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ALS: THE BASICS AND BEYOND

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ABSTRACT

Lou Gehrig's disease, sometimes also known as amyotrophic lateral sclerosis (ALS), is an incurable neurological disorder affects motor neurones in the brain and spinal cord. Primarily recognised by Jean-Martin Charcot in 1869, ALS develops muscle weakness, paralysis, and finally respiratory failure. Still completely unknown is the aetiology; environmental and genetic components have been connected. Pathologically, ALS's accumulation of proteins and motor neurone destruction demonstrate Pathophysiologically, it correlates with the development of oxidative stress, mitochondrial dysfunction, and neuroinflammation. Treatment is basically supportive; riluzole and edaravone are FDA-approved medications with moderate advantages; confirmation is dependent on clinical signs as well as symptoms, electromyography, and exclusion of other illnesses. Multidisciplinary cooperation with a value on inflammation of the neurones, stem cell treatments, and gene therapy has founded present investigations (2022–2024) on controlling symptoms. Especially remarkable advancements include ongoing investigation of antisense oligonucleotide therapies for C9orf72-related ALS and the Food and Drug Administration's approval of tofersen for SOD1-ALS in 2023. Under investigations are pharmacological treatments using small compounds focussing at mitochondrial function and protein aggregation. Future treatments might call for combination medications covering several pathways in addition to customised approaches depending on genetic profiles. About 2–3 per 100,000 people worldwide suffer with ALS. Well-known people impacted are Lou Gehrig and Stephen Hawking. Research advances bring cautious

hope for better therapies and maybe a cure for this terrible illness. Early symptoms of ALS include trembling of the muscles and lack of energy, growing to paralysis and difficulties breathing, whereas mental impairment may occur in later stages and progression varies; most people remain 2-5 years after symptom onset.

KEYWORDS: Motor neuron disease, Lou Gehrig's disease, Muscle weakness, Progressive paralysis, Stem cell research.

Introduction & History

Contributing to nerve cells in the brain and spinal cord, Amyotrophic Lateral Sclerosis (ALS), sometimes referred to as Lou Gehrig's disease or motor neurone disease, is an incurable form of neurodegenerative disease. Greek terms "a" (no), "myo" (muscle), and "trophic" (nutrition) translate as "amyotrophic"—that is, "no muscle nourishment". While "sclerosis" characterises the hardness of the spinal cord when motor neurones deteriorate, "lateral" refers to the parts of the spinal cord where the afflicted nerve cells are found. As motor neurons—which provide information from the brain to muscles that are voluntary across the body—die in ALS, the brain decreases its capacity to start and regulate muscle activity. ALS patients could lose their capacity to eat, talk, move, and breathe, therefore rendering them paralysed and finally dead.[1] [2]

ALS initially came to be described in 1824 when Scottish anatomist and surgeon Charles Bell examined and recorded a case of increasing muscle atrophy. Whereas French physician Jean-Martin Charcot presented only an in-depth explanation of the illness, segregating it from other neurological disorders, in 1869. Work by Charcot resulted in the name "Charcot's disease" used in several regions of the globe. When baseball icon Lou Gehrig was indeed with ALS in 1939, the condition attracted a lot of public recognise in the United States. Gehrig's high reputation and his heartfelt farewell message at Yankee Stadium on July 4, 1939, raised general knowledge of the illness. In North America, ALS thus became generally recognised as "Lou Gehrig's disease". ALS research become more intense throughout the 20th century. When researchers found abnormalities in the SOD1 gene as an explanation of some familial ALS cases in 1993, an incredible discovery occured. This finding introduced fresh directions for knowledge of the disease causes and possible treatment development. The ALS Ice Bucket Challenge created a worldwide sensation in 2014, generating almost $220 million for ALS research and significantly enhancing public awareness of the condition, therefore driving faster research activity and fresh field discoveries.

Though its frequency and rates of occurrence vary across various groups of individuals and geographic areas, ALS affects individuals across all geographical areas, nationalities, and cultures. ALS has been determined to be somewhat common worldwide, approximately 4-6 per 100,000 people. The results indicate that at any one time, approximately 300,000 and 450,000 people globally are most likely suffering with ALS. The overall worldwide incidence rate of ALS would be around 2 per 100,000 person-years, which translates to roughly 150,000 new cases reported year worldwide.[3]

A) Western Pacific: Although these particles, recognised as the ALS-Parkinsonism Dementia Complex (ALS-PDC), possessed rates of occurrence up to 100 times higher than the worldwide average, these rates have been declining in recent years. Guam, the Kii Peninsula of Japan, and West Papua have been most affected.

B) Europe: Although rates vary considerably between 2.1 to 3.8 per 100,000 person-years, the prevalence of ALS is rather homogeneous; still, rates have been recognised to be considerably higher in Scandinavian countries in comparison to Southern European countries.

C) North America: With about two newly identified instances per 100,000 person-years, North America's incidence rate is comparable to Europe's.

D) Asia: With percentages of 0.7 to 0.8 per 100,000 person-years, studies demonstrated a lower rate of infection in Asian populations in a comparison to countries in the West; this could be somewhat related to differences in diagnosing approaches and reporting systems.

E) Africa: Though there is little information on African nations, several research point to lower the rates of incidence than in Western countries; this could be affected by variations in life span and the availability of medical care, even.[4][2][5]

Although more detailed epidemiological examinations are required, the incidence frequencies in Latin American nations seem to be rather comparable with those in Europe and North America.

However, it can strike adults of any age, the average year of development for occasional cases of ALS is 55 years and it most typically strikes across individuals between the ages of 40 and 70. According to certain studies, ALS frequency and incidence vary substantially depending on racial and ethnic groupings. For example, some studies show that ALS might

be a not as frequent across African and Asian populations rather than among Caucasians, but these variations are rather minor and further study is required to completely explore the effect of ethnic background and racial background on ALS risk. Although ALS is an across the globe disease that affects populations all around, its appearance shows some geographical differences; hence, continuous research helps us to better understand these patterns, which could provide important information on the biological and genetic elements influencing the emergence of ALS.

ETIOLOGY OF ALS (Amyotrophic Lateral Sclerosis)

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that primarily affects motor neurons in the brain and spinal cord. The exact mechanism of ALS is not fully understood, but several key processes are involved

1. GENETIC FACTORS (which leads to families ALS): As per the latest research conducted on development of new medication of ALS by *Food & Drug Administration* (FDA), the main cause of the ALS is still unknown but most of the researches & cases related to ALS says that the genetic factors like C9 or F72 gene causes the genetic mutation in ALS patients. The ALS caused due to the genetic mutations/factors is also called as the familiar ALS.

Familier ALS: Da Chromosome paarweise auftreten, besitzt jede Zelle (außer Spermien und Eizellen) zwei Kopien fast jedes Gens. Zum Beispiel befindet sich das C9- und das F72-Gen auf Chromosome 9. As there are two copies of these chromosomes, each cell will contain two copies of the C9 or F72 gene. Moreover, if at least one copy of the C9orf72 gene is mutated, it can result in ALS. For most ALS genes, inheriting a single mutated copy is sufficient to cause or elevate the risk of disease development. A mutation is termed dominant if having only one copy of the mutated gene can result in disease. Either one copies of a gene must be mutated to cause disease, it is called a recessive mutation. This mutation thereby encompasses a growth of genetic disorder characterized by adult on set loss of upper and lower Motor neuron system, which also involve the other parts of nervous system.

Other than C9 and F72 genes, there are more genes SOD1, FUS and TARDBP genes involved familier ALS mutation factor. This genes handle about the 25 to 30% of the familier ALS cases. There are more of such types but there identification is still in progress no ALS gene has exclusive been associated with ALS only,these says that the ALS is a multi system

neurodegenerative syndrome with the propensity for targetting the motor system. We can also say that ALS is a progressive oligogenic inheritance disorder.[6]

2. MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction has been suggested to contribute to motor neuron death in ALS. Mitochondrial fragmentation and alterations in mitochondrial morphology, as well as changes in the expression of fusion/fission proteins, are thoroughly documented in ALS. These changes significantly impact normal mitochondrial function. Mitochondrial transport that is not functioning properly could account for the buildup of irregular mitochondria in motor neuron axons, as observed in both animal models of ALS and in human patients. Aberrations in oxidative metabolism associated with alterations in electron transport chain activity and impaired ATP production have been demonstrated through studies conducted on cell culture models and transgenic animals. Mitochondria from patients with ALS exhibit deficient Ca2+ homeostasis and heightened production of reactive oxygen species (ROS), leading to oxidative-related damage such as alterations in protein carbonylates and tyrosine nitration. In fact, in spinal motor neurons from transgenic ALS animals, neurotoxicity mediated by glutamate receptors has been associated with an excess of mitochondrial calcium and ROS production. These studies collectively illustrate that alterations in mitochondrial function and dynamics are a critical and shared characteristic of ALS pathogenesis. It remains unclear, though, whether mitochondrial dysfunction is a primary or secondary event in these processes.[5][7]

3. NEUROINFLAMMATION CAUSING ALS: Even in the presymptomatic phases of ALS, neuroinflammation characterised by synaptic and astrocyte activation, T lymphocyte destruction, and excess cultivation of inflammatory cytokines has been identified in conjunction with losing neurones in both animal and human tissues. Although the mechanism is far from completely clear, accumulating information gathered through preclinical research has linked immune cells to having either exerting negative or protective effects on MN survival as determined by the degree of illness progression.

MICROGLIA: Microglia serve as the initial immune defines in the brain and spinal cord. They assess the environment around them and react to “danger signals” from injured tissues. Reports indicate that in ALS, damaged MNs and astrocytes release misfolded proteins (like mSOD1), which activate microglia via pathways dependent on CD14, toll-like receptor (TLR) 2, TLR4, and scavenger receptors. Using positron emission tomography (PET), direct

evidence was provided that widespread microglial activation occurs in the brains of living ALS patients and SOD1G93A mice, with a significant correlation between the degree of microglial activation in the motor cortex and the severity of clinical MN deficits. Research conducted on mSOD1 transgenic mice denote that substituting mSOD1 microglia with wild-type microglia, along with diminishing mSOD1 levels in microglia, retard MN degeneration and increased the animals' lifespan. O'Rourke et al. recently showed that C9orf72 expression is highest in myeloid cells, and that loss of C9orf72 function in mice causes lysosomal trafficking defects, a reduced ability of microglia to clear aggregated proteins, altered microglial responses, and neuroinflammation. Macrophages also exhibited comparable outcomes. Specifically, even a haploinsufficiency of C9orf72 seems to play a role in the modification of inflammatory responses in macrophages. The results indicate that C9orf72 might influence neurons and myeloid cells in two different ways.[8]

ASTROCYTES: Genes associated with ALS are expressed in astrocytes as well as in MNs. In vitro and in vivo studies have demonstrated that astrocytes expressing mSOD1 are toxic to both normal motor neurons (MNs) and MNs derived from embryonic stem cells (ESCs) carrying the mSOD1 gene. It is noteworthy that astrocytes expressing mSOD1 led to the selective death of spinal MNs in ALS, while not affecting spinal GABAergic neurons, dorsal root ganglion neurons, or ESC-derived interneurons. By selectively silencing or blocking the mSOD1 gene in astrocytes, or through the transplantation of healthy astrocytes, it may be possible to reduce astrocyte-mediated toxicity and MN loss, slow disease progression, and extend the lifespan of mSOD1 mice. On the other hand, the transplantation of astrocytes that express mSOD1 caused localized degeneration and mortality of MNs in the spinal cords of wild-type rats. Moreover, astrocytes that were reprogrammed from fibroblasts of ALS patients negatively affected the survival of MNs. Consequently, the manifestation of mutant proteins linked to ALS in astrocytes plays a role in non-cell autonomous toxicity. It was recently demonstrated by Qian and colleagues that in the spinal cord transplanted with ALS astrocytes, both MNs and non-MNs underwent degeneration. Significantly, they noted that the loss of non-MNs occurred prior to that of MNs. This implies that the non-cell autonomous toxicity of ALS astrocytes on neural degeneration extends beyond MNs and may involve non-MNs in the degenerative process.[9]

4. IMPAIRED AXONAL TRANSPORT CAUSING ALS: Motor neurons are characterized by their long axons, and for these neurons to survive, it is essential that axonal

transport is finely tuned. As a potential cause of neuronal dysfunction in various neurodegenerative motor neuron diseases, the obstruction of axonal transport is becoming increasingly recognized. Reducing of dynein and dynactin-1, motor molecules that control axonal trafficking, lead to disruptions in axonal transport in flies and result in motor neuron degeneration due to mutations in their genes in humans and rodents. In mouse models of amyotrophic lateral sclerosis (ALS), defects in axonal transport are one of the initial molecular events that contribute to neurodegeneration. Gene expression profiles show that dynactin-1 mRNA levels are reduced in the degenerating spinal motor neurons of autopsy patients with sporadic ALS. In a mouse model of spinal and bulbar muscular atrophy, which is a motor neuron disease resulting from triplet CAG repeat expansion in the gene for the androgen receptor, Dynactin-1 mRNA levels are diminished in the affected neurons. Pathogenic androgen receptor proteins hinder kinesin-1 microtubule-binding activity and interfere with anterograde axonal transport through the activation of c-Jun N-terminal kinase. Pathogenesis of spinal muscular atrophy and hereditary spastic paraplegias is also rooted in the disruption of axonal transport. The observations imply that the disruption of axonal transport is a crucial factor in the pathological processes underlying motor neuron degeneration and represents a significant focus for developing therapies for motor neuron diseases.[4][10]

Moreover, although axons can represent more than 99% of the volume of a cell, protein and lipid syntheses occur almost exclusively in the cell body. Thus, for the axon to receive newly synthesized materials and for neurotrophic factors and damaged organelles to be moved from the axon terminal to the cell body, active transport is necessary. Axonal transport primarily relies on specialized motor proteins and the cytoskeletal networks formed by microtubules and actin filaments. More and more reports are connecting imperfections in axonal transport with degenerations of motor neurons, including amyotrophic lateral sclerosis (ALS), spinal and bulbar muscular atrophy (SBMA), spinal muscular atrophy (SMA), and hereditary spastic paraplegias (HSPs). Furthermore, a number of studies have pinpointed mutations in microtubule-based motor proteins belonging to the kinesin and dynein superfamilies in specific hereditary forms of motor neuron diseases (MNDs): these include mutations in the genes for kinesin 1 motors (KIF5A) in certain types of HSPs, two missense mutations in the dynein gene within the Loa and Cra mouse models of ALS, and a mutation in the dynactin-1 gene associated with a familial lower motor neuron disease. Motor neuron diseases can also derive from dysfunctions of various membrane-associated proteins, which hamper the

effective transport of cargos like endosomes and mitochondria. This article gives us briefly information of what is currently known about the links between axonal transport defects and the development of motor neuron diseases.

DYNEIN/DYNACTIN COMPLEX: – Comprising two homodimerized heavy chains along with various accessory proteins (such as intermediate, light intermediate, and light chains), cytoplasmic dynein serves as a primary motor for retrograde transport within cells. Dynein plays a role in various intracellular motile processes, such as mitosis, the maintenance of the Golgi apparatus, and the transport of membranous vesicles and other intracellular particles. In a gene screening aimed at late-onset MND, two mutant mouse strains with dynein mutations were discovered: Legs at odd angles (Loa) and Cramping1 (Cra1). Mice with these mutations in a heterozygous state show, as they age, a progressive decline in muscle tone and ability to move. The ways in which these mutations lead to neurodegeneration are still under discussion. Hafezparast et al. showed that the Loa mutation leads to an axonal transport defect through an assay using a fluorescent fragment of tetanus toxin (TeNT HC) to visualize and quantify axonal retrograde transport in motor neuron cultures from Loa/Loa mice. However, in a mutant superoxide dismutase 1 (SOD1) mouse model of ALS, heterozygous knockout of dynein did not worsen but rather improved axonal transport. Furthermore, Ori-McKenney et al. indicated that in the Loa+/− mutant mouse, neurodegeneration is probably not due to the dissociation of dynein subunits or dynein from its cargo, but rather to a changed interaction between dynein and microtubules.[10] [11]

Conversely, another dynein mutation, sprawling (Swl), causes an early-onset sensory neuropathy in heterozygous knock-out mice for this gene, but does not lead to progressive motor neuron loss. This highlights the confusing relationship between dynein mutations and axonal transport. Besides the changes in dynein, a G59S mutation in the P150Glued subunit of dynactin (dynactin-1) has been discovered in families experiencing a slowly progressing autosomal dominant form of lower motor neuron disease. Dynactin, a complex of multiple proteins, is linked with dynein and is necessary for the attachment of dynein to its cargos. In fact, the Drosophila dynactin depletion model showed disrupted axonal transport The G59S substitution is found within the CAP-Gly motif of dynactin-1, which is highly conserved. This domain directly binds to microtubules and slows organelle transport in vitro. Additionally, the protein with the G59S mutation displays an increased tendency to misfolded and forms aggregates that contain trapped organelles like mitochondria. While early

degeneration of axons and neuromuscular junctions is observed in three different mouse models of mutant G59S, the presence of an axonal transport defect in these models remains to be determined. However, Chevalier-Larsen et al. showed us the absence of axonal transport defects in their transgenic mouse model by performing a double ligation assay on sciatic nerves. To resolve this difference, further experiments, such as in vivo imaging of axons, are needed to analyze the transport of cargos, and it is also important to generate and analyze dynactin-1 depletion models.[12]

5. OTHER EXTERNAL FACTORS FOR CAUSING ALS: - Apart from genetics factors causing ALS, there are other several factors that are also been responsible for ALS. As per the case study about ALS"The age "&"male sex "factors are at the most risk. The apart physical factor like smoking, body mass index, physical exercise, occupational and environmental exposure to metals, head injury, beta-methyl-amino-L-alanine, viral infection, etc. also has the causal relationship with ALS.[13]

PATHOLOGICAL STUDY OF ALS

Damage to muscle neurones in the spinal cord, brainstem, and frontal cortex is what makes ALS what it is. The signs of ALS that it is a disease are:

- Motor neuron loss and atrophy
- Astrocytosis and microgliosis
- Inclusion bodies (e.g., TDP-43, SOD1)
- Axonal degeneration and Wallerian degeneration.[14]

Pathophysiology of ALS

Many genetic and environmental factors together lead to ALS. These involve:

Mitochondrial dysfunction

Oxidation stress and Neuro-inflammation

Excitotoxicity

Protein misfolding and aggregation.[15]

1. Mitochondrial dysfunction

Mitochondrial dysfunction is also known as one of the most important neuro-pathological characteristics of ALS. The respiratory origin of reactive oxygen species in ALS is the oxidation chain and exchange brought about by mitochondrial failure. Oxygen and oxidative stress are the results of mitochondrial impairment in AIS function. They are changes found in

the patient and animals with mutations in SOD1. Antioxidant dismutase in some cases of ALS occurring within families, there is SOD1 mutation (superoxide dismutase). Outer membrane, matrix, and intermembrane space of mitochondria all have mutant SOD1 protein. The enzyme that reduces toxic oxygen from cells is SOD1, which detoxifies free radicals and safeguards cells from excitotoxicity. Protein import is disrupted in patients with mitochondrial intermembrane space dysfunction, as can be seen in SOD1 models with protein aggregates that are silenced in the sod1. The respiratory system of the patient also undergoes changes aside from mitochondrial protein degradation. A close junction associated with abnormal FUS and TARDBP mutations favors control of a number of processes between the mitochondria and endoplasmic reticulum in ALS. TARDBP mutation augments mitochondrial localization of TDP43 and TDP43 can bind to mRNAs. In cellular models with mTDP43, inhibiting localization of TDP-43 to mitochondria improves mitochondrial function and decreases neuronal death. The dipeptide repeat protein poly (GR) seems to impair mitochondrial function, causing oxidative stress and DNA damage in C9orf72-associated ALS models. Familial ALS-associated mutations of CHCHD10 can interfere with the preservation of mitochondrial genome, cause the loss of mitochondrial cristae junctions, and interfere with apoptosis by inhibiting cytochrome-C. Encoding respiratory change in complexes in subunits, leading one disassembly to build up in ALS patients' mitochondria.[15][16]

2. Oxidation stress and Neuro-inflammation

In SALS and FALS, neuro-inflammation damages the motor regions of the central nervous system (CNS) and is characterized by reactive astrocytes and microglia, moderate peripheral immune cell infiltration, and elevated inflammatory mediators. The primary active immunological defense of the brain is mediated by microglia. These remain in a state of reactivity and continue to attract astrocytes and oligodendrocytes, leading to a chronic inflammatory process, if they fail to eliminate a toxic attack. The abnormal astrocyte proliferation (astrogliosis) surrounding the dying MNs has been observed in animal models and ALS patients. In ALS reactive astrocytes, inflammatory mediators such as cyclo-oxygenase-2, inducible NOS, and neuronal NOS are expressed, as well as inhibitory factors that suppress the regrowth of a damaged axon. Astrocytes have been found to be cytotoxic to MNs in culture when isolated from the spinal cord of patients with SALS or FALS. In addition, it has been shown that mast cells and neutrophils accumulate around motor axons in the sciatic nerve, ventral roots, and extensor digitorum longus muscle in mouse ALS models,

indicating immune cell invasion has extensive implications along the entire peripheral motor pathway .Remarkably, dystrophic glial cells exhibit increased endoplasmic reticulum stress in addition to an appreciable profusion of secretory and autophagic vesicles, which are characteristic of inflammatory activation and cellular stress. The MNs can be neuro-toxically influenced by the pro-inflammatory cytokines (e.g., TNFα, IL1β, IL12, and IFNγ), mitogenic factors (e.g., MCP-1 and M-CSF), neurotrophic factors (e.g., IGF-1), and anti-inflammatory factors (e.g., TGF-β) produced by activated microglia. It has been shown that cytokines produced by activated microglia, such as IL1α, TNFα, and C1q, further activate the A1 subtype of reactive astrocytes, which play a crucial role in neuronal death in neurodegenerative diseases like ALS. In addition, the cerebrospinal fluid (CSF) of patients with ALS was found to contain unusually elevated concentrations of numerous cytokines, such as G-CSF, IL2, IL15, IL17, MCP-1, MIP1α, TNFα, and VEGF. In addition, SALS patients were found to exhibit increased levels of IL-6 in astrocyte-derived exosomes. This implies that CNS-derived exosomes could be beneficial in detecting CNS neuro-inflammation in ALS patients and be positively associated with the pace of development of the disease. ALS pathophysiology is also implicated in neuro-inflammatory processes by all these events. Most importantly, recent work shows that neuro-inflammation is linked with the fronto-temporal dementia (ALS/FTD) symptomatic phase and has a similar pattern in at random and genetic cases. One of the explanations for variable manifestations of ALS/FTD can be due to the divergent neuro-inflammatory profiles in ALS and FTD. The immune response is apparently protective at initial stages in ALS, with escalating evidence demonstrating neuro-inflammation mechanisms involving neuron death. The anti-inflammatory mechanisms that contribute to MN viability involve glia and T cells such as M2 macrophages/microglia, T helper (Th) 2 cells, and regulatory T (Treg) cells. Nevertheless, a second fast-developing phase characterized by high levels of inflammatory Th1 and Th17 T cells and M1 macrophages/microglia arises as the disease progresses and MN damage accelerates. A self-sustaining inflammatory acceleration of disease progression has been suggested to result from the reduced levels of the protective M2/Treg/Th2-mediated pathways and the induction of the cytotoxic M1/Th1/Th17 pathways. Oxidative stress (OS) and neuro-inflammation are interlinked in the pathophysiology of neurodegenerative diseases. OS is a consequence of an increase in the generation of reactive oxygen species (ROS), which is usually coupled with a decrease in antioxidant defences. Glial and infiltrating immune cells are considered to be among the primary sources of reactive nitrogen species (RNS) and ROS in diseased states of the central nervous system. ROS are believed to

worsen the progression of the disease even though they are not believed to be the cause of ALS.ROS can possibly be involved in ALS neuromuscular junction deterioration. ALS models of mice have shown enhanced nerve terminal sensitivity to ROS, which may facilitate presynaptic decline in neuromuscular junctions. Moreover, overstimulation of MNs by excitatory amino acids results in abnormal acetyl cholinesterase production, which reduces the level of acetylcholine in the synaptic cleft (a mechanism that can be tasked with the loss of muscle strength observed in ALS patients). Neuro-degeneration may ultimately cease from these initial-stage dysfunctions, which are further supplemented by inflammatory mediators and the absence of trophic support. There is also evidence that ALS patients show a diminished response to OS. Motor cortex of ALS patients contains decreased levels of glutathione (GSH), an antioxidant ubiquitously found in mammalian cells, compared to healthy volunteers. A master controller of detoxification and antioxidant, anti-inflammatory, and other cyto-protective processes, nuclear factor E2-related factor 2 (Nrf2), is also nuclearly accumulated when mutant TDP-43 is expressed in an MN-like cell line, leading to OS and mitochondrial damage. Dysregulated Nrf2-dependent antioxidant pathways have been implicated in ALS, and studies are underway on treatment strategies that target the Nrf2 antioxidant response element. ALS patient post-mortem tissues contained reduced Nrf2 mRNA and protein levels, and studies in ALS mice models have shown that elevated Nrf2 levels in astrocytes—the major GSH suppliers for adjacent neurons have a significant beneficial effect. In addition, through repression of the cytotoxic activity of activated microglia against neurons, Nrf2 signalling is very important in preventing neuro-inflammation in ALS.[10][2][6][17]

3. Excitotoxicity

Since they possess a diminished calcium buffering capacity compared to other neuronal subtypes and a-amino-3 3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which are more calcium permeable (as they have less of the GluR2 subunit), motor neurons are especially susceptible to toxicity resulting from calcium entry following overstimulation of glutamate. Additionally, the main synaptic glutamate reuptake transporter, excitatory amino acid transporter 2 (EAAT2), is an astroglial protein that is affected in ALS. This is hypothesized to cause synaptic glutamate overload and motor neurone toxicity. EAAT2 depletion has been observed in animal models and familial and sporadic ALS individuals. While there is presently limited data to back this up, excitotoxicity is hypothesized to be a mechanism common to all forms of ALS. One hypothesis is that riluzole, a licensed drug for

neuro-protection in ALS, can limit glutamate release and slow disease progression. It is not clear, however, whether this is precisely what causes riluzole's therapeutic effect.[18]

4. Protein Misfolding and Aggregation

These include C9ORF72, TDP-43, SOD1, and FUS

(a) C9ORF72

The hexa-nucleotide repeat expansion is within the first intron of the C9ORF72 gene. The true sizes of these repeats differ considerably among C9ORF72 patients. While the threshold for pathogenic repeat size is unknown, a cut-off of 30 repeats is used in the majority of studies. Normal individuals have fewer than 11 repeats, whereas most patients have several hundreds to thousands of repeats. A minor group of patients also have shorter expansions from 45 to 80 repeats. The expansion in the C9ORF72 gene is a significant ALS and FTD genetic cause that explains about 40% of FALS, 30% of FFTD, and about 8% of SALS cases, especially in primarily Caucasian populations. The finding of the C9ORF72 mutation in ALS and FTD has prompted researchers to investigate its possible implication in other neurodegenerative conditions as well As concerns cell type distribution, C9ORF72 expression is considerably high in myeloid cells, especially in CD14+ monocytes, eosinophils, and neutrophils, and lower in lymphoid cells and other tissues. In general, the C9ORF72 protein is predominantly expressed in the brain, spinal cord, and immune system, but lower levels were found in other organs like the lungs, heart, liver, kidney, and skeletal muscle, corresponding to the expression profile of the transcript. The C9ORF72 gene codes for three different mRNA isoforms (V1–V3), which correspond to two proteins: C9ORF72-long (C9-L), a 481-amino acid protein, and C9ORF72-short (C9-S), a truncated protein isoform of 222 amino acids. The 481-amino acid C9-L isoform is the most prevalent. C9ORF72 is primarily cytoplasmic in mouse tissues and in the human brain, with punctate staining in neuritis, suggestive of synaptic terminals. C9ORF72 is also involved in stress granule (SG) assembly and disassembly. Stress granules (SGs) are ribo-nucleoproteins devoid of membranes, which include mRNA and aggregate in the cytoplasm upon arrest of translation initiation, fading upon relief from stress Under stress-related signals, C9-L is targeted to SGs. Without C9ORF72, these granules are not formed, and other SG-associated proteins such as TIA-1, G3BP1, and HuR are repressed. C9ORF72 is also essential for cellular recovery after stress since it partners with p62 to mark SGs for degradation by autophagy. In addition, C9-L interacts with SMCR8 via its DENN (differentially expressed in normal cells and neoplasia) domain, and upon the C9-L-SMCR8 complex binding to

WDR41, it acts as a GTPase-activating protein that may be implicated in membrane trafficking, such as endolysosomal pathways and autophagy. The deletion of C9ORF72 in mice and motor neurons from iPSCs results in synaptic plasticity changes and glutamate receptor homeostasis defects. Current research has also linked C9ORF72 with modulating neuronal nucleo-cytoplasmic transport through interference of importin β1-nucleoporin interactions. In research done by Celona et al., the amplification of a six-nucleotide GGGGCC repeat within the first intron of the C9ORF72 gene is the most common inherited reason for amyotrophic lateral sclerosis (ALS) and fronto-temporal dementia (FTD). These repetitive structures in RNA have the capacity to accumulate in cells and are translated by a process known as repeat-associated non-AUG (RAN) translation, forming dipeptide-repeat (DPR) proteins that are very toxic. The research identifies the zinc finger RNA-binding protein Zfp106 as essential in countering these toxic effects. Zfp106 was found to suppress the generation of RNA foci, significantly reduce RAN translation initiated by GGGGCC repeats, and block the accumulation of toxic DPRs in C9ORF72 patient-derived cells. The study also discovered that Zfp106 interacts with RNA G-quadruplex structures, causing a conformational change. This interaction seems to be a primary component of Zfp106's ability to prevent the cytotoxic activity that accompanies GGGGCC repeats, emphasizing its therapeutic target status for C9ORF72-associated ALS and FTD. It is general agreement that the highest neurotoxicity among many model systems are seen in arginine-rich dipeptide repeats (DPRs) like glycine-arginine (GR) and proline-arginine (PR). Given increasing interest in such arginine-rich DPRs, there has been increased interest in PR, GR, or both, in relation to other DPRs. Consequently, several mechanisms have been associated with PR and GR expression, including nucleo-cytoplasmic transport, DNA damage, translational disruption, and stress granule dysfunction. Drosophila models have been particularly valuable in elucidating these toxic mechanisms, which have subsequently been validated in mouse models, induced pluripotent stem cells (iPSCs), and patient tissues. Recent developments with fly models still place a high value on studies on repeat-associated non-AUG (RAN) translation and DPRs due to their involvement in C9orf72 hexa-nucleotide repeat expansions. RAN translation regulators are being explored, and a suggested mechanism of DPR-induced toxicity in C9orf72-linked neuro-degeneration is repressed translation by interactions among ribosomal proteins and DPRs, namely poly-GR and poly-PR. There is evidence that the three main hypotheses about DPR toxicity are not exclusive. For instance, one research showed that diminished C9orf72 activity increases susceptibility to degenerative stimuli, including glutamate-induced excitotoxicity and compromised DPR clearance. In essence, haplo-

insufficiency enhances toxic gain-of-function effects, a conclusion upheld by studies indicating that C9orf72 reduction inhibits autophagy, resulting in DPR accumulation and cell death. Studies of autophagy in Drosophila C9orf72 models have revealed that, in motor neurons, 30-repeat DPRs interfere with the morphology and dynamics of the endoplasmic reticulum(ER), inhibiting autophagosome formation. In spite of ER disruption within both axons and synapses, autophagosomes were intact in axons, but their biogenesis was impaired at synaptic terminals. Motor neurons also can be investigated for synaptic dysfunction. In a new study utilizing Drosophila C9orf72, they demonstrated a novel cell-autonomous excitotoxicity mechanism preferentially linked to arginine-rich DPRs in glutamatergic neurons. Such DPRs—poly-GR and poly-PR—had modest toxicity at 36 repeats, causing synaptic boutons, active zones, extracellular glutamate, intracellular calcium, and presynaptic NMDA receptor activation. This implies a mechanism to neuro-degeneration through glutamate excitotoxicity and synaptic overgrowth, which is presynaptic NMDA receptor-dependent and cell-autonomous. More toxic 100-repeat DPRs resulted in loss of active zones, which suggests extreme neuro-degeneration through synaptic degeneration. These results encourage the therapeutic potential of glutamate inhibition therapies and highlight the necessity of further exploration of synaptic dysfunction in C9orf72-FTD pathology.[12][8][18]

(b) TDP43

A critical RNA/DNA-binding protein, TDP-43 TAR DNA-binding protein 43 (TDP-43) plays a role in transcription, splicing, and transport, among others of RNA metabolism. The pathogenic forms of amyotrophic lateral sclerosis (ALS) are largely associated with TDP-43. TDP-43 forms ubiquitinated and insoluble inclusions in the cytoplasm following mis-localization from the nucleus in ALS. Fronto-temporal lobar degeneration (FTLD) and ALS share these pathogenic aggregates. Mutations within the TARDBP gene, post-translational modifications including phosphorylation and ubiquitination, and the tendency of TDP-43 to form amyloid-like fibrils are primarily responsible for causing its misfolding and aggregation. Neuronal toxicity from this mis-localization's disturbance of RNA processing and cellular equilibrium is necessary in understanding the pathways involved in TDP-43 pathology in a bid to devise specific treatments against ALS. TDP-43 toxicity in Drosophila, adues' cytoplasmic accumulation of human TDP-43 (hTDP-43) is sufficient to induce degeneration. This finding agrees with previous models of toxicity such as the mis-localization of genes associated with ALS. Additionally, the study discovered that no phenotypic changes were observed upon knockdown of TBPH, the Drosophila homolog of TDP-43, which indicates

that disease could be facilitated by a toxic gain of function induced by cytoplasmic TDP-43. Yet, this hypothesis is doubtful since loss of nuclear TDP-43 function could also be involved in disease onset. An alternative model of toxicity in Drosophila has been proposed to involve mitochondrial dysfunction. In heat shock-inducible human TDP-43 (hTDP-43) transgenic flies driven by the pan-neuronal Elav-Gal4 driver, mitochondria in the eye showed a dramatic decrease in size relative to controls. In addition, 85% of the mitochondria within the photoreceptors of hTDP-43-expressing flies had vesicular or swollen cristae. Such mitochondrial cristae damage reflects that found in the brain tissues of individuals with TDP-43 proteinopathy and supports the value of using Drosophila as a model system to investigate this gene. Since mitochondria are well-documented to be a source of reactive oxygen species (ROS), mitochondrial dysfunction would cause the accumulation of ROS, which would detrimentally affect neuronal survival and function. Mitochondrial ROS levels were found to be elevated in hTDP-43-expressing motor neurons in Drosophila using confocal imaging and are indicated to result from hTDP-43 expression in motor neurons causing mitochondrial dysfunction and contributing to oxidative stress.[19]

(c) SOD1

The SOD1 gene (superoxide dismutase 1 [Cu/Zn]). SOD1 is a metallic enzyme made up of 153 amino acids and is one of three superoxide dismutase enzymes in humans.

It sequesters zinc and copper ions and exists in a very stable homodimer form. Dimers of SOD1 exist in the mitochondria's intermembrane space and cytosol and play an important function in antioxidant defense by catalytically converting the superoxide radicals generated during the process of respiration into hydrogen peroxide and oxygen. A critical element in the pathophysiology of amyotrophic lateral sclerosis (ALS) is superoxide dismutase 1 (SOD1). Approximately 20% of cases of familial ALS result from mutations in the SOD1 gene, which is the primary genetic etiology of the disease. The SOD1 protein misfolds and forms aggregates due to these changes, which is very toxic to motor neurons. Several causes such as oxidative stress, mitochondrial failure, and disruption of protein homeostasis are believed to be responsible for the deleterious effects. Mutant SOD1 protein aggregates induce apoptosis, disrupt mitochondrial function by localizing to the outer mitochondrial membrane, and disrupt cellular activities. In addition, it has also been demonstrated that aggregated SOD1 enhances the aggregation of other proteins involved in ALS, like TDP-43, thus speeding up the neurodegenerative process. Achieving specific therapeutics reducing oxidative stress and increasing mitochondrial function to stop the progression of the disease has been facilitated

by improved comprehension of the role of SOD1 in ALS. Elucidation of the role of the SOD1 gene in amyotrophic lateral sclerosis (ALS) has been facilitated in significant part by Drosophila melanogaster models. Superoxide dismutase-1 is the antioxidant enzyme encoded by SOD1, the initial gene linked to familial ALS (FALS). Scientists have made significant advances in understanding the mechanisms of ALS through the application of genetic techniques to express human SOD1 (hSOD1) and the mutations associated with the disease in specific Drosophila organs. These models reveal that hSOD1 mutations can lead to neuro-degeneration characterized by motor impairment, reduced lifespan, and abnormal synapses. They are also capable of inducing toxic gain of function (GOF) effects as well as loss of function (LOF). Of particular note, unlike vertebrate models, these models often fail to have significant neuronal loss even with profound symptoms like developmental abnormalities and reduced mobility. This is a testament to the complexity of SOD1 associated ALS and the necessity of employing Drosophila to study the molecular and cellular origins of the disease. These models have also proved effective in the screening of promising medicinals, having identified compounds which may mitigate mutant SOD1's neurotoxic effects. In addition, with Drosophila models of the human mutant SOD1 genes (A4V and G85R), Liguori et al. (2024) demonstrated that these mutations lead to reduced survival and compromised motor function, as well as the up regulation of immune pathways with antimicrobial peptides (AMPs) and the activation of early inflammatory markers such as the glial marker. In addition, the research illuminated the increased oxidative stress and the occurrence of chromosome aberrations, which suggest that genomic instability and disrupted cellular homeostasis are some of the most significant points in the initial phases of ALS pathogenesis. These observations contradict the conventional wisdom that motor neuron degeneration is the key initiating event in ALS, but rather highlight the potential that early neuro-inflammation and oxidative stress could be preceding and even triggering the chain of neuronal damage, thus proposing new avenues for early therapeutic intervention. Exacerbation of the SOD1-G93A ALS onset because it causes a more oxidative phenotype of muscle fibers, which worsens muscle denervation, and stimulates motor neuron loss. Moreover, because of enhanced immune cell invasion in the sciatic nerve, the development of ALS is hastened. Thus, even though physical exercises are a healthy practice, endurance exercises are risk factors in the case of ALS.[20][19][5]

(d) FUS

FUS encodes for a constitutively expressed 526-amino-acid protein, a member of the FET family of RNA-binding proteins. In normal circumstances, FUS is found predominantly in the nucleus but also translocate to the cytoplasm, where it is involved in nucleo-cytoplasmic transport. FUS plays a variety of roles homologous to TDP-43, including a role in gene expression, transcription, pre-mRNA splicing, transport of RNA, and regulation of translation. Although they share this, TDP-43 and FUS bind distinct RNAs with different sequence-binding specificities. Researchers have made over 50 different variants of the FUS gene that contribute to autosomal dominant ALSs. Missense mutations, which consist of single amino acid substitutions, are responsible for most of these genetic alterations. Infrequently, however, patients have also been found to comprise nonsense mutations, insertions, deletions, or splicing errors. The variety of the genetic presentations manifesting in ALS associated with abnormalities of the FUS gene varies depending on these various mutations. Many of these gene alterations are explained by missense mutations, which entail single amino acid substitutions. Now and then, however, patients have also been discovered to bear nonsense mutations, insertions, deletions, or splicing mistakes. The spectrum of the genetic presentations seen in ALS associated with FUS gene anomalies is impacted by these various mutations. Numerous pathogenic variants lie within the nuclear localization signal, which causes the mislocalization of FUS to the cytoplasm. Other mutations are found in glycine and arginine-rich regions, the prion-like domain, and the 3' untranslated region (3′UTR).Some mutations in these areas make it more likely that the protein will form solid aggregates, suggesting more than one pathogenic mechanism in FUS-related ALS. Tabolism can be toxic in several ways, some of which are associated with proteostasis. According to the central dogma of molecular biology, RNA serves as the "messenger" between the DNA and the machinery for protein synthesis, making RNA responsible for the pathogenicity of protein misfolding diseases such as ALS. The lifecycle of RNA is, however, intricate and includes many regulatory RNA-binding proteins (RBPs) that are responsible for RNA transport, post- transcriptional editing, translation, and degradation. RNA and RBPs can form membrane-less organelles called ribonuclear protein (RNP) granules, which are vital for RNA metabolism and gene regulation. Functions of these RNP granules vary depending on the specific RNA and RBPs they contain. Recent studies have focused on particular RNPs, such as stress granules and paraspeckles, both of which have been implicated in ALS pathogenesis. The function of stress granules, specifically, has been contested as a central mechanism of ALS-related aggregation. Nevertheless, since ALS can emerge irrespective of

stress granules, they will not be discussed further here as a drug target, although they have been discussed in other research. The management and upkeep of RNA pathways through RBPs and RNP granules are essential for cell homeostasis. Of particular interest, a number of robust genetic associations with ALS have been identified in RNA metabolism pathways, such as mutations in C9ORF72, SOD1, TDP-43, and FUS. These and other mutations highlight the significance of RNA production, editing, and localization in the development of ALS, with compelling evidence that deregulated RNA metabolism is a major contributor to the disease. The subsequent sections will highlight the relevance of RBPs and the formation of RNP granules in ALS and their therapeutic promise to achieve normal RNA metabolism and proteostasis.

Importantly, C9ORF72, SOD1, TDP-43, and FUS mutations are amongst the several major genetic associations with ALS identified in RNA metabolism processes. These mutations, and others, underscore the importance of RNA synthesis, editing, and localisation in the pathogenesis of ALS and provide strong evidence that the disease is strongly impacted by dysregulated RNA metabolism. The significance of RBPs and RNP granule assembly in ALS will be emphasized in the following sections, as well as their potential as therapeutic targets to enable ALS patients to restore proper RNA metabolism and proteostasis.[21][22][3]

Symptoms of ALS: Though everyone suffers separate from amyotrophic lateral sclerosis (ALS), several symptoms are usually observed. People may have problems with basic actions such breathing, eating, and speaking as the disorder increases; initially, people may feel weaknesses or uncontrollable activity in their arms, legs, or face while frequently have discomfort and muscular constriction. Reflexes weaken or disappear; muscle mass decreases; some people report blurred vision or even total loss of vision; whereas muscle weakness and motor neurone failure are actually central to the disease's advancement, so producing stiffness and difficulty moving around.

Other symptoms could be disturbed sleep and a compromised immune system, which increases the person's potential to infections; some individuals might exhibit aggressive behaviour, trouble with focus, and suffer from memory loss. As the body loses capacity to operate, a lack of energy become more prevalent. As ALS progresses, the person who has been impacted loses their capacity to care personally independently, so stressing the disabling nature of the problem and each of these symptoms introduces to the severe impact ALS has on daily life, consequently early detection and management are especially important for

patient care. A high temperature and general feelings of deficiencies can present themselves.[23]

Effects on the Body

ALS effects many parts of the body, such as

- The muscular system includes weak muscles, muscle loss, and disability.
- Problems with breathing or failure of the respiratory system.
- Nutritional system: losing weight and not getting sufficient nourishment.
- Neurological: some people with frontotemporal dementia have this problem.[23]

DIAGNOSIS

A very small number of genetic risk factors for ALS have been found. UNC13A is a gene that puts people at risk for getting ALS, and ATXN2 intermediate repeat extensions raise the risk of getting ALS. There are no such Diagnosis Test for ALS, but can observed through the various symptoms of the body conditions that occur in this Neurological Disorder, with the help of The combination of suggestive clinical signs with negative laboratory test and imaging Studies for other Pathologies Studies. The clinical feature of this conditions includes, slowly progressive lower motor neuron signs in the balbar region and proximal limbs and 50% of affected patients have gynecomastia [The condition in which, Male breast tissue swells due to reduced male hormones (testosterone) or increased female hormones (estrogen)]. The pure lower motor neuron Syndrome with family history demonstrating no male to make inheritance should therefore alert thr physician to this possible diagnosis. In patient's diagnosis with ALS, the absence of disease progressive, the present of unusual symptoms should trigger a search for mimic syndrome. Generally, patients with common mimic syndrome do not program as rapidly as those with ALS, and tend to survive for longer period. The diagnosis is majorly based on the characteristics signs of progressive weakness, atrophy, fasciculation and Hypereflexia affecting serval regions of the body. The early different diagnosis may include various different conditions such as musculoskeletal, neurologic or systemic conditions. The diagnosis procem mainly involves history and Physical examination repeated at regular intervals, for the documentation for progressive Hypereflexia, fasciculation and upper and lower motor neuron involvement.

To confirm a diagnosis of ALS, multiple forms of

- A clinical examination includes a medical history of the patient, A physical determination of the patient.

- Electromyography (EMG): checks the amount of activity the muscles happen to be.
- Nerve conduction tests (NCS) check how well nerves are working.
- Diagnostic examination, such as magnetic resonance imaging (MRI rule out other diseases.[23][22][9]

TREATMENT

Although there is no curative treatment for ALS, there are treatments that can slow the progression of the syndrome (such as riluzole and edarabon), subsequently take steps to manage the issues you are facing (such as conversation or physical therapy), and improve quality of everyday life (by means of diet and respiratory condition). Neuronal treatment may be helpful; patient must be in regularly stay in touch with the doctor. In these the medicaments taken and may gave some adverse effect on the body. The sedative and hypnotic's medicines such as tofranil, sinequan they show similar action, but in day time can cause sedation. Anti depressant medicine can give to relieve the few symptoms of the patient from pain. Diphenylhydramine dosage 25 to 50 mg three times daily, may helpful in suppressing siarrhoea. Some non steroidal anti inflammatory and carbamazepine (Tegretal) is a dosage of 200 mg three times daily on phenytoin (dilatin), in a dosage of 300 mg at bedtime may be useful. Avoiding the intake of caffeine and nicotinic or abusive intake. Lorazepam may cause severe relieve fasciculations. Getting adequate rest, eating protein rich food or maintaining healthy diet and controlling the aggression, yoga relieves in muscle stiffness and muscle twitching (fasciculations). Breathing device must be provided to the patient at serious condition mostly used in night for proper ventilation.[24][25]

Pharmaceutical Research

Developing creative remedies for the internationally significant disease ALS dominates modern day pharmaceutical research and business activities; these novel techniques involve stem cell therapy, gene therapy, immunotherapy, along with small molecule therapy. Using these cutting-edge methods, researchers hope to develop more successful treatments and maybe raise outcomes for ALS sufferers all around.[26] [40]

A) Stem cell therapy: Stem cell treatment aims to stop or potentially slow down ALS's progress by replacing damaged motor neurones and supporting cells. Research on many types of stem cells is under progress for ALS treatment

1. Mesenchymal stem cells: By advantage of their multitasking ability to develop into several cell types and generate neurotrophic compounds, MSCs could assist to develop a

greater neuroprotective environment, reduce inflammation, and contribute to the survival of located motor neurones.

2. Neural stem cells (NSCs): Two types of neural stem cells, NSCs, are able to substitute lost motor neurones and assist surviving neurones by differentiating into glial cells and neurones.

3. Induced pluripotent stem cells (iPSCs): Adult cells transformed to an embryonic-like condition are capable of being distinguished into motor neurones or glial cells, and iPSCs have the benefit of being patient-specific, therefore perhaps lowering the risk of immunological rejection. Made up in the mechanisms allowing stem cell treatment are those allowing ALS people suffering: Stem cells is capable of growing into newly formed motor neurones or supporting cells, therefore helping to restore lost function, cell replacement therapy. The cells of stem cells can produce drugs that reduce inflammation and development factors that protect present motor neurones from additional damage, by neuroprotection. Stem cells could assist in helping the immune system being according to control, therefore reducing inflammation and stopping of neurone damage, by Immunomodulation. Enhanced cellular surroundings: Stem cells could contribute to slow breakdown disease spread by allowing a more suitable environment for maintaining neurones.

Although some studies showing minor enhancements in the development and survival while others have showed limited advantages, several difficulties in stem cell therapy for ALS were considered highlighted by clinical trials looking at this treatment for ALS.

1. Guaranturing correct absorption and continuation of transplanted cells.
2. Delivering therapeutic cells all across the central nervous system.
3. Finding the best delivery technique, dose, and timing for stem cell treatments.
4. Taking care of any safety issues include rejection from the immune system or tumour development.

Without these obstacles, constant research keeps improving stem cell treatments for ALS. As our knowledge of ALS pathogenesis and stem cell biology develops, combination approaches—such as using gene therapy to maximise the therapeutic value of transplanted stem cells—are also under investigation and could become a practical treatment choice for this terrible disease, so providing patients with better quality of life and longer survival.[26][27][28]

B) Gene therapy

While conventional treatments have proven mainly useless, gene therapy has become an interesting path for possible intervention since it shows promise for tackling Amyotrophic Lateral Sclerosis (ALS). Targeting the fundamental genetic causes of ALS or offering neuroprotective elements to stop or slow down disease development is the main objectives of gene therapy for the condition.

Several techniques are being used as a treatment and are as follows as

1. Gene replacement: When ALS results from mutations in particular genes (e.g., SOD1, C9orf72), gene therapy can insert functioning copies of these genes into motor neurones, therefore offseting the defective genes and restoring regular function to cells.

2. Gene silencing: Often performed using The technique of RNA interference or antisense oligonucleotides (ASOs), gene therapy can be utilised to quiet the mutant genes for ALS caused by dangerous gain-of- function mutations.

3. Neuroprotective factor delivery: To promote motor neurone survival and function, gene therapy may result in genes encoding neuroprotective compounds like IGF-1 (Insulin-like Growth Factor 1) or BDNF (Brain-Derived Neurotrophic Factor).

4. Modulation of disease pathways: Genes involved in cellular processes affected in ALS, such as protein degradation or mitochondrial function, can be targeted to improve overall motor neuron health.

Usually, viral vectors are used to deliver therapeutic genes to motor neurones; adeno-associated viruses (AAVs) are a common choice because of their safety profile and capacity to efficiently convert neurones; these vectors can be injected intratheally (into the spinal fluid) or intravenously with engineered vectors successful of crossing the blood-brain barrier. Promising outcomes have come from recent preclinical research and early-phase clinical trials; for As an instance, gene therapy techniques aiming at SOD1 mutations have showed decreased progression of the disorder in animal models and are now under human testing.

Therapies providing neuroprotective elements have also showed effectiveness in maintaining motor neurone activity; Still, there are difficulties in applying these treatments generally to practical practice. Among these are controlling possible immunological reactions to viral vectors, guaranteeing effective gene delivery to motor neurones across the central nervous

system, and addressing the variability of ALS cases—many of which have unidentified genetic roots. Considering these difficulties, gene therapy marks a major advance in the ALS difficulty. More polished and efficient gene therapies providing potential for ALS affected individuals and their families should flow through the therapeutic path as our knowledge of the disease mechanisms develops and gene delivery technology advance.[29][30][31]

CONCLUSION

Amyotrophic lateral sclerosis (ALS) is a severe and progressive neurodegenerative disorder marked by the degeneration of upper and lower motor neurons, leading to muscle atrophy, respiratory failure, and eventual death. Since its first detailed clinical characterization by Jean-Martin Charcot and its increased public recognition following the diagnosis of Lou Gehrig, major advances have transformed the scientific understanding of the disease.

Current evidence identifies ALS as a multifactorial and multisystem disorder driven by complex interactions among genetic mutations—particularly in C9ORF72, SOD1, TARDBP, and FUS—and pathogenic mechanisms such as mitochondrial dysfunction, oxidative stress, excitotoxicity, impaired axonal transport, protein aggregation, and dysregulated RNA metabolism. Pathologically, ALS is characterized by motor neuron loss, TDP-43 inclusions, neuroinflammation, and glial activation, highlighting that it is not solely a neuron-autonomous disease but involves widespread cellular interactions within the central nervous system. Disease progression reflects cumulative molecular disturbances rather than a single causative pathway.

Although approved treatments, including riluzole, edaravone, and certain gene-targeted therapies, provide modest survival benefits, they do not prevent progression. Nonetheless, advances in antisense oligonucleotide therapies, stem cell research, and improved molecular classification of familial and sporadic cases offer cautious optimism. Overall, ALS represents a biologically complex disorder in which genetic susceptibility and environmental influences converge. Continued interdisciplinary research integrating molecular biology, genetics, and translational neuroscience is essential to develop effective disease-modifying therapies.

FUTURE DIRECTION

Despite substantial progress in elucidating ALS pathogenesis, several critical challenges remain. Future research should prioritize the following directions.

1. Precision Medicine and Genetic Stratification

Advances in genomic sequencing enable patient stratification based on mutation status. Personalized therapeutic strategies targeting specific genetic mutations—such as antisense oligonucleotides for SOD1 and C9ORF72 expansions—should be expanded. Broader implementation of precision medicine approaches may optimize therapeutic responsiveness and minimize adverse effects.[32]

2. Combination Therapeutic Strategies

Given the multifactorial nature of ALS, monotherapy targeting a single pathway is unlikely to provide durable clinical benefit. Future interventions should explore rational combination therapies addressing oxidative stress, mitochondrial dysfunction, neuroinflammation, and protein aggregation simultaneously.[33]

3. Targeting Neuroinflammation and Glial Dysfunction

Emerging evidence highlights the critical role of microglia and astrocytes in disease progression. Modulating immune responses and restoring protective glial phenotypes (e.g., M2 microglial polarization) may represent a promising therapeutic avenue.[34]

4. Biomarker Development and Early Diagnosis

Reliable biomarkers—such as neurofilament light chain levels, inflammatory cytokine profiles, and exosomal markers—are needed for early detection, disease monitoring, and therapeutic response evaluation. Earlier diagnosis could significantly enhance the effectiveness of disease-modifying treatments.[35]

5. Advances in RNA and Proteostasis-Based Therapies

Given the central role of RNA-binding proteins and stress granule dynamics in ALS, therapeutic modulation of RNA metabolism and protein homeostasis pathways represents a compelling research focus. Small-molecule chaperones, autophagy enhancers, and RNA-targeted interventions warrant further investigation.[36]

6. Stem Cell and Regenerative Approaches:

Stem cell–based therapies aimed at replacing lost motor neurons or providing neurotrophic support remain under active investigation. While challenges persist regarding long-term integration and safety, regenerative medicine may offer future restorative strategies.[37]

7. Global Epidemiological and Environmental Studies

Expanded multinational cohort studies are necessary to clarify environmental risk factors, gene–environment interactions, and geographic variability in disease incidence. Such insights may uncover modifiable risk factors and preventative strategies.[38]

8. Improvement in Multidisciplinary Care Models

While curative therapy remains elusive, optimized multidisciplinary management—including respiratory support, nutritional intervention, and psychological care—can substantially improve quality of life and survival outcomes. Future research should also emphasize patient-centered care and supportive technologies.[39]

In conclusion, the future of ALS research lies in integrating molecular biology, genetics, immunology, and clinical neuroscience within a precision medicine framework. Although a definitive cure remains beyond current reach, rapid advancements in targeted therapies, biomarker development, and translational research provide a realistic prospect of transforming ALS from a fatal condition into a manageable chronic disorder in the coming decades.

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