AMYOTROPHIC LATERAL SCLEROSIS: A REVIEW

SWETA THAKUR¹, SUMAN KUMARI#

¹, #School of Allied Medical Sciences, Lovely Professional University

ABSTRACT
Amyotrophic lateral sclerosis is a disorder especially affecting motor neuron and generally characterized by degeneration of upper and lower motor neuron. It even leads to death within 3 to 5 years causing respiratory failure. There are number of factors which are responsible for causing a neuron disease. It mainly affects older age group i.e. above 60 years. Men are highly at risk as compared to women. The overall ratio is about 1.5 men to every woman. The clinical history of the patients helps in diagnosis. Primarily it affects the control muscles which we needed to speak, move, eat and breathe. In this review the diagnosis, pathogenicity, therapies, current scenario has been discussed. The understanding of pathological physiology of ALS will help in development of rapid and improved diagnostic tools and effective therapies for recovery. This review will help the readers and scientist to gain broad information regarding ALS disease.

Key words: Amyotrophic lateral sclerosis, Neurodegeneration, Familial type ALS, Paralysis

INTRODUCTION
Amyotrophic lateral sclerosis (ALS) is a life threatening neurodegenerative disorder which is characterized by continuously deterioration of motor neuron at the spinal region [1]. It is a paralytic disorder which is progressive in nature. It even leads to death because of respiratory failure within 3 to 5 years. The deterioration of motor neurons results in weakness, muscular atrophy and other complications like hyper reflex activity. The French neurologist Jean-Martin Charcot was the first individual who described about amyotrophic lateral sclerosis in 1869 [2-4]. Thus this disease is also known as Charcot disease. The ALS condition broadly categorized as sporadic and familial type ALS. The inherited genetic defect may also responsible for familial type ALS (FALS) condition. But in sporadic form, there is no linkage of genetic disorder. FALS is one of the most common type of disorder that is in 90-95% cases [5, 6]. The initial clinical course of ALS can vary in different patients. In some cases spinal onset of diseases takes place i.e. the onset of muscle weakness where as other patient presents other bulbar onset of diseases which is characterized by dyspnea and dysphagia [7, 8]. In most of the cases, the disease is unknown. ALS is a type of motor neuron disorder which affects the neuron cells that are involved during activity of voluntary muscles and are known as motor neuron. Such activity takes place in the muscles of arm, face and legs. Motor neuron is found in the brain and spinal cord. In case of ALS cell get degenerated and become dysfunctional. Thus muscles are unable to receive any message from motor neurons resulting loss of voluntary actions performed by muscles and get paralyzed.

EPIDEMIOLOGY
The onset of ALS disorder is average among the age group of 55 to 65 years [2]. ALS is one of the most common type of motor neuron disease occurring in 60-85% of cases. The individuals of younger age group are the least affected by ALS. A study shows that amyotrophic lateral sclerosis is predominant in men as
compared to women with a ratio of 1.5:1 [9, 10]. The smokers are at higher risk of developing ALS [11]. Similarly a study revealed that ALS incidences are higher among football and soccer player [12, 13, 16]. The physical activity and exercise reduces the risk factor of ALS [14, 15]. In India the prevalence of ALS is 6 per 100,000 of total population as compared to globally. The most cases found in India are above the age of 50 years. Only 10% case in India is familial type ALS while the remaining 90% are not. The ratio is 2:1 (male to female). According to the foundation for research on rare disease and disorder chiefly ALS case in India is 5 in 100,000 [17].

PATHOGENESIS
There are certain factors which are responsible for Amyotrophic lateral sclerosis. These factors are discussed below.

Genes
The familial type of ALS i.e. approximately 10% cases are caused by genetic defect or gene mutations [18-21]. Most common genes are C9orf72, TDP43, cytosolic superoxide dismutase (SOD1), TARDBP and FUS [26, 27]. In North America, the gene responsible for ALS in 40-50% cases is C9orf72 [22-24]. Cytosolic superoxide dismutase (SOD1) gene mutation is responsible for familial type of ALS in 20% cases [25]. The common clinical features of FTD are loss of empathy, appetite, abnormal eating, behavior, preservative, stereotype etc. 5% of cases with ALS is found with mutation of TARDB. TARDNA- binding protein 43 is a protein that is encoded by the TARDBP. TDP43 and FUS are RNA binding protein and mutation in these genes leads to familial type of ALS and rare FTD in 5% cases [1]. These gene mutation causes impairment of nuclear localization by reducing rotein complexity. This leads to aggregation of formed stress granules, misfolded proteins and disease approaches to nervous system by manipulating protein trafficking process.

Epigenetics
Recent evidences proved that epigenetic mechanism plays important role in ALS pathogenesis. The main epigenetic factors are DNA methylation, microRNAs and histone proteins modifications [43]. Epigenetics provide a link between environmental factor and genetic mechanisms.

Propagation
There is a range of potential mechanism which reflects the range and process of neurodegenerative. ALS analysis is the result of two pathways according to the GWAS (Genome wide association study) Alzheimer’s disease and Parkinson’s disease. The propagation of pathological proteins like SOD1, C9ORF72 and TDP-43 is the main cause of ALS [44].

RNA processing
The RNA processing proteins like FUS/TLS, TDP-43 etc. found to aggregated and misfolded in ALS patients because of mutation [45]. These mutations lead to disruption of RNA processing and aids in etiology of ALS.

Protein aggregation
It is common feature that are found in ALS. There is improperly folded protein present in the neuron cell which clump together and form protein aggregation. It disturbs normal proteostasis and cellular stress. The
aggregation of protein inhibits the normal functioning of cell, RNA and other proteins. The aggregation of proteins may cause abnormal protein degradation and impaired axon transport. The turnover of misfolded protein may relate to the energetic exhaustion of motor neuron [36].

**Oxidative stress**

SOD1 mutation gene plays a significant role in generation of free radicals or reactive oxygen species (ROS) and causes cytotoxicity. Oxidative stress shows pathogenesis of neurodegenerative disease, including ALS. The CNS biopsies, urine and serum of ALS patients show elevated level of free radicals [41, 42].

**Mitochondria**

Dysfunction of mitochondria is a commonly found in many neurodegenerative disorders. In ALS patients the presence of defective mitochondria is found in soma, axon and neuron of skeletal muscles and spinal cord [30-36]. In spinal cord of ALS patients, mutated and misfolded SOD1 deposits over the cytoplasmic face of outer membrane of mitochondria which leads to mitochondrial dysfunction [37, 38]. This mutated SOD1 also cause disruption of calcium homeostasis leading to motor neuron damage [39, 40]. Not only impaired mitochondrial support evidence of ALS pathogenesis, but there is also possible factor related to the endoplasmic reticulum stress, calcium signaling or metaphase. 

**Glutamate excitotoxicity**

Glutamate is chemical that are common in the nervous system and neuron use it to send signal to other neuron. Glutamate helps in activation of post synaptic receptors during neurotransmission. After that glutamate are removed from synaptic cleft to maintain concentration gradient with the help of excitatory amino acid transporters. This prevents excitotoxic damage of nerve. It is found that the levels of excitatory amino acid transporters are very low in ALS patients which results in excess of glutamate concentration and induction of excitotoxic neurodamage [28, 29]. There is one medicine which is used for inhibit the glutamate rate i.e. Riluzoleis. This medicine inhibits the release of glutamate.

**Axoplasmic flow**

Axon is a special feature of nerve cell. For maintaining the axon structure it is essential that it provide essential protein, mitochondria and other important supply which they required. The normal supply occurs through nuclear and cell body, neuromuscular junction or other neurofilaments. They form neuronal cytoskeleton. In most cases impaired transport of material due to disrupted axoplasmic flow. It is secondary or most important method.

**Myogenic**

VCP, MATR3 and CHCHD10 are the genes with different phenotype which affects muscle. VCP (valosin containing protein) contain mutation in the motor neuron cell, charcot –mane-tooth-disease type 2 which create early onset paget disease and FTD. MATR3 (MATRIN 3) mutation may found in ALS condition. CHCHD10 (coiled-coil-helix-coiled-coil-helix domain containing protein 10) mutation may occur in ALS cases.

**DIAGNOSIS**

There is no particular diagnosis for ALS. The diagnosis of the ALS is based upon clinical historical of patient, muscle atrophy and the physical signs of motor neuron defects. There are some important
investigation for ALS such as imaging of spinal cord, and sometime brain to exclude compressive or inflammatory lesion, nerve, conduction studies to exclude conduction block. Electromyography is done for the confirmation of muscle denervation, Nerve conduction study – nerve conduction study is used to measure that types of nerve have ability to send impulse to muscle. Magnetic resonance imaging- for brain and spinal cord imaging. It can detect spinal cord tumors, herniated disks in neck or other symptoms. Blood and urine sample is also used for detection of the symptoms. Lumber puncture fluid specimen is used for detection of ALS. Muscle biopsy is also performed.

**TREATMENT**

Two medications are used for treating the ALS which is approved by food and drug administration. One is Riluzole tablets or pills which are used for reducing the level of a chemical messenger in the brain that present higher level in people with ALS. Second is Edaravone. It is an intravenous medication which is used to treat the ALS.

**THERAPIES**

There are some therapies which are also used for recovery of ALS.

**Breathing care**

By providing a to assist patients breathing at night, ALS can be treated through surgery a tube is inserted by creating a hole at the front of neck in which insert into the windpipe and that tube is connected with respiratory.

**Physical therapy**

A physical therapy provide exercise chartsto cure the pain, walking, mobility, bracing etc.by doing exercise maintaining of the cardiovascular fitness, muscle strength and range of motion. It also promotes the ability to move, reduce pain, restore function and prevent disability. Daily exercise required.

**Occupational therapy**

It determines the personal goals to improve the person ability by performing daily activities. In generally worked with the people with mental health problem, disability, injuries, or impairments.

**Speech therapy**

In case of ALS patients those muscles are affected which helps in speaking process. In this therapy it teaches the adaptive therapy which makes the speech more clearly understood. It can also promote other method of communication such as alphabet board or simple paper and pen.

**Nutritional support**

Nutritional support is gained by having the food which is rich in carbohydrates, proteins and lipids which is easy to ingest and meet with the nutritional requirement. To fulfill the nutrition needs it may require a feeding tube in case of ALS patients.

**Psychological and social support**

There are some social workers who help for financial issues, insurance, getting equipment and paying for devices that person requires for treatment or therapy.
PREVENTION
Prevention of ALS is start from birth. It can be prevented by having an appropriate diet and also stress avoidance. According to the medical sciences for the prevention of ALS, eating bright colored fruits and vegetable are required nowadays and also doing exercise on regular basis leads to reduce the effect of ALS in patients. There is no particular prevention for ALS because it is an unknown disease.

CONCLUSION
Amyotrophic lateral sclerosis is a life threatening motor neuron disorder chiefly affecting upper and lower motor neuron. In most of the cases ALS lead to the muscular paralysis. Globally the ALS case is 3 to 5 per 100,000 of population and in India 6 per 100,000. Some factors which are responsible for causing neuron disorder are discussed in this review which will help in developing improved treatments. According to the future perspective there are therapeutics interventions like non –invasive ventilation and also stem cell therapy. These are important steps towards the development of cellular therapies for the treatment of ALS. According to some published studies the number of ALS cases will be increasing across the world in upcoming years from 222,801 in 2015 to 376,674 in 2040. So there is a need to take steps toward earlier diagnostic techniques and improved therapies without delay. There is a good scope of research in cell therapy and gene therapy related to ALS.

CONFLICT OF INTEREST
The author declares no conflict of interest.

REFERENCES


