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REVIEW BASED BOOK CHAPTER

PATHOPHYSIOLOGY AND TREATMENT APPROACHES FOR AMYOTROPHIC LATERAL SCLEROSIS (ALS): A NARRATIVE REVIEW

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Abstract

A complicated neurodegenerative disease, amyotrophic lateral sclerosis (ALS) mostly affects motor neurons, resulting in a gradual weakening and atrophy of muscles. This review focuses into the pathophysiology of amyotrophic lateral sclerosis (ALS), providing insight on the complex genetic and molecular pathways at work and the ways in which it overlaps with frontotemporal dementia. Oxidative stress, excitotoxicity, mitochondrial dysfunction, disruption of axonal transport, neuroinflammation, DNA damage, and poor protein homeostasis are key pathological characteristic features of amyotrophic lateral sclerosis (ALS). Important hereditary factors include mutations in genes such as SOD1, FUS, and C9ORF72. About 15% of amyotrophic lateral sclerosis (ALS) patients also show signs of frontotemporal dementia, in addition to the characteristic motor symptoms and cognitive and behavioral abnormalities. The condition is characterized by aberrant TDP-43 or FUS protein aggregates, and the C9ORF72 gene mutation is the most prevalent genetic component. Physical therapy, dietary therapies, and respiratory support are all parts of the multidisciplinary care that is currently available to patients in an effort to reduce symptoms and enhance their quality of life. Gene therapies and novel pharmacological medicines that target specific disease pathways are among the novel treatments being researched. In order to address the complex nature of amyotrophic lateral sclerosis (ALS) and enhance patient outcomes, the field is shifting towards early intervention techniques and personalized medication.

Keywords
Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia, C9ORF72 Gene, Neuroinflammation, ALS Therapy

Introduction

A form of motor neuron disease that often manifests in adults, amyotrophic lateral sclerosis, is often called a neuromuscular complaint due to the fact that its symptoms are characterized by a reduction in muscle strength and size. The medical community has been under pressure due to advancements within the last two decades in the fields of clinical, genetic, and molecular biology. Similar to ALS with regard to cognitive, behavioural, and motor impairment, frontotemporal dementia is a unique kind of neurodegenerative illness. Fifteen percent of ALS patients exhibit frontotemporal dementia, while the remainder patients have varied levels of dysfunction in thinking or acting [1]. But in primary progressive aphasia (18%) and behavioural variant frontotemporal dementia (15%), ALS is present [2, 3]. In the cerebral cortex, inappropriate aggregates of transcription factor 43 (TDP-43) or fused in sarcoma (FUS) form in the cytoplasm of neurons. In individuals of European heritage, this can result in frontotemporal dementia, ALS, or both [4-6]. C9ORF72 is the most common gene involved in this process. Thus, amyotrophic lateral sclerosis (ALS) is commonly perceived as a complex neurodegenerative disease that falls within the spectrum of frontotemporal dementia-motor neuron disease (MND) [7, 8]. The recent development of amyotrophic lateral sclerosis (ALS) among this group of disorders has provided new possibilities for investigating the pathophysiology of the disease and developing novel therapeutic strategies.

Loss of both lower and higher motor neurons, alterations in muscle denervation, and degeneration of the corticobulbar/corticospinal pathways are the main symptoms of ALS. TDP-43 proteinopathy is involved in around 97% of cases of ALS, where TDP-43 forms cytoplasmic clumps after mislocalizing from the nucleus [9-11]. On the other hand, it is due to mutations in the cu-Zn superoxide dismutase 1 (SOD1) or FUS proteins exhibits distinct cytoplasmic protein aggregation and does not contain TDP-43 [12-15]. The most common genetic variant is characterized by excess p62-positive aggregates from dipeptide repeat proteins (DPRs) and TDP-43 mislocalization. These are linked to hexanucleotide expansions in C9orf72 [16].

A battery of blood tests, spine and brain imaging to eliminate out structural pathology, and a neurophysiological evaluation are among the diagnostic procedures that are ruled out due to mimic disorders of ALS [17]. For the diagnosis of ALS, the updated. The criteria of El Escorial [18], AWAJI Shima's specifications [19], in addition to the streamlined Gold Coast norms [20] were added. An ALS-prone patient is most affected by neuromuscular respiratory failure produced on by non-invasive ventilation [21, 22].

Enhancing the dosage used to cure ALS is the goal of cellular therapy [23]. By energy conservation and stretching exercises, physical therapy assists with problematic symptoms of ALS, such as fatigue and muscle stiffness [24]. It has been demonstrated that PT drastically improves an ALS patient's quality of life [25]. Various physical, psychological, and cognitive difficulties are faced by people with ALS, which can make it challenging to provide each aspect of their care. More research is needed to create nonpharmacological treatments for ALS that could lessen the emotional impact that the disease has on patients and those who care for them [26].

Epidemiology

Worldwide, ALS probability and occurrence were determined to be 4.42 and 1.59 per 100,000 people, respectively. Geographically, south Asia has the lowest and western Europe the highest. The incidence of ALS increases year by 0.00013, and more males than women are affected [27, 28].

PATHOPHYSIOLOGY

Genetic Makeup

In 1993, familial ALS (fALS) was estimated to be caused by SOD1 mutations in 10–21% of ALS patients. As of right now, 60–70% of cases are identified as fALS [29]. However, ALS is usually brought on by a combination of hereditary and environmental factors in 90–95% of cases. Genetic factors can cause ALS even in individuals without a family history, but the majority of cases (90–95%) are sporadic and have an estimated 50% heritability [30]. Genome-wide association studies have revealed that rare alterations have a significant role in shaping the molecular structure of ALS. The categorization of ALS has evolved from simple fALS and sALS to an enhanced complex risk gene-based molecular sub

classification [31]. Nearly thirty genes have been linked to ALS. In European families, a significant portion of cases, around 70%, are familial and have connections to FUS, C9ORF72, SOD1, and TARDBP. A recent study has uncovered 15 previously unknown risk loci [32], emphasizing the fact that ALS risk and disease severity are genetically independent. Neuroinflammation, mitochondrial dysfunction, and oxidative stress play crucial roles in physiological mechanisms. Every ALS patient has experienced positive outcomes from thorough genetic screening, as 21% of them have shown harmful mutations that can be clinically reported, while another 21% have variations of unclear significance [32, 33]. Genetic profiling has the potential to replace the outdated classifications of fALS and sALS, leading to advancements in therapy development and drug screening. The age of onset can vary even among members of the same family who have the same genetic mutation; in some cases, the mutation can exist for over 50 years prior to the beginning of disease. This indicates more than one process influenced due to a mixture of hereditary, behavioural, and ecological variables [34].

Oxidative Stress

Presently, significant existing research suggesting that vital significance of oxidative damage within the development of ALS, along with the compromised ability to defend against oxidative stress in the disease. This involves disrupting the cytoprotective system mediated by the antioxidant response element (ARE) on nuclear factor erythroid 2-related factor 2 (Nrf2), as well as glutathione homeostasis [35-40]. It has been demonstrated that both human ALS specimens and models of the illness exhibit changed oxidative stress biomarker profiles [41]. Aggregates of acetylated TDP-43 are enhanced by biochemical and cell-based methods, even though acetylation of TDP-43 prevents RNA binding and encourages the formation of hyperphosphorylated TDP-43 species, which are comparable to the harmful inclusions observed in the central nervous systems of ALS patients and in human ALS bio samples [42]. The phosphorylation of TDP-43 by GADD34 is enhanced by prolonged oxidative stress [43]. When TDP-43 aggregates in the cytoplasm, mitochondrial function is dysregulated [44]. Oxidative stress plays a role in the interaction between nearby astrocytes, microglia, and motor neurons [45, 46]. In a specific case, data suggests that astrocytes upregulate the

antiporter for cysteine and glutamate in reaction to elevated oxidative stress, which releases glutamate and can result in motor neuron excitotoxicity [47, 48].

Excitotoxicity

In ALS, excitotoxicity is caused by excessive postsynaptic glutamate receptor activation [49]. Prolonged elevation of glutamate at synapses in motor neuron excitotoxicity activation, increases amounts of calcium within cells, and inhibits the glutamate–cysteine antiporter, which lowers cysteine absorption. Long-term pathological alterations carried on by excitotoxicity include mitochondrial calcium excessive and ER stress [50-52]. In motor neurons that are affected by ALS, excitotoxic damage is more likely to occur because of decreased the expression of proteins that buffer calcium and increased expression of calcium-permeable AMPA receptors [53]. Metabolic glutamate receptors are becoming new potential therapeutic targets in ALS because of the possibility that their control will both reduce glutamate release and stimulate neurotrophic factor synthesis (NTFs).

Mitochondrial Dysfunction

Patient biosamples and ALS model systems describe disruptions to the mitochondria (axonal transport, structure, and dynamics), excessive production of ROS and decrease in ATP, disruption of calcium buffering, and induction of apoptosis [54, 55]. Several pathways have established a connection between mitochondrial dysfunction and mutations in certain amyotrophic lateral sclerosis (ALS) genes [56]. Numerous medications that target reactive oxygen species (ROS) and/or mitochondrial function, including creatine, coenzyme Q10, dexpramipexole, olesoxime, and dexpramipexole, performed well in animal models used for research but failed human trials [57].

Impaired Protein Homeostasis

Protein synthesis and degradation remain in control by a complex network that reacts to stress signals. This network includes the cytosolic heat shock response, unfolded protein responses in the endoplasmic reticulum (ER), and mitochondria [58]. Protein aggregates and a compromised proteome are hallmarks of age-related neurodegenerative disorders including spinal cord injury (the condition). Dysfunctional

proteostasis is a key component in the pathogenesis of amyotrophic lateral sclerosis (ALS), and several proteins associated with the disease either directly or indirectly control proteostasis [58-60]. Specifically, maturation is regulated by ubiquilin 2, alsin, FIG4, VCP, and CHMP2B, whereas autophagy initiation is dependent on ubiquilin 2, optineurin, sequestosome 1/P62, and C9ORF72 [61]. Motor neurons are particularly vulnerable to proteome stress due to their large size, minimal heat shock response, and restricted expression of ubiquitin proteasome genes. One of the main characteristics of ALS is intracellular protein aggregates, particularly TDP-43 mislocalization, which causes abnormal splicing, increases DNA damage, changes the transcriptome, and impairs axonal translation [62, 63]. UNC13A mRNA has cryptic exon inclusion due to TDP-43 loss from the nucleus, which lowers UNC13A protein expression and may have an impact on vesicle development and neurotransmitter release [64, 65].

Neuroinflammation and Glial Contribution

Inflammation of the nervous system or brain pathogen-induced cause of the preclinical stage of ALS [66]. Astrocytes control inflammatory signalling and maintain the integrity of the blood-brain barrier by the production of either pro- or anti-inflammatory cytokines, such as prostaglandin E2 and transforming growth factor (TGF)-β [67-69]. Motor neurons cocultured with astrocytes generated from fibroblasts from ALS patients are hazardous to them [70]. The specific ways this toxicity occurs are still unknown, however decreased bioenergetic support due to lactate release and activation of the pro-nerve growth factor-p75 receptor are possible causes [71]. One major process of neuroinflammation in amyotrophic lateral sclerosis (ALS) is the activation of the microglial NLRP3 inflammasome. Regarding its possible use as a therapeutic target, NLRP3 inhibition has one that potential to decrease microglia-induced neuroinflammation and halt the progression of amyotrophic lateral sclerosis (ALS). The NF-κB protein is a master regulator of inflammation in persons with amyotrophic lateral sclerosis (ALS), according to recent discoveries [72].

DNA Damage and Repair

Oxidized deoxyguanosine (OdG) levels are greater in neurons and other postmitotic cells in central nervous system (CNS) tissues and biofluids from amyotrophic lateral

sclerosis (ALS) patients [73, 74]. New research has connected amyotrophic lateral sclerosis (ALS) to DNA damage response (DDR) activation and an increase in apurinic/apyrimidinic DNA sites, which are areas where DNA bases are damaged [75].

Impaired Axonal Transport and Integrity

In many models of amyotrophic lateral sclerosis (ALS) and across human patients, pathological buildups of organelles and phosphorylated neurofilaments within the terminals of motor neurons have been associated to defects in axonal transport [76]. New evidence suggests that amyotrophic lateral sclerosis (ALS) is the result of genetic mutations ANXA11 (a protein that hinders axonal RNA transport) and KIF5A (a protein that encodes a microtubule motor) [77, 78]. In SOD1-mutant rats, P38 MAPK inhibitors reverted back normal axonal transport, but in a targeted manner, IGF1R inhibitors improved the axonal transport of signalling endosomes. The presence of signalling endosomes in retrograde axonal transit is essential for maintaining axonal integrity [79, 80].

Advances in ALS Therapy

Multidisciplinary Care

American amyotrophic lateral sclerosis (ALS) patients may see a multidisciplinary team of healthcare professionals during a single clinic visit, including a pulmonologist, a speech-a social worker, a dietitian, a linguist, a physiotherapist, an occupational therapist, and an ALS specialist. An integrative strategy is used in the treatment of ALS. Connections to ALS/MND groups are made in order to obtain further assistance [81, 82].

Modulators of Disease

Excitotoxicity, oxidative stress, mitochondrial dysfunction, protein homeostasis, neuroinflammation, cell death, cytoskeletal integrity, axonal transport, DNA repair, RNA metabolism, and stress granule modulation have been the primary areas of emphasis for ALS therapy in the last 20 years [83, 84]. To ensure the effective development of ALS therapy, the worldwide ALS community must prioritize future initiatives such as improving data exchange, endpoint harmonization, and trial design and analysis and ensuring

equity of access. A treatment for amyotrophic lateral sclerosis (ALS) has been approved by the US Food and Drug Administration (FDA): a combination of sodium phenylbutyrate and taurursodiol. This medication targets mitochondrial malfunction, endoplasmic reticulum stress, and cell death [85]. Other approved medications include riluzole, an anti-glutamine medication [86], and edaravone, which decreases oxidative stress [87] does not have European approval with the purpose of addressing amyotrophic lateral sclerosis [88, 89].

Pulmonary Intervention

As mentioned earlier, the main cause of death for ALS patients is respiratory failure. For the treatment of amyotrophic lateral sclerosis (ALS), it is essential to do pulmonary tests such as spirometry, polysomnography, transdiaphragmatic pressure, sniff nasal pressure, arterial blood gas, and nocturnal pulse oximetry. Regular evaluations are crucial for spotting respiratory muscle weakness and facilitating early non-invasive ventilation intervention, both of which can improve survival and quality of life. Even though there isn't much thorough research on the advantages of mechanical insufflation-exsufflation, it's commonly used to help people cough and clear their airways. Research on integrating respiratory muscle training with swallowing exercises to improve coughing and swallowing is still ongoing [90, 91].

Diet and Nutritional Intervention

Reduction in ALSFRS-R scores is associated with a decrease in body mass [92]. Losing weight is complicated and associated with several problems, such as fatigue, hyper metabolism, dysphagia, reduced meal intake, and impaired dexterity of the limbs when using utensils [21]. A shorter survival time was linked to body mass index extremes (<18, >40), while the 30-35 body mass index range showed the best survival [93]. Most agrees that antioxidants, fruits, fiber, and carotenes should be included in the diet [94]. According to clinical guidelines, patients who have symptomatic dysphagia, prolonged feeding times, severe weight loss (more than 5–10%), and, in some situations, deteriorating respiratory function, should be evaluated for gastrostomy tube placement. Proper treatment, procedure scheduling, and patient selection are critical to the success of a gastrostomy. An excellent resource for ALS patients, caregivers, and

doctors, the Simplifying ALS initiative (www.alsuntangled.com) has evaluated the data for numerous dietary supplements and vitamins. Nevertheless, the majority of clinical trials have not shown a lower incidence of ALS progression [95, 96]. Studies have shown that vitamin E may protect against amyotrophic lateral sclerosis (ALS), and a recent phase 3 experiment found that treating patients with an ultrahigh dose of methylcobalamin (50 mg) somewhat slowed their clinical deterioration compared to placebo [56, 97, 98].

Emerging Treatments

An increase in ALS research treatments has occurred due to the ineffectiveness of FDA-approved drugs. The ALS platform trial makes use of a centralized infrastructure and a shared master protocol, enabling the simultaneous evaluation of several agents [99]. At least fifty tiny compounds are being studied for various uses. The FDA-approved medication tofersen (2023) has demonstrated efficacy in treating pathogenic gene expression in SOD1-ALS patients. Phase 1 studies are being conducted on gene therapy vectors that use adeno-associated viruses to reduce SOD1 levels, while phase 1-2 trials are now being conducted on antisense oligonucleotides that target C9ORF72 and FUS. Phase 2 trials are also evaluating monoclonal antibodies that target misfolded proteins.

Conclusion

Over the past twenty years, we have seen a significant advancement in basic ALS research. But one of the main reasons for patient and caregiver frustration is the absence of substantial progress in converting this amount of knowledge into practical treatments. By consolidating biomarkers, developing systematic and innovative clinical trials, and concentrating on early disease among carriers of pre-symptomatic gene mutations, the discipline is drawing nearer to translating fundamental scientific discoveries into treatments that affect disease. As with cancer therapeutics, the hope is that the larger population of people living with sporadic amyotrophic lateral sclerosis (ALS) can find a personalized solution that limits disability and allows them to live with dignity by identifying risk gene variants and finding ways to identify the dominant mechanism (e.g., pathogenic inflammation, activation of retro-transposons, and oxidative stress) serving as the agent responsible for spreading some diseases.

Conflicts of Interest

The authors declared no conflict of interest.

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