo gastroscopy due to difficulty in opening mouth.[71] A cannula for the feeding tube is inserted through the abdominal wall with the help of local anesthetics.[67,72] RIG can be performed for the patients those who have VC below 50% and can be used with NIV. Studies show that RIG had a higher survival rate than PEG in ALS patients and suggested safe than PEG in patients with moderate to severe respiratory impairment.[72] The avoidance of endoscopic route of placement lower the intrinsic risk of aspiration as compared to PEG.[73] The major disadvantage of RIG reported was the smaller caliber of the tube and which may lead to obstruction. However, after 15 to 30 days the tube can be replaced with greater caliber.[72]

### 5.4. Respiratory management: Non-invasive ventilation (NIV)

Non-invasive positive pressure ventilation (NIPPV) for ventilator support during percutaneous endoscopic gastrostomy is highly recommended for ALS patients and which improves the alveolar hypoventilation in patients and reduces decline of FVC.[46,74,75,76,77] Negative pressure ventilation (NPV) is the another one NIV procedure, and it is reported that NPV may stabilize or temporarily improve the respiratory status in patients with neuromuscular diseases.[78] Studies indicate that NIV prolongs survival, improves quality of life, and improves quality in sleeping, although patient-ventilator asynchronies are positive.[77,79,80,81] It is also being noted that NIV shown to be much effective in ALS patient with normal or only moderately impaired bulbar function in which the impairments affected to the muscles that are involved in speaking, chewing and swallowing. Studies also supports the application of NIV in ALS patients with advanced respiratory impairment.[82] Tracheal ventilation is the other option when NIV become insufficient.[77,81] However, Sirala *et al* suggest that effect of NIV on survival is depends up on age of ALS patients and reported that there was an improved survival observed among patients older than 65 years.[83]

### 5.5. Augmentive and Alternative communication (AAC)

AAC can improve the quality of life of ALS patients by optimizing the function, assisting with decision making, and by providing better opportunities for personal growth. This will improve the verbal communication skill of patient.[84] It includes sign languages, symbol or picture boards, electronic devices, and synthesized speech. A communication assessment should be made before starting AAC. For that a licensed speech language pathologist, assistive technology specialists, or rehabilitation engineers who have experience in AAC required. AAC can be categorized as unaided AAC and aided AAC. Unaided AAC includes body movements, facial expressions and gestures and different signs to promote communication. Aided AAC can be achieved by using different object or object symbols, photographs, communication board, and other communication devices.[85] In advanced state, utilization of electronic communication devices or computers will allow the user to have voice output, send mail, and surf the websites.[86]

### 5.6. Methods to preserve mobility

Today technology allows us everything to preserve the mobility and communication of the ALS patient. For preserving hand function, it is recommended to use special grips for writing and eating. It will help to make the weakening hands more active and functional. Eye-Gaze technology make easier the hands to access internet, write and the use of other communication devices. For preserving mobility orthotics can be used. Ankle-foot orthosis is the one of them.[87,88] Other than that, the patient is recommended to use walkers, manual wheel chairs and power wheel chairs to support mobility. Power wheel chairs will relieve the pressure and prevent the breakdown of skin.

## 6. Comorbidities of ALS

### 6.1. Cognitive and behavioral changes

Most of the ALS patients display cognitive and behavioral changes because of frontal lobe dysfunction.[18,89,90,91,92,93] The behavioral changes are more common in cognitively normal people.[18] The cognitive impairment is mainly due to the deterioration of the frontal regions adjacent to the motor cortex or the dysfunction of dorsolateral prefrontal cortex [94]. Spongiform neuronal degeneration in layers of prefrontal and temporal cortex were observed in the ALS cases.[91,95,96] Studies show that, bulbar onset ALS patients experiences cognitive impairments and neuronal loss in anterior cingulate gyrus. Subsequently this will result profound neuropsychological dysfunction and both language and speech abilities comparatively preserved in these patients. Cognitive abnormalities include lack of attention, working memory, cognitive flexibility,[93] inhibition of response alternatives,[97] planning, problem solving, recognition memory[93] and motor free visual-perception.[93,98] Other than that, intrinsic response generation, i.e. verbal fluency independent of dysarthria, and high distractibility factor related to dysarthria has also been identified.[18,93,97,99] Apart from these, behavioral abnormalities include irritability, lack of social interactions, exaggerated display of emotions and decision-making problems.[18,100]

### 6.2. Depression and anxiety

Studies reported that, patients with ALS were at higher risk of depression and anxiety diagnosis and the antidepressant use was more common among ALS patients.[101] The negative impact of these comorbidities will seriously affect the quality of life in ALS.[102] In most of the cases the depression may masked by other ALS related symptoms.[103] However, the patients with early stage or during diagnostic phase are more likely to be depressed and in a high level of anxiety than those who are in late stage.[104,105] More than that, spiritual beliefs, spouse as care partner, financial background, psychological health of care giver, and hospice participation did not distinguish patients who experienced depression and there is no connection exists among ALS patients with depression. Also, studies claim that risk of depression does not necessarily increase with the approach of death.[104,106] The psychological distress is associated with the worsening of their physical functioning. The studies show that, depression is more likely to be affect to the care givers and the family members of the ALS patient.[106] Moreover, the patient with depression usually exhibit hopelessness, loss of interest in activities, worthlessness, suicidal thoughts, difficulty in concentration, helplessness, and self-hatred.[107,108,109] Likewise, the anxiety level is more connected to the duration of the disease, physical loss, depression, and lower satisfaction with life.[108,110]

### 6.3. ALS and Vision

Generally, it has been assumed that the oculomotor system is not involved in ALS. However, several authors reported that the patients indicate oculomotor abnormalities in some ALS patients. As per the studies of Cohen-adad and Caroscio, some patients have problems in generating voluntary saccades, convergence, pursuit eye movements due to deficit in visual suppression of vestibule-ocular reflex (VOR) and in optokinetic nystagmus (OKN) and some has ophthalmoplegia due to loss of neurons in and around ocular motor nuclei.[111,112,113] Later, several studies confirmed the existence of ocular abnormalities in ALS, even at early stages.[114] Recent studies showed that there is both visual dysfunction and retinal imaging abnormalities in ALS patients. There is an evidence of intraretinal inclusions and ganglion cell axon death, and finally clinical and optical coherence tomography (OCT) findings supports important anterior visual pathway involvement in ALS. These structural changes are representing neuronal degeneration, could correlate with visual dysfunction in patients with ALS. From animal studies, the scientists detected ALS-related protein deposits in the retina of mice. The same protein deposition was observed in patients with ALS. These deposits accumulated in a single layer of the retina, affecting a subclass of retinal neurons that are important in color perception and contrast sensitivity.[115]

### 6.4. Relation with Cardiovascular diseases

The association between ALS and cardiovascular diseases (CVD) are quite uncommon. However, the involvement of sympathetic nervous system affecting cardiac function has been described, predominantly sympathetic over activity.[116] Even though the exact pathogenesis behind the cardiomyopathy in ALS patients is not clear, a positive association with CVD was proved.[117] The studies show that the ALS patients were experienced cardiac symptoms before onset of neurological symptoms. Some patients showed aortal valve stenosis during treadmill electrocardiography. Studies suggests a routine cardiological evaluation and yearly echocardiography for ALS patients.[118]

### 6.5. Malnutrition and Hypermetabolism in ALS

The origin of hypermetabolism in ALS remains unknown but it has been reported that about an average of 10 % ALS patients are in a stable hypermetabolic state as compared with a healthy population. Also, most of the patients are malnourished due to difficulty in pave the way swallowing.[65,119,120,121] Per Kaplan-Meier method, studies reported that survival is difficult for malnourished patients with ALS. Malnutrition itself causes neuromuscular weakness and adversely affects the patient's quality of life.[122] Fat-free mass (FFM), age, sex, manual muscular testing, the modified Norris limb score, weight, and an increase in neutrophil counts in circulating leukocytes correlated with the hypermetabolic state. Resting energy expenditure (REE) is the energy required for the maintenance of normal bodily functions and for homeostasis. Hence, by monitoring REE it is possible to determine the identity factors related to metabolic level.[120] Studies show that REE is positively correlated with FFM, body mass index, energy and protein intakes and albumin level, inversely related with age, and is greater in men than in women.[65,120] However, hypermetabolism is not associated with a reduction in respiratory function, tobacco use, hyperthyroidism, spasticity and fasciculation intensities, or infection.[65]

### 6.6. Sleep-disordered Breathing problem

There are reports which show the presence of respiratory muscle weakness at diagnosis and respiratory failure in ALS patients.[123] Most of the ALS death cases are reported because of hypercapnic respiratory insufficiency or respiratory failure.[123,124,125] Quality of life of the patient is strongly related to respiratory muscle function. Similarly, it is also reported that sleep disorders likewise sleep disruption, possibly due to apneas or rapid eye movement (REM) related desaturation, is common.[123] These sleep disruptions are mainly correlated with hypoventilation and nocturnal $O_2$ saturation.[126,127,128] Studies reported that mouth occlusion pressure (MOP) and exercise testing are the most sensitive and reliable parameters to evaluate nocturnal $O_2$ saturation. Findings show that ALS patients with low MOP have a decreased $O_2$ saturation during ET.[128] Also, ALS patients are reported to have a respiratory disorder during slow wave sleep (SWS) and REM sleep and is due to the diaphragm dysfunction. Diaphragm is the only active inspiratory muscle during REM sleep maintenance of ventilation. Hence the sleep during REM is completely depends up on the diaphragm contraction because of intercostal and accessary inspiratory muscle inhibition.[129] Other than that, sleep disorders are associated with immobility, muscle cramps, and anxiety.[127]

**Table 1: Prognostic factor in ALS.**

| | | |
|---|---|---|
| Demographic factors | Age: 40-70 | Decreasing survival time with increasing age<br><40: Longer survival, may exceed to 10 year<br>>80: Survival duration will be less than 2 years.[11,12,13] |
| | Gender | Male > Female (ratio of males to females is 1.56).[14,15,16] |
| | Race | Whites are about twice as likely to develop ALS as blacks.[15] |
| Clinical factors | Psychological distress | Lower mood and self-esteem predicted a faster disease progression and a shorter survival.[17] |
| | Cognitive functions | Frontotemporal lobar degenerations or subtle impairment of temporal and frontal lobe cognitive function.[18] |
| | Nutritional status | Survival worsen for malnourished patients.[19] |
| | Respiratory status | Impairment in respiratory muscle, Decline of respiratory function with lower the percentage of vital capacity (VC %).[20] |
| | Muscle exercise | Professional soccer players, marathonians or military veterans and heavy workers are more prone to ALS.[21] |
| | Smoking | Increased risk in current cigarette smokers.[22,23,24] |
| Environmental factors | Chemical exposure | Exposure to pesticides, fertilizers, herbicides, insecticides, and formaldehyde will increase the risk.[24,25] |
| | Metal exposure | Lead and aluminium in high concentrations will leads to ALS.[26,27,28] |

**Table 2: Diagnostic tests for ALS.**

| | |
|---|---|
| General medical tests | • Automated biochemistry panel<br>• Complete blood count<br>• Erythrocyte sedimentation rate<br>• Urinalysis<br>• Liver function tests: ALT, AST<br>• Electrolytes: $Na^+$, $K^+$, $Cl^-$, $Ca^{2+}$, $PO^4$<br>• Glucose<br>• Lactate dehydrogenase |
| Neuromuscular-related tests | • Acetylcholine receptor antibody titters<br>• Collagen vascular tests<br>• Electrophoresis of proteins<br>• Endocrine evaluation: Thyroid panel; Parathyroid function; Testosterone level<br>• Enzyme evaluation: Hexosaminidase A/B<br>• Gangliosidase antibody titters: GM1; Asialo GM1; GD1B<br>• Heavy metals: Lead; Mercury; Aluminum; Zinc; Copper<br>• Immunoglobulins dosage: IgA; IgG; IgM<br>• Infection-related tests: Syphilis; Lyme; HIV; HTLV-1 and 2; Hepatitis B and C<br>• Muscle enzymes: CK; ALT; AST; LDH<br>• Tumor markers: Alpha fetal protein; CEA; CA 15.3; CA19.9; CA 125; PSA; HU<br>• Vitamins: Vitamin B12; Folate |
| Cerebral spinal fluid | • Electrophoresis of proteins<br>• Specific dosage of globulins<br>• Immune reactions<br>• Cell count<br>• Glucose |
| Biopsy | • Muscle<br>• Nerve<br>• Bone marrow |
| Neurophysiology | • Nerve conduction velocities<br>• Sensory and motor amplitudes<br>• Presence of focal motor conduction block<br>• Features of denervation on electromyography<br>• Motor unit morphology |
| Image evaluation | • MRI of brain and spinal cord<br>• CT scan of brain and spinal cord<br>• Chest radiography |

| | |
|---|---|
| DNA evaluation | • SOD1<br>• VAPB<br>• Kennedy's disease |

HIV: Human immunodeficiency virus, HTLV: Human T-cell lymphotropic virus, CK: Creatinine kinase, ALT: Alanine transaminase, AST: Aspartate transaminase, LDH: Lactate dehydrogenase, CEA: Carcinoembryonic antigen, CA: Cancer antigen, PSA: Prostate-specific antigen, HU: Neuronal nuclear antibody, SOD: Superoxide dismutase, VAPB: Vesicle-associated membrane protein.

**Table 3: Symptomatic treatments and management of ALS.**

| Symptoms | Commonly used treatments |
|---|---|
| Dysphagia | Morphine, Suction |
| Spasticity | Baclofen, Botulinum toxin, Dantrolene, Tizanidine, Benzodiazepines |
| Cramps | Quinine sulfate, Vitamin E, Phenytoin, Diazepam, Baclofen, Gabapentin |
| Convulsions | Gabapentin |
| Pain | NSAIDs or aspirin, acetaminophen or propoxyphene, Opioids, Physiotherapy |
| Dysarthria | Communication aid |
| Disability and weakness | Orthotics, Physiotherapy, Adaptive aids |
| Sialorrhea | Glycopyrrolate, Amitriptyline, Botulin toxin inj., Atropine sulfate, TCA, Scopolamine transdermal patch, Hyoscyamine sulfate, Diphenhydramine, Radiation of salivary gland, suction, mouth care |
| Thickened saliva | Ensure adequate hydration, nebulized N-Acetylcysteine, Suction of mouth, mouth care |
| Fatigue | Amantadine, Modafinil, Pemoline, Bupropion SR, Fluoxetine, Venlafaxine, Pyridostigmine, Occupational therapy |
| Fasciculation | Gabapentin, Phenytoin |
| Depression | SSRIs, TCA, Venlafaxine, Bupropion, Mirtazapine, Counselling |
| Anxiety | Benzodiazepines, Buspirone, Counselling |
| Sleep disturbances | NIV, Benzodiazepines, TCA |
| Constipation | Dietary changes (Increased fluid and fiber intake, Regular oral aperients (Movicol or suppositories), Laxatives |
| Emotional liability | Educate patient and care givers, NuedeSxta, Amitriptyline, Benzodiazepines, Dextromethorphan hydrobromide, Quinidine sulfate, Citalopram |
| Cognitive problems | Neuropsychology, occupational therapy |
| Urinary urgency | Oxybutynin, Amitriptyline, Tolterodine, Oxytrol patches |

NSAIDs: Non-steroid anti-inflammatory drugs, TCA: Tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors, NIV: Noninvasive ventilation.[1,63]

## 7. DISCUSSION

ALS is a fatal neurodegenerative disease. As several diseases mimics ALS, the diagnosis of the disease become a challenge in its early stages. Proper diagnosis will access to improve the quality of life of the patient at the earliest. Symptomatic treatments and the preservation of the mobility and communication also halt the progression of disease. As the disease is incurable, the only choice left is to slow down the progression. Hence, it is necessary to treat symptoms associated with the disease. Modern technology helps the ALS patients to access supportive devices which improves the mobility, respiratory functioning, and communication skill of the patient. Still, scientists seeking the mechanism that trigger ALS, and the effective treatments to prevent the progression of disease. Several preclinical and clinical studies were conducted to figure out the exact cause of the disease and to halt the disease progression. The hypothesis state that the progression of the disease can be halt by combatting misfolded proteins, modulation of immune system, nerve cell protection via control and regulation of genes and pathways, improving mitochondrial function, muscle function, and respiratory function. As there is no treatment to cure the disease, the ALS will remain as incurable, fatal, multifactorial, devastating neurodegenerative disease.

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