Available online on 15.05.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Amyotrophic Lateral Sclerosis: An Overview

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ABSTRACT

Amyotrophic Lateral Sclerosis is an adult-onset neurodegenerative disease that causes paralysis. Presently it is incurable and rapidly progressive with a survival of 4-5 years from onset. It is degeneration of upper and lower motor neurons which results in weakness and wasting of muscles in arms, legs, trunk and bulbar region. There are two types sporadic and familial amyotrophic lateral sclerosis. The age of onset of people with familial is widely reported as being about 10 years younger than for those with apparently sporadic amyotrophic lateral sclerosis. Epidemiological studies show a worldwide incidence of 2-3 per year per 100-000 population over age of 15 years. About 10% of individuals have a family history of amyotrophic lateral sclerosis. The cause is unknown. Genes linked to diseases have been identified including one (C9ORF72) that seems to be particulary important. Researchers are studying several causes of ALS like gene mutation, chemical imbalance, disorganized immune response and protein mishandling. Riluzole and Radicava were approved for the treatment by the Food and Drug administration. The diagnosis of ALS is devastating for patient and family members. People with ALS should be delivered with multidisciplinary team. The current hope is that stem cells of neural or extraneural origin might be modified in vitro to neurons that may migrate to the sites of motor neuron loss. The quality of life is important not just the duration of survival.

Keywords: Amyotrophic Lateral Sclerosis, Motor neuron diseases, Sporadic, Familial, Pathogenesis.

Article Info: Received 25 March 2019; Review Completed 04 May 2019; Accepted 07 May 2019; Available online 15 May 2019

Cite this article as:

Saudagar R, Garge L, Amyotrophic Lateral Sclerosis: An Overview , Journal of Drug Delivery and Therapeutics. 2019; 9(3):613-616 http://dx.doi.org/10.22270/jddt.v9i3.2874

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INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is an adult-onset neurodegenerative disease that leads to paralysis. Presently it is incurable and rapidly progressive with a mean survival of 4–5 y from onset.[1] Amyotrophic lateral sclerosis or motor neuron disease in its purest form is a readily identified clinical condition. It is rapidly progressive degeneration of upper and lower motor neurons, which results in weakness and wasting of muscle in the arms, leg, trunk and bulbar region. Amyotrophic lateral sclerosis which is one of the most common motor neuron degenerative diseases typically attacks adults during midlife. Although ALS cases have been detected all over the world interestingly the prevalence of the geographic location of the Western Pacific form of ALS is 50–100 times higher than elsewhere world. One of the first studies performed in this population in 1957 described a genetic origin of ALS associated with Parkinsonism and dementia independent of environmental changes. However recent studies have noted a decreased incidence in these areas over the past 40 years.[2] A combination of upper and lower motor neurone dysfunction was named amyotrophic lateral sclerosis (ALS) by Charcot and Joffroy. In the united states ALS or Lou Gehrig's disease are terms used to describe all forms of the disease where the combination of upper and lower motor neurone involvement. It is the third commonest neurodegenerative disease after Alzheimer's and Parkinson's diseases. Despite its rarity the disease has gain a lot of attention as its devastating course places it at the centre of the ethical dispute about end of life decision making and physician assisted suicide.[3]

TYPES

Sporadic and Familial Als

There is arresting heterogeneity in the genetic causes of familial amyotrophic lateral sclerosis but familial and sporadic amyotrophic lateral sclerosis have similarities in their pathological features and in their clinical features suggesting a convergence of the cellular and molecular events that lead to motor neuron degeneration. [5] The age of onset of people with familial Amyotrophic lateral sclerosis is widely reported as being about 10 years younger than for those with apparently sporadic amyotrophic lateral sclerosis.[6]

PATHOGENESIS

1. Background Vulnerability

Epidemiological studies of ALS show a worldwide incidence of 2–3 per year per 100 000 population over the age of 15 year and an overall lifetime risk of developing amyotrophic lateral sclerosis of 1:350 for men and 1:400 for women. An outward increase in incidence in the disorder in the last few decades may be due to improved diagnosis an aging population or a genuine increase the frequency of the disease. Around 10% of individuals have a family history of ALS. A study of twin data suggested that heritability contributes 60% to the risk of developing amyotrophic lateral sclerosis and environment 40% but an analysis from three genome-wide association studies found a lower heritability of 21%.[8]

2. Genes

Although the majority of amyotrophic lateral sclerosis cases are sporadic in the past 2 decades mutations identified in several genes have provided insight into potential disease mechanisms and presented opportunities for disease modelling. The brief introduction of some of the most commonly studied mutations as well as some recently identified that are relevant to our current understanding of pathogenesis. An increasing number of genes are recognized as associated and causative of amyotrophic lateral sclerosis. The most common are C9orf72, SOD1, TARDBP and FUS.[8-10]

C9ORF72

C9orf72 is the most frequent genetic change identified in patients with amyotrophic lateral sclerosis. Expansions are found in around 39% of familial ALS patients and 7% of apparently sporadic cases of European ancestry but with significant differences between populations. For example study of 563 patients with ALS in japan identified expansions in 0.4% of sporadic and 0% of familial ALS patients and in less than 1% of chinese sporadic ALS patients. Patients with ALS often display cognitive changes with features of apathy, disinhibition, socially inappropriate behaviour, abnormal eating behaviours, loss of empathy and stereotyped or obsessive-compulsive behaviour. Hallucinations and delusions may occur. Within a family some individuals may have amyotrophic lateral sclerosis. The genetic feature is hexanucleotide repeat of GGGGCC either in the promotor or intron 1 of the gene. The normal range of repeats is uncertain but usually considered up to 20 repeats while patients with ALS usually have repeats of several hundred to thousands. Inheritance is autosomal dominant. There is no clear intergenerational anticipation however short expansions 45-78 repeats have been associated with age at onset and C9ORF72 families displayed possible anticipation. There is TDP-43 pathology. There are also p62-positive neuronal cytoplasmic inclusions composed of dipeptide repeat proteins (DPR) formed by translation from the abnormally expanded repeat in C9ORF72. A particular feature of the C9ORF72 expansion is repeat-associated non- ATG (RAN) translation that can occur in all six sense and antisense frames resulting in five different DPR proteins. The mechanisms of toxicity remain unclear but a richer understanding is gradually being achieved.[8]

SOD1

Copper zinc superoxide dismutase (SOD1) was the first genetic cause of amyotrophic lateral sclerosis to be identified in 1993. Mutations are commonly estimated to be present in around 20% of familial patients and 1% of apparently sporadic. The frequency will vary between populations and in an Italian population SOD1 mutations were identified in 14% of familial amyotrophic lateral sclerosis patients.[7] Founder haplotypes may have significant effects on frequency. The mutations are predominantly point mutations. Inheritance is autosomal dominant. There are over 170 different genetic alterations recognized although many of these are private to individuals and causation may be difficult to prove outside large families. Disease pathogenesis remains uncertain but an unusual feature is the absence of TDP-43 pathology now supposed to be typical of ALS otherwise. The disease mechanism appears to be a gain of function and not a loss of enzyme function. Protein misfolding and oxidative stress are amongst the possible mechanism.[8]

TARDBP

TAR DNA-binding protein 43 (TARDBP/TDP-43) mutations are found in around 5% of patients with familial amyotrophic lateral sclerosis. Inheritance is autosomal dominant. TDP-43 is the protein typically found in the tau and alpha-synuclein-negative, ubiquinated, cytoplasmic inclusions or aggregates found in amyotrophic lateral sclerosis and a subset of FTD. TDP-43 is an RNA and DNA binding protein that regulates transcription, mRNA splicing, transport and stability.[8] Current pathogenic include a gain of function toxicity of mutant TDP-43 in disruption of stress granules that aggregate and form cytoplasmic ubiqutinated protein inclusions. Loss of function may occur through depletion of TDP-43 in the nucleus of the motor neuron when the TDP-43 is included in the cytoplasmic ubiquitinated protein inclusions induced by mutant TARDBP it resulting in dysregulation of nuclear RNA metabolism.[9]

FUS

Fused in sarcoma translated in liposarcoma (FUS) is also found in around 5% of patients with familial amyotrophic lateral sclerosis.(8) FUS is a nucleoprotein that regulates RNA and DNA binding, gene expression and mRNA splicing. FUS colocalises with TDP-43 to stress granules in the motor neuron. Potential pathogenic mechanisms are similar to those of TDP-43.[9]

SYMPTOMS

The symptoms of ALS usually appear when a person is in their after 50s or before 60s but it can happen at other ages. Progression varies between individuals. In the early stages the symptoms may be barely noticeable but the weakness becomes more visible over time.

Early symptoms and signs include:

1. Difficulty carrying out daily activities including walking.
2. Increased clumsiness.
3. Weakness in the feet, hands, legs and ankles.
4. Cramping and twitching in the arms, shoulders and tongue.
5. Difficulty in sustaining the good posture and holding the head up.
6. Uncontrolled outbursts of laughing or crying (emotional liability).
7. Cognitive changes.
8. Slurring of speech and struggle with voice projection.
9. Pain.
10. Fatigue.

11. Problems with saliva and mucus.
12. Difficulty in breathing and swallowing in the later stages.

Researchers are studying the several possible causes of amyotrophic lateral sclerosis including:

1. Gene Mutation

Several genetic mutations can lead to inherited amyotrophic lateral sclerosis which causes nearly the similar symptoms as the noninherited form.

2. Chemical Imbalance

People with amyotrophic lateral sclerosis usually have higher than normal levels of glutamate a chemical messenger in the brain around the nerve cells in their spinal fluid. Too much glutamate is known to be toxic to several nerve cells.

3. Disorganized Immune Response

Sometimes a person's immune system begins attacking some of his or her body's specific normal cells which may lead to the death of nerve cells.

4. Protein Mishandling

Mishandled proteins within the nerve cells may lead to a gradual accumulation of abnormal forms of these proteins in the cells destroying the nerve cells.

Progressive muscle weakness occurs in all cases of amyotrophic lateral sclerosis but this may not be the first indication of the condition. Early symptoms often include clumsiness, abnormal limb fatigue, muscle cramps and twitches and slurred speech. Symptoms will spread to all portions of the body as amyotrophic lateral sclerosis progresses. Some people may have difficulties with decision making and memory eventually leading to a form of dementia called frontotemporal dementia. Emotional lability can cause instabilities in mood and emotional response.[13]

DIAGNOSIS

It is not widely appreciated outside of specialist clinics that there are a number of symptoms associated with motor neuron diseases which are highly amenable to treatment. The aim of these interventions is primarily palliative and aimed at maintaining quality of life rather than to prolong the duration of illness.[3] Riluzole drug was approved for ALS treatment by the Food and Drug Administration (FDA) in 1995 and it appears to slow the progression of the disease. In May 2017 Radicava (Edaravone) was approved to treat ALS. The most significant benefit of riluzole is observed after intervention in the early stages of the disease. Thus an early diagnosis of ALS could provide the most effective results. Since diagnosis of ALS relies on clinical symptoms and the time from the first symptoms to diagnosis is about 12 months there is a delay hindering a successful therapy. This phenomenon underlies the importance of the development of screening tests able to detect the disease in early stages. The diagnosis of amyotrophic lateral sclerosis is devastating for the patient and family members and must be handled sensitively. Scheduling a follow up appointment soon after diagnosis is beneficial to answer questions not dealt with during the initial consultation and can help provide further information about support networks which are well established in most developed nations.[11]

Tests that may help diagnose amyotrophic lateral sclerosis are:

I. Electromyography (EMG) which identifies electrical energy in muscles

II. Nerve conduction study (NCS) which tests how well the nerves direct signals.

THERAPY

Physical therapy :

It can help people with ALS achieve pain and report mobility issues. A physical therapist can provide help and information with:

a. Low-impact exercises to enhance cardiovascular fitness and overall well-being.
b. Mobility aids such as walkers and wheelchairs.
c. Devices to make life simple such as ramps.

Occupational therapy :

It can help a patient to keep their independence for longer by:

a. Helping patients select adaptive equipment and assistive technologies to help them keep up their daily routines.
b. Train them in ways to compensate for hand and arm weaknesses.

Breathing therapy :

It is required in time as the respiratory muscles get weaker. Breathing devices can support the patient breathe better at night. Some patients may need mechanical ventilation. One end of a tube is attached to a respirator while the other end is inserted into the windpipe through a surgically-created hole in the neck or tracheostomy

Speech therapy :

It is useful when ALS begins to make it harder to talk. Speech therapists can help by teaching adaptive techniques. Other methods of communication include writing and computer based communications equipment.

Nutritional support :

It is important as struggle with swallowing can make it hard to get enough nutrients. Nutritionists can advise on preparing nutritious meals that are easier to swallow. Suction devices and feeding tubes may help.[13]

MANAGEMENT

People with MND and their carers have complex needs which can only adequately be delivered by a multidisciplinary team experienced in the management of progressive neurological disability. This should routinely include a physiotherapist to advise on mobility, postural support and prevention of contractures a speech and language therapist to assess swallowing and provide communication aids an occupational therapist to provide aids to maintain function (wheelchair, mobile armsupports, etc) a dietitian to advise on maintaining weight and percutaneous endoscopic gastrostomy feeding. Symptomatic treatments remain the cornerstone of management for patients with ALS. For some patients these treatments not only alleviate symptoms but also improve survival and quality of life. Multidisciplinary models of care have developed as a predictor of survival reducing the risk of death by 45% at 5 years. Compared with patients managed in a general neurology clinic patients managed in a specialised clinic had a better quality of life possibly attributable to more effective use of resources, with benefits derived after a single visit.[12,13]

FUTURE PROSPECTS

Although described in the mid-19th century amyotrophic lateral sclerosis has proved to be one of the most puzzling neurodegenerative diseases and remains largely untreatable. Much of our knowledge of the pathogenesis of Amyotrophic lateral sclerosis comes initially from analysis of postmortem material in which the disease process is advanced and many of the changes reflect the end stage of a cascade of metabolic derangements resulting in motor neurone degeneration. Despite the intense research activity of the last y the use of miRNAs as biomarkers for diagnosis of amyotrophic lateral sclerosis and clinical management of patients is still in an early stage of development. Several interesting data have been obtained so far with important insights into the disease processes. At the same time when possible future studies should try to combine data obtained from multiple source of sample (blood, CSF and muscle) of the same patient. Up to date only few studies have performed this kind of analysis and their results are quite conflicting.The ultimate objective is to include these biomarkers in all phases of Amyotrophic lateral sclerosis management from the diagnosis to the clinical trials and in perspective to the identification of future therapeutic approaches.[11] The recent hope is that stem cells of neural or extraneural origin might be changed in vitro to differentiate into neurones that would migrate to sites of motor neurone loss and form functional networks to restore the motor pathways lost in motor neuron diseases. It is important that quality of life not just duration of survival is part of the measure of effectiveness of drug regimens.[13]

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