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THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS IN MODULATING NEUROINFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS: A CURRENT ADVANCE AND FUTURE PERSPECTIVES

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a severe neurological illness characterized by the progressive loss of both upper and lower motor neurons, leading to atrophy, paralysis, and respiratory failure. With an average lifespan of two to five years following the ALS is one of the most challenging neurological disorders that modern medicine must treat when symptoms first appear. This comprehensive summary covers the epidemiology, pathophysiology, genetics, clinical symptoms, diagnostic procedures, and available treatments for ALS The most frequent genetic cause of ALS is the increase of the C9orf72hexanucleotide repeat, which has been linked to over 20 genes in recent molecular genetic research. Effective disease-modifying treatments are still scarce despite tremendous advancements in our understanding of disease mechanisms, such as protein aggregation, RNA processing errors, mitochondrial failure, and neuroinflammation. The survival advantages of currently approved therapies, such as

edaravone and riluzole, are minimal. However, patients now have more hope thanks to novel therapeutic techniques, especially gene-targeted treatments like antisense oligonucleotides and stem cell-based interventions. This study highlights the vital significance of early diagnosis, multidisciplinary therapy, and the continuous shift to precision medicine methods that are customized to each patient's unique genetic and molecular profile.

KEYWORDS: Progressive Neurodegenerative Disease, Multifactional Pathophysiology, Genetic Contribution to ALS, Precision medicine for ALS.

INTRODUCTION

The French neurologist Jean-Martin Charcot discovered in 1869 that Lou Gehrig's disease, also known as amyotrophic lateral sclerosis (ALS), is characterized by the degeneration of upper motor neurons in the motor cortex as well as lower motor neurons in the brainstem nuclei and anterior horn of the spinal cord.[1,2] Both motor neurons are involved in a rare clinical disease that is characterized by progressive atrophy, stiffness, fasciculations, and muscle weakness, which ultimately results in paralysis and death, typically from respiratory failure.[3,4] The disease usually begins in a limb or bulbar region and then predictably spreads to other body areas.[1,3] Even though it was once thought that ALS only affected the motor system, recent studies have identified important extra motor symptoms. Frontotemporal dementia (FTD) is diagnosed in 10–15% of patients, while behavioural and cognitive deficits are present in up to 50% of patients.[1,3] Understanding disease mechanisms and creating therapeutic options are significantly impacted by the pathological and clinical similarities between FTD and ALS.[5]

ALS is a complicated disease that is impacted by numerous hereditary and environmental variables. With an autosomal dominant inheritance pattern in the majority of instances, 90% of cases are categorized as sporadic (sALS) and 10% as familial (fALS).[1,2] Using non-familial heritability estimates Since genetic factors are now known to contribute to cases that seem to be sporadic, this distinction has grown hazier as the prevalences of ALS can reach 37%.[6] Regardless of whether the disease is familial or sporadic, the discovery of causal genes and pathogenic mechanisms has altered our knowledge of ALS by exposing shared molecular pathways that converge on motor neuron degeneration.[7,8]

Despite considerable progress in understanding the pathophysiology of ALS, the disease is always fatal and has no known treatment,[1,3] and.[9] ALS is always fatal and has no known

cure, despite major advances in our understanding of its pathogenesis,.[1,3] and[9] The focus of modern management is on interdisciplinary supportive care, which includes respiratory control, nutritional support, and symptom management. Interdisciplinary supportive care, which includes symptom treatment, nutritional support, and respiratory control, is the main focus of modern management. To some degree, these activities can enhance survival and quality of life.[4,10]

However, new advances in genetics, the discovery of biomarkers, and innovative treatments particularly gene-targeted therapies approaches. To some degree, these activities can enhance survival and quality of life,[4,10] But recent advances in genetics, biomarker discovery, and innovative therapeutics especially gene-targeted strategies have rekindled hope that efficient disease-modifying treatments would soon be available.[5,11,12]

EPIDEMIOLOGY

With a frequency of roughly 4-6 occurrences per 100,000 people in Western countries and an estimated incidence of 1-3 cases per 100,000 person-years, ALS is a relatively uncommon disease,[1,3] Although there is a slight male predominance in the illness, the gender gap gets smaller as people age. having a male-to-female ratio of approximately 1.3–1.5:1.[3] Sporadic forms of ALS typically manifest later than familial variations, with an average age of onset between 55 and 65 years.[1,4] Although ALS can occur at any age, it rarely manifests before the age of 40 or after the age of 80. Juvenile-onset instances are also uncommon and frequently linked to certain genetic abnormalities.[3] It has been shown that the incidence of ALS varies by region, with some areas having greater rates than others. Guam and the Japanese Kii Peninsula are two Western Pacific populations that have historically shown unusually high rates of occurrence, indicating the potential for environmental impacts.[1] Geographic clustering may result from intricate gene-environment interactions, while the exact mechanisms are yet unclear.[13]

The median survival period in ALS ranges from two to five years after the onset of symptoms.[1,3,4] Nevertheless, only 10% of patients live past the age of ten, and a small percentage may have the illness for decades.[3] The presence of cognitive impairment, area of origin (bulbar-onset disease typically has a poorer prognosis than limb-onset disease), and age at onset (younger patients typically survive longer) are some of the prognostic markers that affect survival.[4,14] Respiratory failure is the main cause of death, and prognosis is significantly predicted by forced vital capacity (FVC), a measure of respiratory function.[10]

Beyond death rates, ALS has a burden. For patients, families, and healthcare systems, the illness has significant financial, psychological, and physical effects.[1] Higher standards of care, medical procedures, and assistive technologies are required for progressive impairment.

Due to the disease's quick progression, patients and their families might not have the opportunity to adapt and make plans.[4] Planning healthcare, allocating resources, and finding potentially modifiable risk variables that could guide prevention efforts all depend on an understanding of ALS epidemiology.[13]

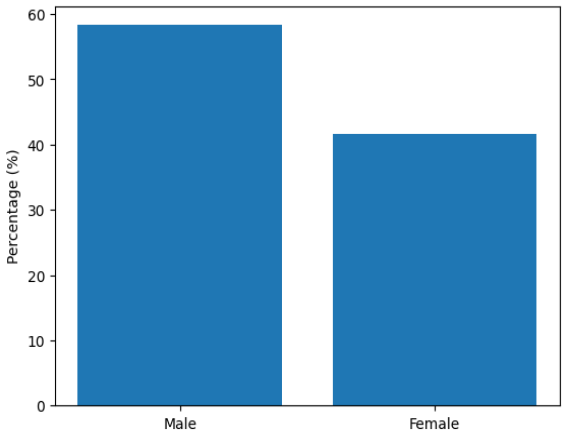

Fig. 01: Gender Distribution in ALS Patient.

Global Burden of ALS (WHO–GBD Estimates)

Based on estimates from the Global Burden of Disease (GBD) study, which is widely used by the World Health Organization for global health reporting, ALS is categorized as a motor neuron disease (MND). There were around 222,801 ALS patients worldwide in 2015. By 2022, this number had increased to approximately 272,732 common cases globally, suggesting a steady upward trend. According to estimates, the annual incidence of ALS is between 1.5 and 2.5 cases per 100,000 people, although the global prevalence rate is between 3 and 6 cases per 100,000 people. Despite recurring event cases, the incidence is still minimal due to the incredibly short survival period. The median survival is between two and five years.[17]

Country and Regional Trends

High-income regions like North America and Europe have higher prevalence rates than low- and middle-income countries, largely because of better diagnostic tools, established disease registries, and longer survival times Between 32,000 and 33,000 Americans had ALS as of 2022. There were between 50,000 and 55,000 prevalent cases in Europe within the same

period. Although there are only 4,000–5,000 ALS patients in India, underdiagnosis is believed to be widespread.[18]

FUTURE PROJECTIONS

Future projections based on demographic modelling and age-specific incidence rates indicate that the global burden of ALS will increase dramatically over the next few decades. By 2030, there will be about 310,000 ALS patients worldwide. By 2040, there will likely be 376,674 cases worldwide, an increase of almost 69% from 2015. This expected rise is primarily due to: As ALS mostly affects individuals between the ages of 50 and 75, the population is getting older. Increased awareness of diagnostics and reporting Slow improvements in supportive care that increase life expectancy According to country-level estimates that also indicate increased prevalence, long-term neurological and palliative care services are expected to be more in demand for healthcare systems in the US, Europe, and developing nations like India.[19]

Public Health Implications

As ALS becomes more common, policymakers, caregivers, and healthcare systems must deal with a number of challenges. The projected rise in patients highlights the urgent need for: The infrastructure for neurological treatment is being developed, even if ALS remains incurable. An increase in ALS registrations, especially in low- and moderate-income countries. Promoting research into disease-altering therapies; enhancing palliative and supportive care services.[20]

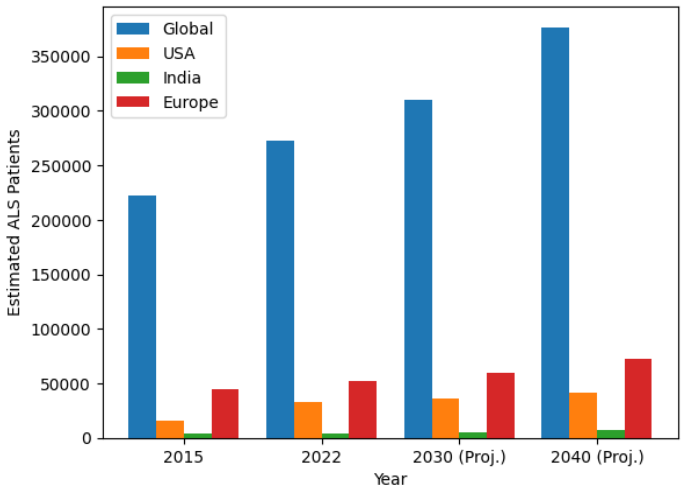

Fig. 02: Amyotrophic Lateral Sclerosis patients by year and country [Historical and future projection].

PATHOPHYSIOLOGY

The intricate pathophysiology of ALS includes a number of molecular and cellular processes that combine intricately to cause the degeneration of motor neurons,[2,8] and.[15] Through genetic research, cellular models, and post-mortem tissue analysis, numerous important pathogenic pathways have been discovered, even if the precise sequence of events leading to motor neurone death is still unknown.[7,16] Amyotrophic lateral sclerosis (ALS) is believed to be caused by a complicated interaction between genetic and molecular pathways. Astrocytic excitatory amino acid transporter 2 (EAAT2) failure reduces glutamate absorption from the synaptic cleft, which results in glutamate excitotoxicity and sets off Ca2+-dependent enzymatic pathways that cause neurodegeneration. This is an important mechanism of pathogenicity. Mutations in C9orf72, TDP-43, and FUS impair RNA metabolism, causing aberrant protein translation and intracellular neuronal aggregation.[21] Genetic variables also have a crucial role. Similarly, mutations in superoxide dismutase-1 (SOD1) cause aggregation formation, oxidative stress, axonal transport disruption, and mitochondrial malfunction. Microglia activation increases neurotoxicity by generating proinflammatory cytokines, in addition to these neuronal and genetic pathways.[1]

Protein Aggregation and Proteostasis Dysfunction

A significant accumulation of misfolded proteins in motor neurons and glial cells is characteristic of ALS[5,15] TDP-43 (TAR DNA-binding protein 43) is the primary source of cytoplasmic inclusions in over 97% of ALS cases.[5,6] The nuclear protein TDP-43, which is necessary for RNA processing, typically undergoes hyperphosphorylation, ubiquitination, and mislocalization to the cytoplasm in ALS, where it aggregates to death,[5,8] The molecular basis for the clinical overlap between ALS and frontotemporal dementia is provided by a pathogenic TDP-43 proteinopathy.[1,5] The protein known as mutant superoxide dismutase 1 misfolds and aggregates in SOD1-associated ALS, resulting in deadly gain-of-function traits that ultimately lead to motor neurone death.[7,16] Additionally, FUS (fused in sarcoma) mutations cause mislocalization of proteins. Capturing.[2,5] Cellular protein quality control systems, autophagy and the ubiquitin-proteasome system, are overloaded by the accumulation of these abnormal protein species, resulting in cellular stress and malfunction.[5,8,15]

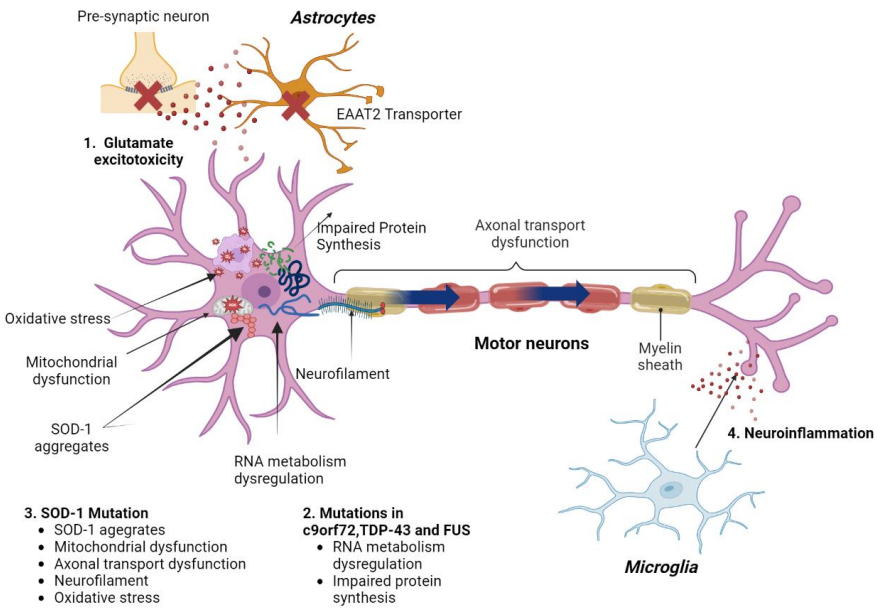

Fig. 03: Pathophysiology of Amyotrophic Lateral Sclerosis.

RNA Processing Defects

Disrupted RNA metabolism has been highlighted as a key element in the pathogenesis of ALS[5,8] Several ALS-associated genes, including TDP-43, FUS, and C9orf72, encode RNA processing, splicing, and transport-related proteins[2,5] When these genes are mutated, correct RNA homeostasis is disrupted, leading to aberrant splicing, poor mRNA transport, and the formation of stress granules, which are aggregates of cytoplasmic RNA and proteins that form in response to cellular stress.[5,8] Through repetition-associated non-ATG (RAN) translation, the amplification of the C9orf72 hexanucleotide repeat produces toxic RNA foci and toxic dipeptide repeat proteins (DPRs), both of which hinder cellular function,[1,5] and.[8]

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial abnormalities, including changed shape, reduced energy metabolism, and increased production of reactive oxygen species (ROS), are common in ALS patients.[4,8,15] Motor neurons are especially prone to mitochondrial dysfunction. due to their high metabolic needs, long axonal projections, and limited capacity for regeneration[7] Oxidative stress, which is brought on by excessive ROS production, damages cellular macromolecules such proteins, lipids, and DNA and contributes to the degeneration of motor neurons.[4,15] Despite being an antioxidant enzyme, mutant SOD1 paradoxically causes detrimental gain-of-function processes that exacerbate oxidative damage.[7,16]

Excitotoxicity

Glutamate-mediated excitotoxicity has long been implicated in the pathophysiology of ALS.[2,7,8] Poor glutamate absorption by astrocytic EAAT2 transporters results in excessive glutamate signalling that overstimulates NMDA and AMPA receptors on motor neurons. Calcium influx and cell damage.[2,7] This mechanism supports riluzole, the first approved treatment for ALS that alters glutamatergic neurotransmission.[2,4]

Neuroinflammation and Non-Cell-Autonomous Mechanisms

ALS is not solely a disease that affects motor neurons; non-neuronal cells, particularly astrocytes and microglia, are essential to its development.[2,6,15] Important elements of ALS pathogenesis include reactive astrocytes and activated microglia, which can have both neurotoxic and helpful effects.[2,15] Dysfunctional astrocytes can actively contribute to the death of motor neurons by releasing toxic chemicals and inflammatory mediators, which prevent them from receiving enough metabolic support.[2] This non-cell-autonomous illness highlights the necessity of focusing therapeutic efforts on multiple cell types and explains why clinical trials including motor neuron-specific therapy have often failed.[6,15]

Axonal Transport Defects

Another important pathogenic cause for ALS is impaired axonal transport.[5,8] Organelles, proteins, and RNA must be efficiently transported in both directions between the cell body and synaptic terminals via motor neurons' extraordinarily long axons.[5] Synaptic failure and "dying-back" axonopathy, in which degeneration starts at the neuromuscular junction and moves proximally toward the cell body, result from disruption of this transport brought on by cytoskeletal abnormalities, protein aggregates, or mitochondrial malfunction.[8] These several pathogenic processes, which are interconnected rather than mutually exclusive, create a complex network of cellular dysfunction that ultimately results in motor neuron death.[8,15] These mechanisms must be understood in order to determine therapy targets. as well as developing effective treatments.[7,11]

PHYTOCHEMICAL IN ALS

a) Oxidative stress in ALS

Compound	Plant Source	Plant Family	General Uses / Biological Activities	Reference
Madecassoside	*Centella asiatica*	Apiaceae	Traditional medicinal herb for	[22,23]

			wound healing, anti-inflammatory, antioxidant, skin protection	
Ampelopsin (Dihydromyricetin)	*Ampelopsis* spp. (e.g., *A. grossedentata*), *Hovenia dulcis*, others	Vitaceae (grape family)	Antioxidant, anti-inflammatory, hepatoprotective, traditional use in hangover remedies and metabolic disorders	[24]
Epigallocatechin gallate (EGCG)	*Camellia sinensis* (Green tea)	Theaceae	Antioxidant, cardiometabolic benefits, used as dietary catechin	[25,26]
Picroside-II	*Picrorhiza* spp. (*Picrorhiza kurroa*, *P. scrophulariiflora*)	Plantaginaceae (often placed in Scrophulariaceae complex)	Antioxidant and anti-inflammatory, traditionally used for liver and digestive health	[27]
Morroniside	*Cornu's officinalis* (Japanese cornel)	Cornaceae	Anti-oxidative and anti-inflammatory properties; used in traditional medicines for pain/neuropathy	[28]
Astragaloside IV	*Astragalus membranaceus*	Fabaceae (legume family)	Major bioactive in traditional Chinese medicine (*Huang Qi*); immune support, anti-inflammatory, cardioprotective	[29]
Diallyl trisulfide (DATS)	*Allium* spp. (garlic, onion)	Amaryllidaceae	Antibacterial, cardioprotective, immune modulation, crosses blood-brain barrier	[30]

b) Neuroinflammation in ALS

Compound	Plant Source	Plant Family	General Uses / Biological Activities	Reference
Celastrol	Tripterygium wilfordii	Celastraceae	Potent anti-inflammatory, immunosuppressive; used in traditional Chinese medicine	[31]
Resveratrol	Vitis vinifera (skin), also *Polygonum*	Vitaceae	Antioxidant, cardioprotective, anti-aging (SIRT1 activation)	[32]

	cuspidatum			
Curcumin	Curcuma longa	Zingiberaceae	Anti-inflammatory, antioxidant, widely used dietary phytochemical	[33,34]
Isorhynchophylline (IRN)	Uncaria rhynchophylla	Rubiaceae	Neuroprotective alkaloid; antihypertensive; anticonvulsant	[35]
Obovatol	Magnolia obovata	Magnoliaceae	Anti-inflammatory, anxiolytic, antioxidant	[36]
Paeonol (PAE)	Paeonia suffruticosa (root bark)	Paeoniaceae	Anti-inflammatory, analgesic, vascular protective	[37]

c) Cytotoxicity in ALS

Compound	Natural Source	Family	General Uses / Biological Activities	Reference
Paeoniflorin	Paeonia lactiflora (root)	Paeoniaceae	Anti-inflammatory, immunomodulatory, analgesic; used in traditional Chinese medicine	[38]
Ligustrazine (Tetramethylpyrazine, TMP)	Ligusticum chuanxiong	Apiaceae	Cerebrovascular protection, anti-platelet, antioxidant; improves cerebral blood flow	[39]
Gastrodin	Gastrodia elata	Orchidaceae	Anticonvulsant, neuroprotective, anti-inflammatory	[40]
Muscone	Moschus moschiferus (natural source; now often synthetic)	Moschidae	Neuroprotective, anti-inflammatory, improves blood–brain barrier permeability	[41]

d) Amino acid toxicity in ALS

Compound	Natural Source	Family	General Uses / Biological Activities	Reference
β-Asarone	Acorus calamus (rhizome oil)	Acoraceae	Neuroprotective, cognitive enhancer, traditional CNS remedy	[42]
Huperzine-A	Huperzia serrata	Lycopodiaceae	Acetylcholinesterase inhibitor; used in cognitive disorders	[43]
Catalpol	Rehmannia glutinosa	Orobanchaceae	Anti-inflammatory, antidiabetic, neuroprotective iridoid	[44]

			glycoside	
Selaginellin	Selaginella tamariscina	Selaginellaceae	Antioxidant, cytoprotective	[45]
Ferulic acid	Oryza sativa (bran), also abundant in cereals	Poaceae	Antioxidant, anti-inflammatory, vascular protective	[46]
Cryptotanshinone	Salvia miltiorrhiza	Lamiaceae	Anti-inflammatory, cardioprotective, anticancer	[47]

GENETICS

The genetic landscape of ALS has changed significantly over the last 20 years due to the identification of over 20 genes that are definitively associated with the disease as well as a large number of additional genetic risk factors.[1,2,5] These discoveries have opened up new avenues for the creation of treatments and provided previously unheard-of insights into the mechanisms underlying disease.[11,12]

Major Genes interrelated with ALS

C9orf72: The hexanucleotide repeat expansion (GGGGCC) in the C9orf72 gene is the most common genetic cause of ALS, accounting for around 7% of sporadic cases and 30–50% of familial cases.[1,3,5] Furthermore, this expansion is the most prevalent hereditary cause of frontotemporal dementia, underscoring the molecular parallels between both conditions,[1] [5] The C9orf72 expansion causes disease through a number of mechanisms, including loss of C9orf72 protein function, the formation of toxic RNA foci, and the production of toxic dipeptide repeat proteins by repeat-associated non-ATG translation.[5,8]

SOD1: Mutations in the superoxide dismutase 1 (SOD1) gene were found to be the original genetic etiology of ALS, accounting for 10–20% of family cases.[2,4,7] Each of the more than 180 different SOD1 mutations that have been identified is associated with a variety of clinical traits and rates of disease progression.[16] SOD1-associated ALS is caused by toxic gain-of-function mechanisms, in which mutant SOD1 protein creates toxic aggregates that disrupt several cellular processes, rather than a loss of enzymatic activity[7,16] SOD1-ALS is a common target for gene-specific therapies because of its proven traits[11,16] **TARDBP**: About 3–5% of cases of familial ALS are caused by mutations in TARDBP, which codes for the TDP-43 protein.[2,5] Since TDP-43 pathology is present in nearly all ALS cases, regardless of genetic aetiology, it has become crucial to understand how TARDBP mutations generate disease. broad impacts on ALS pathogenesis.[5,8] A number of aspects of RNA metabolism are

impacted when the multifunctional RNA-binding protein TDP-43 fails. It is involved in transcription, splicing, and RNA transport.[5]

FUS: Mutations in the FUS (fused in sarcoma) gene account for about 4% of instances of familial ALS.[2,5] Mutations lead to the mislocalization of FUS, an RNA-binding protein involved in RNA processing, from the nucleus to the cytoplasm, where it forms aggregates, much like TDP-43.[2,5] ALS associated with FUS often appears earlier in life and may advance more quickly.[5]

Other ALS-Associated Genes

OPTN, VCP, UBQLN2, SQSTM1, TBK1, and many other genes are also associated with ALS; although each of these genes is responsible for a small percentage of cases, when combined, they aid in our understanding of the mechanisms underlying the illness.[4,5] These genes are involved in a number of cellular processes, including cytoskeletal dynamics, vesicular trafficking, autophagy, and protein degradation, illustrating the range of pathways that could lead to motor neuron degeneration.[5,8]

Genetic Heterogeneity and Phenotypic Variability

One amazing feature of ALS genetics is the significant clinical variation associated with mutations in the same gene, or even the same mutation.[4,16] This heterogeneity is caused by a variety of causes, including genetic modifiers, environmental factors, and stochastic factors.[16] This variance highlights the need for customized approaches to diagnosis and treatment, making genetic counselling more challenging.[5,11]

Implications for Precision Medicine

The molecular characterization of ALS has enabled the development of gene-targeted medications, which has led to a paradigm shift toward precision medicine.[5,11,12] Antisense oligonucleotides (ASOs) aimed at reducing the expression of faulty genes, such as SOD1, are presently undergoing clinical trials with C9orf72, and first results are promising.[5,11] The efficacy of these tactics depends on an accurate genetic diagnosis, underscoring the importance of comprehensive genetic testing for each ALS patient.[11,12]

Clinical Features and Diagnosis

Clinical Presentation

ALS typically presents as a modest onset of localized weakness, either in the bulbar area, which affects speech and swallowing (bulbar-onset ALS, approximately 25% of cases), or in a limb (limb onset ALS, approximately 70% of cases), according to.[1,3,4] The initial symptom of limb-onset disease may be hand weakness, which manifests as problems with fine motor skills, such as foot drop or difficulty climbing stairs, or in the legs when writing or buttoning clothes.[3,4] Bulbar-onset disease manifests as tongue weakness, dysphagia (difficulty swallowing), and dysarthria (slurred speech).[1,3] ALS is characterized by a combination of symptoms related to lower motor neurons (LMN) and upper motor neurons (UMN).[3,4] LMN symptoms include muscular atrophy, weakness, hyporeflexia, and fasciculations (visible twitching of the muscles), while spasticity and aberrant reactions include hyperreflexia and the Babinski sign.[3,4] ALS is highly suggested when these traits coexist in the same body part.[4] As the disease progresses, weakness spreads in a fairly predictable pattern from the initial site of manifestation to other parts of the body.[1,3] Most patients eventually experience respiratory muscle weakening, which can lead to orthopnea, dyspnea, and ultimately respiratory failure, the leading cause of death.[4,10] The rate of progression varies greatly; some patients experience a sharp decline over several months, while others have a longer course that lasts for years.[3,4]

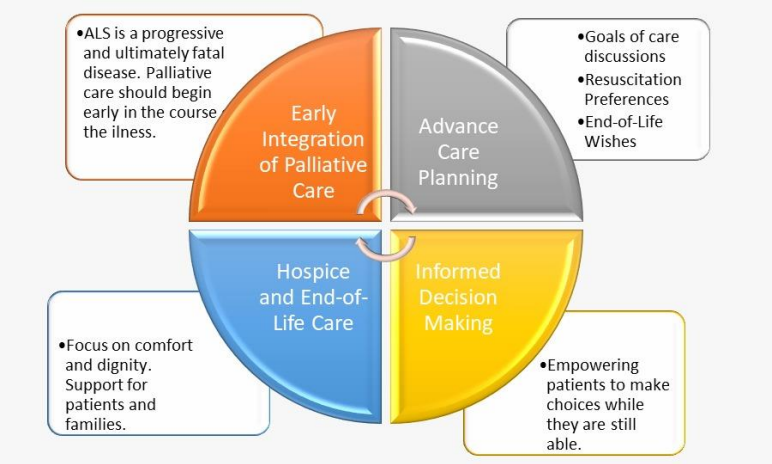

Fig. 04: Clinical Features and Diagnosis.

Extramotor Manifestations

According to current knowledge, ALS is more than only a motor illness.[1,3,5] Up to 50% of patients experience cognitive and behavioural abnormalities, which can range from mild

executive dysfunction to overt frontotemporal dementia in 10–15% of cases.[1,3] Impaired verbal fluency, executive dysfunction, and behavioural abnormalities such apathy, disinhibition, and loss of empathy are examples of common cognitive deficiencies.[3], [5] Cognitive impairment is linked to higher caregiver burden and shorter survival.[4]

Diagnostic Criteria and Investigations

The primary clinical rationale for the diagnosis of ALS is the presence of increased UMN and LMN symptoms in many body regions, which are corroborated by electrophysiological studies.[3,4] By categorizing diagnostic certainty based on the number of affected regions as clinically definite, probable, or prospective ALS, the modified El Escorial criteria and the Gold Coast criteria provide established diagnostic frameworks.[4]

Electromyography (EMG) and nerve conduction tests are essential diagnostic tools that demonstrate both extensive denervation (fibrillation potentials, positive sharp waves) and chronic reinnervation (high amplitude, long duration motor unit potentials) in clinically affected and unaffected regions.[3,4] These findings help rule out ALS mimics such as multifocal motor neuropathy, myasthenia gravis, and cervical myelopathy.[4] While motor cortical atrophy in advanced disease and corticospinal tract hyperintensity on T2-weighted images are common findings, neuroimaging, particularly MRI, is primarily used to rule out structural lesions and other diagnoses.[4] Two imaging techniques that show promise as prognostic and diagnostic biomarkers are diffusion tensor imaging and advanced magnetic resonance spectroscopy.[11] The importance of biomarkers in ALS diagnosis and monitoring is growing.[5,11] Neurofilament light chain (NfL) in blood and brain fluid is elevated in ALS and correlates with the progression of the illness, despite its lack of specificity.[5,11] In relation to C9orf72 ALS may be specifically indicated by dipeptide repeat proteins in CSF.[5]

The objective of current research is to identify biomarker panels that can help with early diagnosis, predict prognosis, and monitor therapeutic response.[11,12]

DIFFERENTIAL DIAGNOSIS

Since many diseases might mimic ALS, careful evaluation is required to avoid misdiagnosis.[4] Myasthenia gravis, inclusion body myositis, Kennedy's disease (spinal and bulbar muscle atrophy), multifocal motor neuropathy with conduction block, and cervical spondylotic myelopathy.[4] A comprehensive clinical evaluation, electrophysiological study, and appropriate laboratory tests are necessary to distinguish these conditions from ALS.[4]

Current Treatment Approaches

Disease-Modifying Therapies

Despite decades of study and numerous clinical studies, there are only a few approved disease-modifying medications for ALS, and their impact on survival and function is negligible.[4,10,11]

Riluzole: Riluzole, the first ALS disease-modifying medication, was authorized in 1996.[2], [4], [10] By controlling glutamate release and disrupting the NMDA receptor via anti-glutamatergic pathways, it mostly lessens excitotoxicity. Dialogue.[2,4] Clinical studies show that riluzole increases survival by about two to three months and is generally well-tolerated. Nausea and elevated liver enzymes are the most common side effects.[4,10] Despite its limited efficacy, riluzole remains the mainstay treatment for ALS patients.[10]

Edaravone: A free radical scavenger that reduces oxidative stress, edaravone was licensed in Japan in 2015 and has since been approved in other countries.[5,10] There was a minor pause in functional deterioration in some patient populations, according to clinical trials; nevertheless, the degree of this benefit and the optimal patient selection criteria are still debatable.[5,10] Since edaravone is administered intravenously, long-term use poses practical challenges.[10]

Tofersen: In 2023, the FDA approved the use of tofersen, an antisense oligonucleotide that precisely targets SOD1 mRNA, to treat patients with SOD1-associated ALS.[8,11] This is a significant achievement that validates the efficacy of medicinal method as the first gene-specific treatment for ALS.[11] Tofersen reduces SOD1 protein levels and shows promise in slowing the progression of the disease in SOD1-ALS patients, while long-term efficacy evidence is still being collected.[8,11]

Symptomatic and Supportive Care

Multidisciplinary treatment, which has been shown to improve quality of life and increase survival, remains the cornerstone of managing ALS.[4,10] To meet the varied needs of individuals with ALS, neurologists, respiratory therapists, physical and occupational therapists, speech-language pathologists, nutritionists, social workers, and palliative care specialists work together in comprehensive ALS clinics.[10]

Respiratory Management

Since respiratory failure is the main cause of death in ALS, respiratory treatment is crucial.[4,10] Early respiratory insufficiency is made possible by routine monitoring of respiratory function using forced vital capacity (FVC) and nocturnal oximetry.[10] Non-invasive ventilation (NIV) significantly improves survival and quality of life when initiated correctly, typically with bilevel positive airway pressure (BiPAP).[4,10] Invasive mechanical ventilation and tracheostomy are options that some patients may choose, although this decision requires careful consideration of the treatment objectives.[10]

Nutritional Support

Dysphagia and increased weakness lead to malnutrition and weight loss, all of which are associated with worse outcomes.[4,10] Percutaneous endoscopic gastrostomy (PEG) or radiologically implanted gastrostomy (RIG) tubes provide reliable enteral hydration and nutrition, improving nutritional status and perhaps extending life [4,10] The ideal timing to install a gastrostomy balances the benefits of nutritional supplementation with the risks associated with the procedure.[10]

Symptomatic Treatments

ALS symptoms are targeted by several medications.[2,4,10] Sialorrhea, or excessive salivation, can be treated with radiation treatment, anticholinergic medications, or botulinum toxin injections into the salivary glands.[4,10] Baclofen, tizanidine, or benzodiazepines are effective in treating spasticity.[4] Dextromethorphan-quinidine effectively treats pseudobulbar affect (pathological laughing and sobbing).[4] Strategies for managing pain, cramping, and exhaustion must be tailored to each patient.[10]

Rehabilitation and Assistive Devices

Function and independence are preserved with the use of physical and occupational therapy.[4,10] As the illness worsens, assistive technology—such as wheelchairs, ankle-foot orthoses, environmental control systems, and communication devices—is crucial for preserving quality of life.[10]

Palliative and End-of-Life Care

Since ALS is a progressive and ultimately fatal illness, palliative care should be started early in the course of the illness.[10] Advance care planning, which includes discussions about goals of care, resuscitation preferences, and end-of-life wishes, empowers patients to make

informed decisions. decisions when they have the opportunity to make them.[10] Hospice care provides patients and their families with comprehensive support in the latter stages of illness with a focus on comfort and dignity.[10]

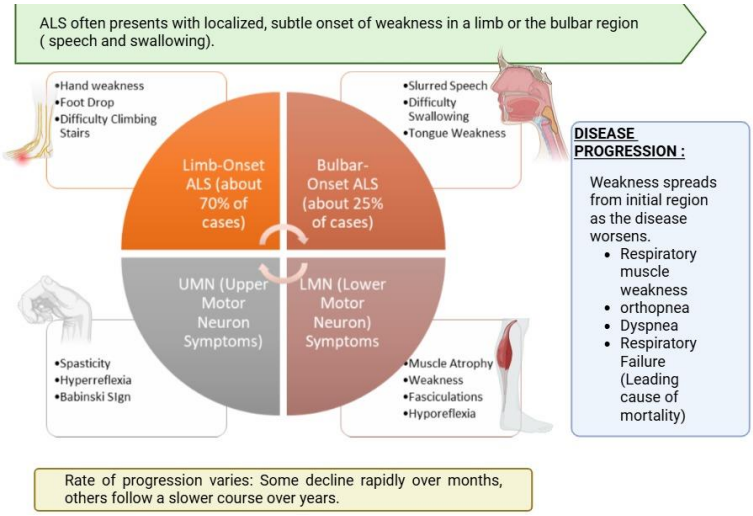

Fig. 05: Palliative and End-of-Life Care.

Emerging Therapies and Future Directions

The field of ALS treatment is changing quickly, with several promising strategies in different phases of development.[11,12] These new treatments signify a move toward precision medicine and tailored interventions and are a reflection of our expanding knowledge of disease mechanisms.[5,11]

Gene-Targeted Therapies

The development of analogous treatments for other hereditary variants of ALS has been prompted by the success of tofersen for SOD1-ALS, which has validated the antisense oligonucleotide (ASO) method.[5,11] Clinical trials are underway for ASOs that target C9orf72 in an effort to decrease hazardous RNA foci and dipeptide repeat proteins.[5,11] Accurate genetic identification is necessary for these gene-specific treatments, which mark a paradigm change toward individualized care.[11,12] In addition to ASOs, other gene-modulating techniques are being studied.[11] RNA interference (RNAi) and small interfering RNAs (siRNAs) are alternative strategies for reducing the expression of dangerous genes.[16] Gene editing technologies, like CRISPR-Cas9, have the potential to correct dangerous mutations, but before they can be applied in clinical settings, ethical and technical challenges must be addressed.[5]

Stem Cell Therapies

Stem cell-based approaches aim to change the disease environment, provide trophic support, or replace injured motor neurons.[2,6,10] Several types of stem cells, including neural progenitor cells, induced mesenchymal stem cells, and motor neurons derived from pluripotent stem cells (iPSCs), have been evaluated in numerous clinical investigations.[6,10] While early trials have demonstrated safety, efficacy has not yet been established.[10] There are difficulties in achieving appropriate cell survival, integration, and functional linkage as well as in addressing the non-cell-autonomous aspects of disease.[6]

Targeting Protein Aggregation and Proteostasis

Modulating Neuroinflammation

Anti-inflammatory treatments have been developed as a result of the understanding that neuroinflammation plays a role in the advancement of ALS.[6,15] Modulating microglial activation, focusing on particular inflammatory pathways, and boosting glial cells' neuroprotective abilities are among strategies.[15] Clinical trials are being conducted on a number of anti-inflammatory substances, although the outcomes have been inconsistent.[11]

Combination Therapies and Multi-Target Approaches

The multifaceted nature of ALS pathogenesis may make combination therapies that target multiple processes simultaneously more successful than single-agent approaches.[6,11,12] Effective strategies for HIV and cancer are comparable to this one.[11] treatment. There are now clinical trials evaluating combination treatments, but their planning and analysis present methodological challenges.[11]

Biomarkers and Precision Medicine

The discovery of trustworthy biomarkers is necessary for the quick development of treatments.[11,12] Biomarkers provide patient categorization for clinical trials, early diagnosis, prognosis prediction, and therapy response tracking.[11] Phosphorylated neurofilament heavy chain and C9orf72-specific dipeptide repeat proteins are two of the most promising alternatives for this neurofilament-based luminous chain.[5,11] Proteomics, metabolomics, transcriptomics, and genomes are examples of multiomic approaches that can be combined to uncover biomarker panels that capture illness heterogeneity and guide tailored treatment.[12]

Artificial Intelligence and Drug Discovery

Artificial intelligence (AI) and machine learning are increasingly being employed in ALS research, from drug discovery to clinical trial design.[6,12] Massive amounts of data may be analysed by AI to improve patient classification, identify new treatment targets, and forecast the effectiveness of drugs. Computer techniques can accelerate the typically expensive and slow drug development process.[12]

Clinical Trial Innovation

Transforming promising preclinical findings into successful treatments requires improving clinical trial design.[11] Adaptive trial designs, platform trials that assess several interventions at once, and enrichment techniques that choose individuals most likely to benefit from certain treatments are examples of innovations.[11] Remote monitoring and the utilization of digital health technologies can enhance data collecting and lessen patient burden.[11] Optimizing the effectiveness and success of trials requires cooperation between academic institutions, business, regulatory bodies, and patient advocacy organizations.[11,12]

CONCLUSION

Amyotrophic lateral sclerosis, one of the most crippling neurodegenerative diseases, is characterized by its relentless progression and lack of viable therapeutic options. However, there have been significant advances in our understanding of the cellular, molecular, and genetic mechanisms underlying motor neuron degeneration throughout the past 20 years. The identification of over 20 ALS-associated genes has not only illuminated disease mechanisms but also enabled the development of gene-targeted precision therapies like tofersen, which was recently licensed for SOD1-ALS.[8,11] There are still a lot of challenges to tackle despite these advancements. Treatment development is difficult due to the genetic and clinical phenotypic heterogeneity of ALS, necessitating customized approaches.[5,11,12] The complex character of disease Pathophysiology, which includes protein aggregation, RNA processing problems, mitochondrial dysfunction, excitotoxicity, neuroinflammation, and non-cell-autonomous processes, suggests that combination therapy that targets many pathways may ultimately prove most effective.[6,11,15]

The limited advantages of current disease-modifying medicines highlight the critical need for more potent therapeutics.[10,11] However, there is true optimism for significant therapeutic advancements in the upcoming years because to the extensive pipeline of developing medicines, which includes further gene-targeted techniques, stem cell therapies, anti-

inflammatory drugs, and novel small molecules.[11,12] Artificial intelligence, cutting-edge biomarkers, and creative clinical trial designs have the potential to expedite the conversion of scientific findings into practical applications.[11,12]

Meanwhile, multidisciplinary care continues to be the cornerstone of managing ALS, enhancing quality of life and prolonging longevity through palliative care, dietary management, symptomatic treatment, and comprehensive respiratory support.[4,10] All patients with ALS should prioritize early diagnosis, genetic testing, and clinical trial enrolment.[11] The advances made by the ALS research community have revolutionized our knowledge of this complicated illness and set the stage for a new era of precision medicine. The convergence of genetic insights, mechanistic understanding, technological innovation, and cooperative research efforts offers realistic hope that effective disease-modifying therapies will emerge to alter the natural history of this devastating disorder, even though a cure is still elusive.[11,12] To achieve this goal and give ALS patients and their families hope, sustained funding for basic and translational research, creative clinical trial approaches, and solid collaborations across all stakeholders will be crucial.

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