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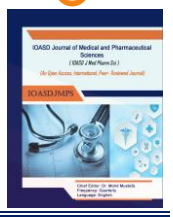

Amyotrophic Lateral Sclerosis: An overview

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease which characterized by pathogenic protein aggregates that correlate with the progressive degeneration of neurons and the loss of behavioral functions. It is now more often recognized as Lou Gehrig's disease in the US. ALS is an uncommon disease; diagnosis is often delayed because more prevalent conditions are taken into consideration before ALS. ALS has a about 1 in 350 lifetime risk. The genes responsible for 10% of sporadic ALS and two thirds of familial A physiology and causation are still mostly unclear. A common pathogenic characteristic of both familial and sporadic ALS is toxicity, which can also result from aggregation of both wild-type and mutant proteins. The goal of ALS treatment is to maximize quality of life and use disease-modifying treatments because the condition is still incurable. This review outline about the ALS disease and discuss the status of ALS in human neurons which may improve care and outcome for ALS patients

Keywords: Amyotrophic lateral sclerosis (ALS), neurons, sporadic Amyotrophic lateral sclerosis (SALS), familial Amyotrophic lateral sclerosis (FALS).

Review Article

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INTRODUCTION

A terminal neurodegenerative illness, amyotrophic lateral sclerosis (ALS) causes the gradual degradation of both upper and lower motor neurons that typically regulate voluntary muscular contraction [1]. ALS-affected neural system components that result in increasing symptoms in the body's skeletal muscles [2]. A degenerative, late-onset motor neuron disease. The disease's name comes from Charcot's observation in the lateral portions of the spinal cord of a distinct "myelin pallor," which represents the degeneration and loss of the axons of upper motor neurons as they descend from the brain to connect directly or indirectly onto the lower motor neurons within the spinal cord. The disease's main clinical features include the premature degeneration and death of upper and lower motor neurons, which causes fatal paralysis. Midlife is when the disease first appears, and it usually lasts one to five years. Originally named as Charcot's sclerosis, it is now more often recognized as Lou Gehrig's disease in the US. With a lifetime risk of roughly 1 in 1000, ALS's impact is underestimated when incidence and prevalence are taken into account [3, 4, 5].

The main neuropathological characteristics of ALS include reactive gliosis, which is the hypertrophy of glial cells in the motor cortex and spinal cord in the areas of degeneration, loss of Betz cells (large pyramidal cell neurons) in the primary motor cortex, degeneration of the lateral corticospinal tracts, that store the axons projecting from the primary motor cortex to the motor neurons, and extensive loss of lower motor neurons from the anterior horns of the spinal cord and brainstem [6, 7, 8]. When motor neurons in ALS gradually deteriorate, they ultimately die. Indeed, ALS is linked to a complex pathophysiology that includes endoplasmic reticulum stress, mitochondrial dysfunction, microglial activation, excitotoxicity, peripheral inflammation, neuron loss, muscle atrophy, oxidative stress, and synaptic remodeling [9, 10].

SYMTOMS OF ALS

During its early stages, amyotrophic lateral sclerosis (ALS), a deadly neurodegenerative disease of the central nervous system, can be hard to diagnose. ALS is an uncommon disease, diagnosis is often delayed

because more prevalent conditions are taken into consideration before ALS. ALS has a about 1 in 350 lifetime risk, while the prevalence is decreased by a short life expectancy [11]. The lifetime accumulation of environmental exposures, including lifestyle choices, is known as the ALS exposome. Several case-control studies have investigated how environmental risk variables related to employment, housing, and leisure affect the risk of ALS [12]. These cell populations' dysfunction and death cause gradual muscle weakness and atrophy, which eventually results in paralysis and death three to five years after the disease first manifests [13].

CAUSES OF ALS

About 10% of cases of ALS are familial, and they might be X-linked, autosomal dominant, or autosomal recessive. The great majority of ALS cases are categorized as sporadic, meaning that there is no known history of another family member having either ALS or frontotemporal dementia. Because of advancements in sequencing technologies, the list of genes that cause ALS has expanded significantly to over 40. The genes responsible for 10% of sporadic ALS and two thirds of familial A physiology and causation are still mostly unclear. Sporadic ALS, which makes up the bulk of ALS cases, is also believed to have a genetic component to its pathophysiology. Nevertheless, there hasn't been much progress in identifying gene abnormalities in SALS cases lately. Numerous organizations have published information on gene variations and correlation analyses discovered in people with sporadic ALS. Only a small percentage of all cases are explained by these studies that relate specific genetic variations to SALS. This suggests that there is a complex pattern of inheritance with extremely low penetrance, a high degree of heterogeneity, and/or the presence of environmental variables that cause ALS. FALS and SALS are not clinically different, with the exception of a small number of familial ALS cases when other neurodegenerative illnesses may occur concurrently. But there are a few small but intriguing variations. Compared to sporadic ALS, which typically manifests at age 56, family instances typically manifest around age 46 [14].

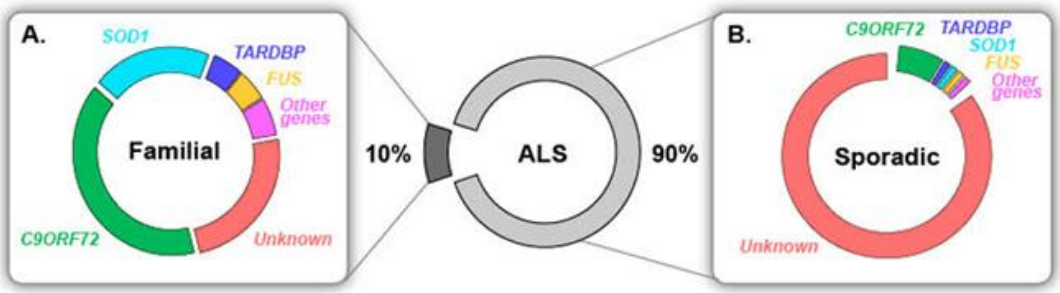

Figure 1

FALS has a male to female ratio of 1:1, whereas SALS has an unexplained male preponderance of 1.5:1 that is recorded globally, albeit this ratio tends to decline and approaches 1:1 beyond age 70 [15]. Family FALS was first identified as having a genetic etiology related to a mutation in Cu–Zn superoxide dismutase 1 (SOD1). Citation 4 Most SOD1 mutations are AD, have a highly penetrant inheritance pattern, and are mostly linked to ALS that develops in the limb [16].

PATHOPHYSIOLOGY OF ALS

Pathological processes in ALS are caused by toxic gain-of-function or loss-of-function mutations in the roughly 40 ALS genes that are now known to exist. A common pathogenic characteristic of both familial and sporadic ALS is toxicity, which can also result from aggregation of both wild-type and mutant proteins [17]. Impaired RNA metabolism, altered proteostasis/autophagy, cytoskeletal/trafficking abnormalities, and mitochondrial dysfunction are the four main categories into which pathophysiological processes can be generally divided [18]. Numerous studies have examined and emphasized the significance of various cell types, including as microglia [19], astrocytes [20], oligodendrocytes [21], muscles [22], Schwann cells [23], the neuromuscular junction (NMJ) [24], and the gut microbiota [25], in the pathophysiological basis of ALS.A surprising finding given the impact of undernutrition on energy balance and the defense mechanisms to reduce energy waste is that over 60% of patients with familial and sporadic ALS have higher resting and non-resting energy consumption, according to various studies [26, 27, 28]. According to a study with a sizable ALS patient population, being physically active was linked to a higher chance of developing ALS [29, 30]. According to the dying forward theory, which has been proposed as the basis for ALS, corticomotoneuronal hyperexcitability mediates neuronal degeneration by a transsynaptic anterograde mechanism [31]. It is crucial to note that some have proposed that cortical hyperexcitability is a compensatory reaction to degeneration of spinal motoneuron [32].

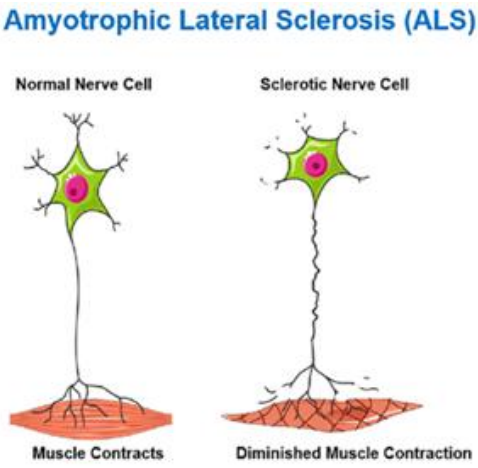

Figure:2

DIAGNOSIS

The diagnosis of ALS is clinical, in view of the set of experiences and actual assessment showing moderate upper and lower engine neuron brokenness. It is typically upheld by electrophysiological review and neuroimaging and research center tests to reject mimickers. The El Escorial rules have been created to normalize the analysis for clinical exploration [33]. Familial ALS is more easily identified when there is a positive family history; however, familial ALS may present as sporadic disease on account of incomplete penetrance or incomplete family history. In the absence of family history, an early age of onset, atypical rapid or slow disease progression, pure lower motor neuron presentation or the presence of dementia may alert to a familial etiology [34]. The disease starts with limb weakness in about two-thirds of patients, often preceded by cramps, and with bulbar weakness causing dysarthria and dysphagia in the remaining one-third. In rare instances, cognitive impairment, behavioral disturbances or early respiratory failure can be the initial manifestation of ALS. The characteristic combination of upper and lower motor neuron dysfunction is usually evident on neurological examination with the presence of weakness, atrophy and fasciculations together with hyper-reflexia and increased tone in the same motor segment and not infrequently an extensor response to plantar stimulation [35].

TREATMENT

The most common known ALS risk gene, C9 or f72, lowers the onset age in males compared to females [36]. Genetics also plays a part; heritability is higher in mother-daughter pairs [11] and ALS results from complex interactions between age, sex, and genetics, which has implications for preclinical and clinical research as well as clinical trials [37]. The goal of ALS treatment is to maximize quality of life and use disease-modifying treatments because the condition is still incurable. According to evidence-based and expert consensus guidelines for managing ALS published by the American Academy of Neurology, the European Federation of Neurological Societies, the National Institute for Health and Care Excellence (NICE) in the United Kingdom [38] and ALS Canada [39] supportive multidisciplinary care increases ALS patients' quality of life and survival [40]. Deciphering pathogenic pathways and identifying disease-causing molecules are necessary to develop therapeutic approaches for treating ALS. Numerous potential external factors have been studied, such as the usage of pesticides, viruses, cyanobacterial toxins, magnetic fields, heavy metals, a medical history, and lifestyle decisions [41,42]. To yet, however, a distinct environmental risk factor has not been discovered. More than 30 genes that cause ALS and frontotemporal dementia (FTD) have been found to have mutations since the original discovery of superoxide dismutase 1 (SOD1) as an ALS causative gene in 1993 [43]. This has been made possible by extensive research efforts and sophisticated genetic techniques [44, 45, 46, 47]. It has also been demonstrated that 147 distinct gene mutations in several pathways contribute to the pathophysiology of ALS [48,49].

CONCLUSION

ALS remains difficult to diagnose and manage. This is due to heterogeneous ALS presentation and phenotype, and symptom and sign overlap with other illnesses. Earlier on in the diagnostic process, physicians should refer patients presenting with progressive dysarthria, dysphagia, limb weakness, or respiratory failure to a neurologist.

It conclude that ALS is a neurodegenerative disease which effect the neurons and this condition is still incurable . It genetically transmitted disease from one generation to another generation. Recently research at Duke University found that a change in the IGFBP7 gene is more common in people who have experienced a reversal of MND. This change may make motor neurons more resistant to the mechanism that lead to motor death. We anticipate that these research efforts will translate into improved outcomes for current and future patients with ALS.

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