IJPSR (2021), Volume 12, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 June 2020; received in revised form, 12 October 2020; accepted, 03 May 2021; published 01 June 2021

AMYOTROPHIC LATERAL SCLEROSIS: RAPIDLY ACCELERATING COMPLEX NEURO-DEGENERATIVE DISEASE

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Keywords:

ALS, Genes, Oxidative stress, Excitotoxicity, Mitochondria

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ABSTRACT: An amyotrophic lateral sclerosis is a group of progressive neurodegenerative disorders of motor neurons that leads to weakness, muscle atrophy, progressive paralysis, and respiratory insufficiency with a life anticipation of only three years after the onset of disease symptoms. It impairs the functions of both upper and lower motor neurons. The specific mechanism for the disease remains largely unidentified. At present, there is no specific treatment to cure or reverse the progression of the disease. ALS is generally diagnosed based upon the medical history and signs and symptoms; however, it is quite difficult to diagnose the disease in its initial stages. Several studies indicate that various predominant disease mechanisms such as oxidative stress, excitotoxicity, mitochondria dysfunction, aberrant protein homeostasis, defective RNA processing, formation of cytoplasmic inclusion, endoplasmic reticulum stress, endosomal dynamic dysfunctions, protein aggregation, neuroinflammation, oligodendrocyte degeneration, and microglial activation are involved in the pathophysiology of ALS. The various gene mutations (c9orf72, TARDBP, SOD1, and FUS) are also associated with disease mechanisms, so ALS is a complex genetic disorder involving multiple combinations of genes in amalgamation with environmental exposures. Through targeting the above-said disease, mechanisms is likely to contribute to the development of novel therapeutic treatments for the patients suffering from ALS. The review papers present the overview of key disease mechanisms and associated gene mutations involved in the pathophysiology of ALS, its clinical features, and several brain regions involved in the disease.

INTRODUCTION: Amyotrophic lateral sclerosis (ALS) is a fatal, rapidly accelerating complex adult neurodegenerative disease that impaired the functions of upper motor neuron (UMN) and lower motor neurons (LMN) that results in motor paralysis and muscle atrophy [1-3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(6).3078-89

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(6).3078-89

The fatality of disease (usually within 3-5 years) is characterized by an escalating and unsymmetrical weakness and atrophy of muscles (limb, thoracic, abdominal, and bulbar muscles) [4-5]. The disease starts with dysarthria and dysphagia, leading to breathing difficulty, resulting in the weakness of respiratory muscles, and the death is due to respiratory failure in the final stage of ALS. There is no such treatment available for the disease except one medication known as riluzole which can cure or reverse the main symptoms of the disease completely [6]. As compared to the females, the disease incidences are higher in males to some extent, with about a 1.5:1 ratio.

The individuals of age group 55 to 75 years are more affected by this disease [7]. In the brain and spinal cord, the nerve cell of motor neurons gets stuck and dies. This phenomenon impaired the motor neurons functioning that ultimately impaired muscle movement control in the brain and spinal cord, which leads to loss of muscle mass, weakness of muscle, and inability to control the movements of the body. The gradual decline in strength leads to paralysis and loss of muscle functions [1, 7].

ALS impaired the functions of UMN such as spasticity, slowness of movements, poor balance, and in coordination, which is present in the brain and also impaired the functions of LMN (muscle weakness, muscle atrophy, twitching, or fasci-culation's), which are present in the spinal cord and brainstem stem[8]. Several studies indicate that various gene mutations such as c9orf72, TARDBP, SOD1, FUS are associated with the disease mechanisms such as like glutamate excitotoxicity, damage of mitochondria, aggregation of the protein, dysfunction of microglia, neuroinflammation, aberrant RNA metabolism, defective DNA metabolism, and defective transport of axon involved in ALS. These are all pathological mechanisms that probably play a role in motor neuron degeneration in ALS [2, 9, 10].

However, major barriers to the development of effective therapeutic strategies in ALS are due to the poor understanding of the pathophysiology of ALS. It also affects all the functions and integrity of brain networks [11-13]. ALS is a multifactorial and multisystem composite disease of the neurons. The various mechanisms entail the pathogenesis of this disease. All the above factors result in the functional loss of the specific body part and causing its paralysis due to impairment of neurons. Through targeting these pathogenic factors, there is a possibility to detect the superior biomarkers and also to enhance the therapeutic approach towards the remedies of ALS [4-5, 12]. This review paper gives a novel understanding of the predominant factors involved in the disease mechanism with associated genes and various brain regions impaired in ALS.

Symptoms of ALS: The prime manifestations of ALS can fluctuate among patients; some may be having a spinal - onset disease (*i.e.,* the outbreak of the muscle fragility of the limbs). The other patients may have a bulbar-onset disease that is represented by dysarthria and dysphagia. The cause of ALS is undetermined in most patients, whilst some patients with familial disease are accompanied with genetic mutations that have a broad spectrum of functions, even in non-motor cells. Almost 50% of victims are prone to cognitive and/or behavioural impairment during the disease course. Dysphagia, muscle weakness, spasticity, concomitant behavioural variant frontotemporal dementia (FTD) is identified in 13% of patients as initial symptoms of ALS [14, 15]. Fasciculation cramps, muscle atrophy and marked weakness, are the manifestations of LMN's degeneration and loss which includes spasticity, hyperreflexia, and modest weakness is due to impairment of UMN's. Language, judgment, personality trait is affected, and the executive functions get altered. The Decision-making capability of patients with ALS and dementia also gets affected for a short duration of time [16].

Emotional symptoms if present, can lead to poor appetite and impairment in sleep quality of life. Degeneration of sensory neurons can occasionally lead to pain and extreme suffering. Pain frequently resulted from contractures, inability to turn in bed and loss of mobility. The primary respiratory manifestations include weakened cough, dyspnoea, morning headache and orthopnoea [17]. Patients may experience depression and anxiety at some stage during respiratory failure. The manifestations of motor neuron disorder typically initiate with focal weakness in one limb. During disease, distal muscles are affected most often, and patients may experience hand clumsiness or foot drop. Head drop is observed when the neck extensor muscles are affected. Upper motor neuron participation may result in muscle cramps and rigidity. In 20% of patients, the manifestations are first observed in the bulbar muscles causing dysarthria and dysphagia [4, 18, 19]. The various clinical signs and symptoms are presented in **Fig. 1**.

Classification of ALS: Motor neuron disorders (MND) is a type of neurodegenerative disease, which leads to significant disability and death throughout the impaired motor system. HSP, SMA, and ALS are the types of MND and HSP is pure LMN type, and SMA is pure UMN type. ALS is a common type of motor neuron disorder. ALS can be systematized into two major categories: sporadic (idiopathic) and familial. Familial ALS occurrence

depends on a dominant trait and affects about 5% to 10% of patients with ALS [20, 21].

Approximately 67% males are influenced by sporadic ALS and it encompasses all other patients with ALS [1]. Familial ALS showed an ailment male to female ratio of 1:1.1 Patients with ALS in early childhood and late teens are more prone to familial ALS, whereas the probability of being infected by sporadic ALS is higher in usually in their mid-to-late fifties. Immune system abnormalities, glutamate toxicity, mitochondrial dysfunctions may be possible causes of ALS [22].

There are four main presentations of ALS are Primary lateral sclerosis (PLS) with pure UMN participation, limb-onset ALS (UMN and LMN type), progressive muscular atrophy (pure LMN implication), bulbar-onset ALS (associated with dysarthria and dysphagia) and as the disease progresses limb features abnormalities occurs. PLS implicates deterioration of the LMN type, and it is associated with speech impairments, spastic tetraparesis, and urinary urgency [22-24]. The manifestations of PLS include the successive amelioration of severe muscle spasticity and rigidity and prudent muscle atrophy [14]. The prime consideration of PLS being diagnosed as ALS requires confirmation of LMN malfunctioning of at least one limb or region, and in the majority of patients, it ended as ALS. At least two body regions are involved in the interpretation of ALS being diagnosed as limb-onset ALS. Relevant genetic testing should be done in the examination of progressive muscle atrophy (PMA), which can only be confirmed as ALS if altered at least two body regions that cancel out the possibility of other motor neuron disease [22]. The major types of motor neuron disorders and specified features with their clinical phenotypes are presented in **Fig. 2** [12, 15, 25-28].

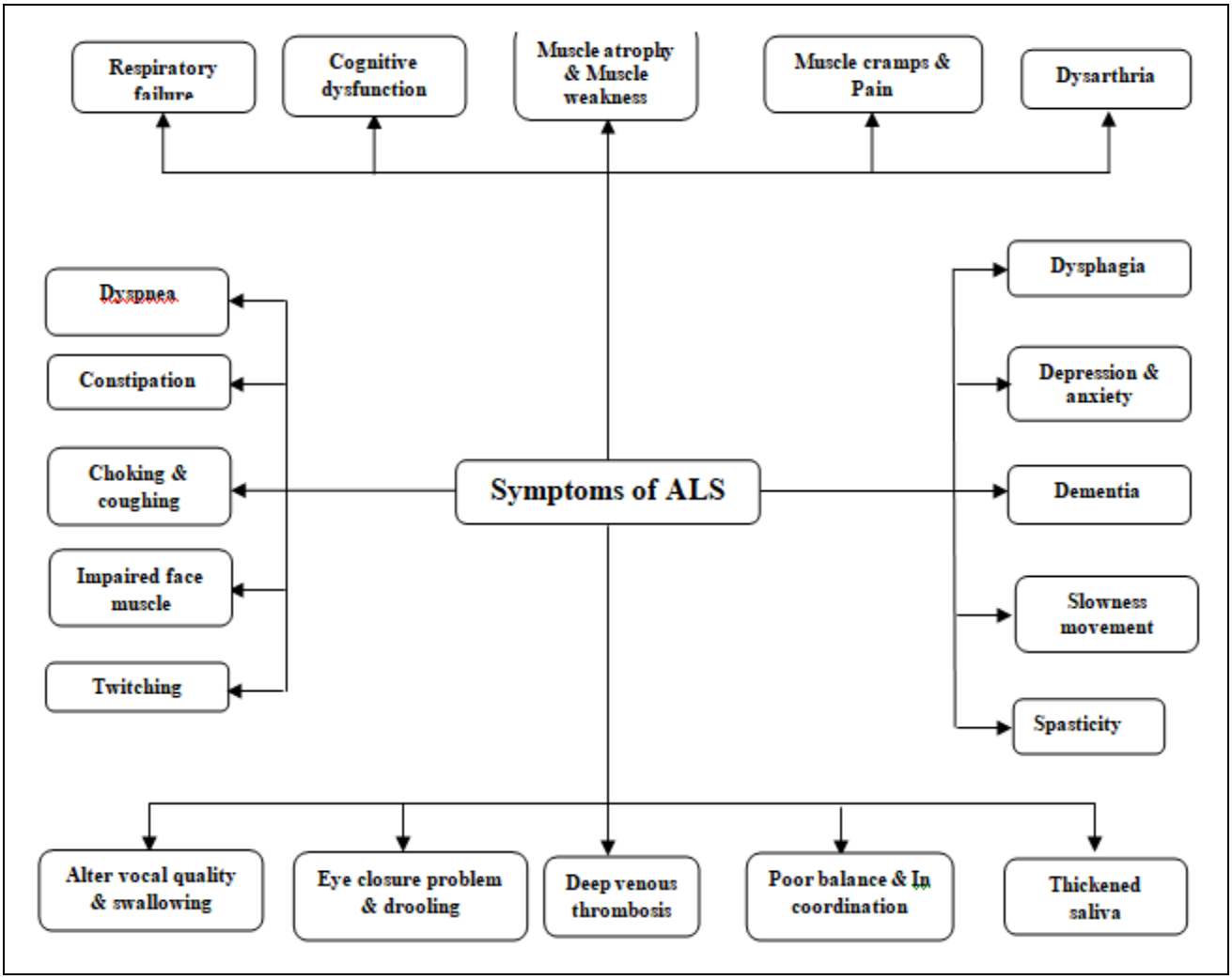

FIG. 1: CLINICAL FEATURES OF ALS

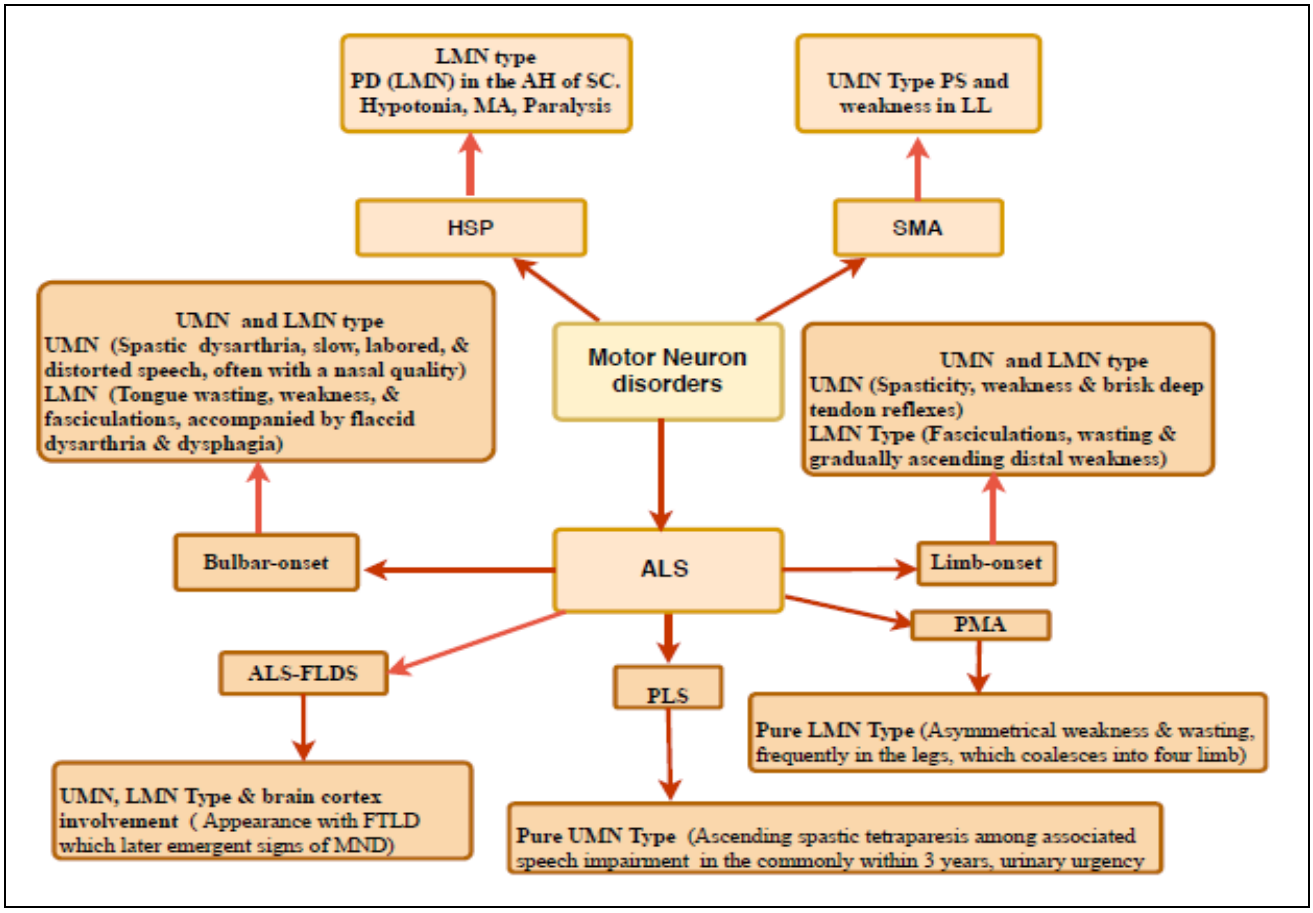

FIG. 2: VARIOUS TYPES OF MOTOR NEURON DISORDERS. PD: progressive degeneration; LMN: lower motor neurons; AH: anterior horn. SC: spinal cord PS: progressive spastkity; UMN: upper motor neurons: MNDs: Motor neuron disorders; SMA: Spinal muscular atrophy; ALS: amyotrophic ateral sclerosis; HSP: hereditary spastic paraplegia; PLS: Primary lateral sclerosis; PMA Progressive muscula atrophy; FLDS: ALS-frontal lobe dementia syndrome ; FTLD: frontotemceal lobar degeneration ; Mk Muscle atrophy): Paralysis; IL: Lower Limb

Pathophysiology of ALS: The oxidative stress, axon dysfunction (transport and retraction), mitochondria dysfunction, aberrant protein homeostasis, defective RNA processing and formation of cytoplasmic inclusion, protein aggregation, neuroinflammation excitotoxicity, oligodendrocyte degeneration, and microglia activation are the various factors involved in the pathophysiology of ALS [9-14]. The impaired protein homeostasis, aberrant RNA metabolism is the chief element linked to multiple genes in ALS which leads to neuronal injury. The mutation in CHCHD10 gene can lead to mitochondrial dysfunction and protein aggregates which give rise to the deficiency of respiratory chain under the influence of others causing ALS related mutations. Both factors can cause an increase in the oxidative stress that ultimately affects the system of protein homeostasis. The dysfunction of astrocytes EAAT2 leads to impaired glutamate excitotoxicity, which further causes mitochondrial dysfunction.

The proinflammatory cytokines and reactive oxygen species secrete from the activated microglia M1 cause the inflammation. Glutamate-induced excitotoxicity is involved in the pathophysiology of ALS. Neurodegeneration is caused by the generation of free radicals, which leads to impairment in the proinflammatory mediators and intracellular organelles [17, 20-24, 26-29]. The common pathophysiology mechanism cascade involved in ALS is summarized in **Fig. 3**.

Motor neuron degeneration results in over-activation of glutaminergic receptors present in the post-synaptic neuron, and the postsynaptic glutamate receptor activation may ascribe to reduced uptake of glutamate by astrocytic processes. This leads to an influx of considerable Ca^{2+} through ionotropic receptors and enhancing intracellular Ca^{2+} levels that result in activation of digestive enzymes (proteases, nitric oxide synthase and phospholipase-A_2. Augmentation in intracellular

Ca^{2+} leads to depletion of mitochondrial function, causing generation of free radicals, depletion of adenosine triphosphate formation and combined with ATP production impairment, nitric oxide etc., leads to Na^{+}/K^{+} pump inactivation, enhancing intra-cellular Na^{+} concentrations, causing depolarization of neurons. As a repercussion, Na^{+}/Ca^{2+} exchange may work reversely to endeavor normal intra-cellular Na^{+} concentration, but due to influx of Ca^{2+} may augment the previously raised intra-cellular Ca^{2+} concentration. Excitotoxicity may lead to degradation of axonal transport. Moreover, the production of aggregates in the cytoplasm (TDP-43, SOD-1, and FUS gene mutations) caused neurodegeneration by unspecified disease mechanisms. Microglia intrusion indicates the progression of neuroinflammatory processes that may intensify excitotoxicity by inflammatory cytokine generation [29-33]. Rothstein *et al.,* found elevated levels of glutamate in the cerebrospinal fluids of patients suffering from ALS. It was concluded from the study that glutamate, which mediates excitotoxicity, plays a key role in the degeneration of motor neurons [30]. Extreme glutamate levels stimulate the AMPA and NMDA presynaptic glutaminergic receptors, which leads to the excitotoxicity through the increase the Ca^{2+} ions, enter the cell [30-33]. Increased Ca^{2+} influx level in cells activates enzymes like phospho-lipases, endonuclease, and cabin as protease. These processes lead to the injury of the neurons and death of cell [31]. Rothstein *et al.,* accounted for the deficit of particular EAAT2 glutamate transport in ALS patients [29]. The atypical splicing of EAAT2 mRNA due to deficit of EAAT2 in affected areas of CNS causes the increased glutamate synapses extent [26]. ALS pathogenesis is associated with glutamate-induced excitotoxicity [33]. Generation of free radicals is a consequence of glutamate-induced excitotoxicity, which results in damaging intra-cellular organelles and up-regulating pro-inflammatory mediators, thus causing neurodege-neration [34, 35]. In relation to glutamate-induced excitotoxicity, structural mitochondrial defects, Na^{+}/K^{+} ion pump dysfunction, altered the system of axonal transport, and autophagy are involved in ALS pathogenesis [36-39].

Mitochondria play a major role in the regulation of cellular metabolism, Ca^{2+} signaling, calcium homeostasis, maintenance of membrane potential, and production of ATP [40]. Impaired intracellular signals such as membrane potential, Ca^{2+} homeo-stasis, bioenergetic and myophagy cause the neuronal death and ultimately lead to mitochondria dysfunction. Several defects in function as well as the structure of mitochondria, such as lack of respiratory control, reduced membrane potential, decreased consumption of oxygen and impaired respiratory functions found in mitochondria of astrocytes of genetically mutated SOD1-G93A rats [41]. Astrocytes and microglia directly caused neurodegeneration by various processes (inadequate release of neurotoxic mediators, neurotrophic factors and glutaminergic receptor modulation). Progressive neurotoxicity caused by microglia dysregulation and its over activation [42, 43].

Axonal transport is accountable for the transport process of various cell organelles, proteins, mitochondria, and lipids in between the neuron cell bodies and axonal cytoplasm. In ALS, the dysfunction of occasional functions and accumulation of organelles in the cell body and other proteins are the main factors which contribute to the pathogenesis of disease. The main cytoskeleton protein in the motor neurons is neurofilament (NFs) and they play a major role in maintaining structural support to the axon, axonal growth and regulating axonal diameter. The unusual accumulation of NFs in the cytoplasm responsible for the motor neurons degeneration and overexpression of the NFs cause the occasional atrophy, dysfunction of motor neurons and peripheral accumulation of NFs[44]. Oxidative stress plays a major part in neurodegenerative disorders. Oxidative stress damages the DNA, lipids and proteins in the tissue of the CNS of transgenic mouse models of FAS expressing SOD1 [35].

The primary cause of disability among patients is muscle weakness. The spinal muscular atrophy, the other age-related cachexia and spinal bulbar muscular atrophy are the major contributors of muscle weakness**.** Several studies indicate that neurobiological changes in brain regions such as the motor cortex, corpus callosum, sensorimotor, premotor, prefrontal, thalamic regions, anterior temporal cortices etc. implicated in ALS, which impaired the cognitive levels, atrophy, compen-satory cortical plasticity, neuronal loss, degeneration, decrease executive functions.

The GABA, serotonin, astrocytes, and activated microglia associated with the brain regions implicated in the ALS [44-54]. The various brain regions affected in ALS which affect the cognitive domains are summarized in **Fig. 4** [11, 44-54].

The neurodegeneration mechanisms underlying ALS are multifactorial and interrelated molecular and genetic pathways. Distinctly, neurodegeneration in ALS may be an outcome of complicated interlinks age of various disease mechanisms associated with mutations of several genes. A majority of gene mutations such C9orf72, SOD1, TARDBP and FUS are recognized to be linked with the disease mechanism of ALS. The various factors involved in the pathophysiology disease mechanism of ALS are summarized in **Table 1,** and the various genes associated with the disease mechanism in ALS are summarized in **Table 2**.

Several disease mechanisms associated with several gene mutations play a major role in the pathophysiological mechanism of ALS. Through targeting the predominant factors in disease mechanism with associated gene mutations, can be base for therapeutic remedies of ALS and play a key role in the development of better management of this complex neurodegenerative disease.

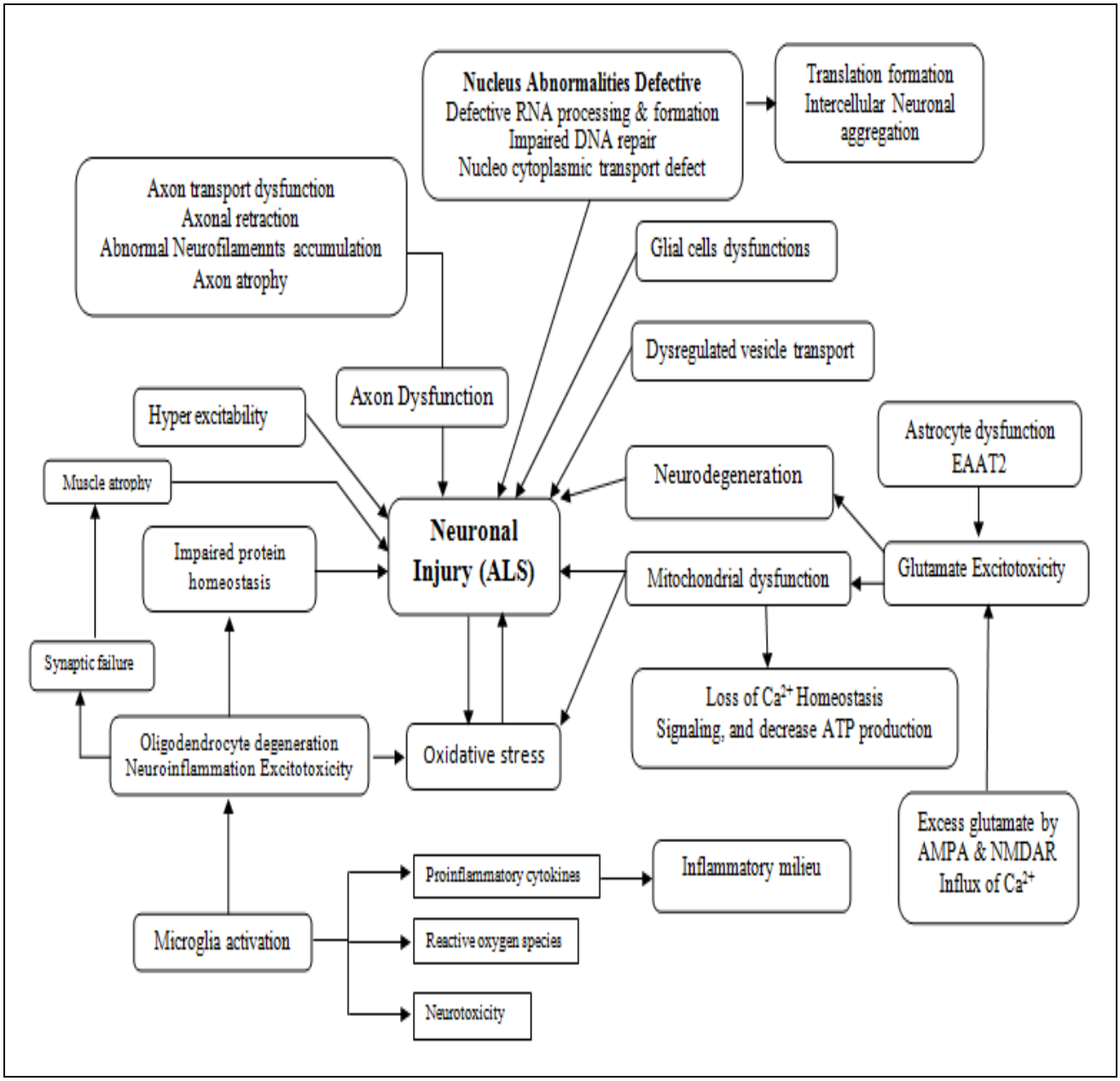

FIG. 3: PATHOPHYSIOLOGY MECHANISM IMPLICATED IN ALS

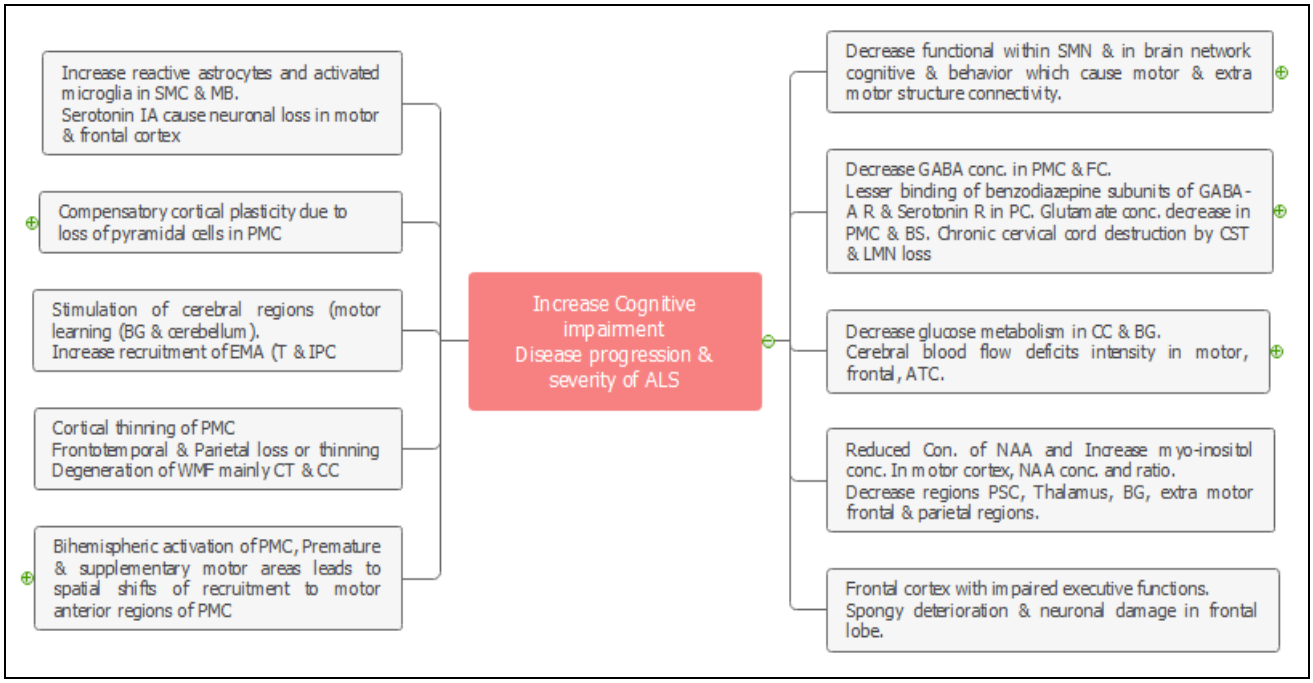

FIG. 4: THE COGNITIVE DOMAINS TYPICALLV AFFECTED IN THE ALS PMC. Prirrery Motor cortex; CC Cerebral Cortex; WMF: Whitte mater fibres; EMA: Extra Motor Area; NAA: N-acetyl as partate; PSC Primary sensory cortex; BG: Basal ganglia; SIC: Sensori Motor Cortex; CT: Corticospi nal tract ; LMN: Lower Motor Neuron; GAGA-AR: Gama amino butyric acid -Areceptors; MEI: Mid brain; MTC Medial Temporal Cortex; PC: Pyramidal cells; SMN: Sensori Motor Network ATC: /InteriorTemporal Cortices; T: Temporal; IOC: Inferior Parietal Cortex

TABLE 1: PATHOPHYSIOLOGICAL MECHANISM IMPLICATED IN ALS

Predominant factors	Pathophysiological mechanism implicated in ALS
Impaired protein homeostasis	ALS leads to disrupted protein turnover by causing mutations in some genes which are involved in the misfitted proteins translation and are abruptly formed and possess atypical cellular compartmentation that diminishes the autophagic or proteasomal cellular machinery. The substrate delivery of UBQLN2 to the proteasome is retarded in the proximity of disease mechanism-associated gene mutations. Besides, SOD1 and TARDBP mutations associated with ALS show dysregulation of chaperone proteins [55-63].
Protein Misfolding	Protein misfolding and accumulation is the cause of neuronal aggregates. The major role of the protein is in mRNA stability, pre-mRNA splicing, regulation of target RNA metabolism, and transport. The alteration in the phase separation properties of TDP-43 represents the main mechanism of RNA mis- processing [16].
Protein aggregation	Presence of some protein aggregates within neurons, involving SOD1, FUS, and TDP- 43. It is expected that the aggregates cause cellular stress and alter normal protein homeostasis (proteostasis). The accumulation may segregate RNA and other proteins vital for proper cellular functioning. The physical consequences of these aggregates include disrupted protein degradation, collapse of ubiquitin-dependent protein degradation, and impaired axonal transport. Misfolded proteins cause enhanced energetic exhaustion of motor neurons [55].
Aberrant RNA metabolism	Mutations in FUS61, C9orf72 and SOD1 causes disruption of gene expression, including alternative splicing of mRNA, changes in transcription, biogenesis of microRNAs and axonal transport of mRNAs. ANG, TARDBP and FUS are the genes which are involved in the ALS progression and these genes are related to RNA metabolism. Apart from them, several ALS- associated proteins are involved in RNA processing which includes SETX and ELP3. The disrupted microRNA expression and processing is indicated as a mechanism of ALS progression. Hence, microRNA (stable in the plasma and serum) represents a potential biomarker in this disease [31, 64, 65].
RNA processing	The mutated genes such as TARDBP and FUS and the role of TDP- 43 in ALS patients contribute to the findings of impaired RNA processing in ALS. Both the genes are involved in RNA translation, RNA transport and pre- mRNA splicing. The pre-mRNA comprising the C9orf72 gene mutation may block NRNA BP, which then are unable to bind with appropriate splicing of other mRNAs. RNA processing genes causes disrupted organization of microtubule and abnormal axonal transport in ALS [66-69].
Endosomal	TDP- 43 is a DNA binding- protein that is involved in the control of endosomal trafficking.

& vesicle transport	Endosomal and vesicle transport are affected by other ALS-associated gene variants, such as mutations UNC13A (responsible for priming synaptic vesicles and thus contributes in neurotransmitter release. The ALS2 variants is associated with endosome trafficking and fusion [70, 71].
Axon structure and function	The structural abnormalities in axonal transport are observed in ALS pathophysiology associated with mutated (TUBA4A, PFN1and DCTN). Besides, NEFH polypeptide has also been found to be mutated in a few patients of ALS. However, implications of these mutations to be involved in the pathogenic mechanism of ALS, which is due to axonal transport dysfunctions, are yet to be found [72-74].
DNA repair	Impairment in DNA repair is associated with FUS mutations and thus possesses a role in ALS pathophysiology. However, the exact mechanism of dysregulation of DNA repair needs to be interpreted. It was suggested that mutations in genes encoding for proteins NEK1 and C21orf2 cause defects in DNA repair, although their pathways need to be endorsed [75-77].
Excitotoxicity	As motor neurons have reduced calcium buffering ability, they are more prone to toxicity caused by calcium influx due to stimulation of glutamate, and AMPA receptors contains less GluR2 subunit, thus are more calcium-permeable than the neuronal subtypes [78-83].
Oligodendrocyte degeneration	Oligodendrocyte degeneration is visualized in ALS. Usually, oligodendrocytes are involved in providing support to the axons by transporting lactate through the monocarboxylate transporter 2. Oligodendrocyte dysfunction implicates motor neuron axonopathy in ALS [84-86].
Neuroinflammation	Neuroinflammation and immune response correlate in ALS: the early immune response leads to a release of protective cytokines and immune polarization, which includes activation of T-cells, dendritic, microglia, and antigen-presenting cells in the motor cortex and in corticospinal tracts of the spinal cord. There is a release of inflammatory markers like cytokines, ferritin, and C-reactive protein. The later response is destructive and accelerates disease progression by the release of monocytes and neutrophils [11, 31].
Mitochondrial Dysfunction	Mitochondrial dysfunction accounts for increased levels of peroxynitrites, superoxides, and nitric oxide. In ALS, implications are made regarding the ineffectiveness of mitochondrial quality control' or enormous workload compelled by chronic and extensive mitochondrial damage. VDAC1, is a physiological receptor of HK. HK1 could be acknowledged for effective therapeutic targets in ALS (the reduction in HK1 concentration enhanced) are involved in the bioenergetics of motor neurons. Interaction of mutant SOD1 with VDAC1 caused mitochondrial dysfunction and cell death. Mitochondrial intermembrane space gets aggregated with mutant SOD1, causing disrupted mitochondrial function, which is attributed to motor neurons vulnerability, hyperexcitability, and fasciculations in patients of ALS [31, 59, 86-88]
Oxidative stress	Oxidative stress is a major biomarker for the pathogenesis of neurodegenerative disorders such as ALS. Primarily, SOD1 gene mutations are supposed to contribute in oxidative stress by altering superoxide dismutase function. Later, it was found that oxidative stress acts as a secondary competent in disease progression [5, 9]

VDAC1: Voltage-dependent an ion channel isoform 1; HK1; Hexokinase 1; VCP: valosin-containing protein; UBQLN2: ubiquilin-2; TER ATPase transitional endoplasmic reticulum ATPase; VAPB: vesicle-associated membrane protein-associated protein B/C; SRSF1: serine/arginine-rich splicing factor 1; NXF1 : nuclear RNA export factor 1; NEFH : neurofilament heavy poly peptide UNC13A : protein UNC-13 homologue A; AMPA : α--amino-3-hydroxy-5-methyl-4- isoxa zolepropionic acid ; NRNA BP nuclear RNA- binding proteins; SETX: senataxin; ELP3: Elongator protein 3; TARDBP: TAR DNA binding protein

TABLE 2: GENES MUTATIONS ASSOCIATED WITH DISEASE MECHANISM IN ALS

Gene Mutation	Genes mutations associated with disease mechanism are involved in ALS
SOD1 Gene Mutations	The main site of SOD1 enzyme is cytoplasm; however it is also localized in, the nucleus, mitochondria, and lysosomes. These gene mutations associated with disease mechanisms such as ROS, oxidative stress, protein aggregates, dysregulated vesicle transport, glial dysfunction, mitochondria damage, neuronal death. Cytoplasmic, axonal transport dysfunction due to augmentation of intracellular aggregates and hyperexcitability [28, 32-37, 55, 56, 87]
TARDBP Mutation	It has been reported that ALS accounts to the depletion of functional TDP-43. The gene mutation is linked to RNA metabolism; protein aggregates cause neurotoxicity. Mutation of TARDBP associated with FUS genes mutation also lead to impair the neurons [28, 58-61]
TARDBP	The conditions such ALS and a subgroup of FTD have been observed with the presence of TARDBP/ TDP-43, that is abundantly localized in the alpha- and tau-synuclein-negative, ubiquitinated, cytoplasmic aggregates or inclusions. TDP-43, being a DNA- and RNA-binding protein, mediates transport, stability, transcription, mRNA splicing, oxidative stress, and mitochondrial dysfunction**.** TDP43 mutations may lead to protein dysregulation. The accumulation of the intraneuronal protein aggregates generally contain the TRA DNA binding protein, and other proteins may aggregates which comprise of superoxide dismutase and neurofilaments [26, 28, 32, 37].

TBK1 Mutation	The TBK1protein being a multifunctional kinase. It phosphorylates a series of proteins associated with autophagy and innate immunity, and optineurin (OPTN). Malfunctioning due to mutations or missense mutations in TBK1 are linked to loss of interactivity with its adaptors or diminished protein expression. It is associated with impaired protein homeostasis [9, 45, 46].
C9orf72 Mutation	*C9orf72* is the utmost genetic variant recognized in patients with ALS. Patients with behavioral variant FTD experience improper social behavior, perseveration, unusual eating patterns, disinhibition and OCD behaviors and loss of empathy. With respect to repeat expansions of C9orf72, several variables are likely to be associated with neuronal damage, and the destructive function of C9orf72 may play a considerable role in disease mechanisms. It is linked to the implicated mechanism of RNA metabolism and autophagy, glial dysfunction [22, 29, 55]
FUS	It is a nucleoprotein that mediates DNA and RNA binding, gene expression, mRNA splicing. FUS mutations are associated with instant progression, young-onset, and prominent bulbar symptoms and are associated with impaired DNA repair. About 5% of patients with familial ALS have been observed with FUS [30, 87]
CHCHD10 genes mutation	It is linked to the implicated mechanism of mitochondrial maintenance. *CHCHD10* mutations, which are associated with familial ALS, can promote the loss of mitochondrial cristae junctions, impair mitochondrial genome maintenance, and interfere with apoptosis by preventing cytochrome *c* release [26, 88]

SODI: Superoxide Dismutase 1); TARDBP: TAR DNA binding protein; FTD: frontotemporal dementia; TBK1: TANK- binding kinase 1; FUS: Fused in sarcoma/translated in liposarcoma; TARDBP/ TDP-43: Transactive response (TAR) DNA-binding protein 43 (TARDBP/ TDP-43); f -ALS familial amyotrophic lateral sclerosis; ROS: reactive oxygen species; *CHCHD10* (coiled-coil-helix-coiled-coil-helix domain-containing 10

CONCLUSION: ALS is a fatal neurodegenerative disorder in which the functions of lower and motor neurons are impaired. Neuronal dysfunction is the main symptom of neurodegenerative disorder which ultimately leads to the death of cells. The various mutations of genes like c9orf72, TARDBP, SOD1, and FUS and associated with several predominant disease mechanisms such as oxidative stress, axon dysfunction, mitochondria dysfunction, aberrant protein homeostasis, defective RNA processing and formation of cytoplasmic inclusion, endoplasmic reticulum stress endosomal dynamic dysfunctions, protein aggregation, neuroinflam-mation, excitotoxicity, oligodendrocyte degeneration and microglial activation are responsible for the disease. Through the understanding of various disease mechanisms involved in the base of the pathophysiology associated with several gene mutations and brain regions impaired in ALS, a suitable therapeutic approach towards the management of the disease can be obtained through targeting these mechanisms of disease progression.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: All the authors declare no conflict of interest.

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How to cite this article:
Arya A, Tyagi P, Yadav S and Kadian R: Amyotrophic lateral sclerosis: rapidly accelerating complex neurodegenerative disease. Int J Pharm Sci & Res 2021; 12(6): 3078-89. doi: 10.13040/IJPSR.0975-8232.12(6).3078-89.