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REVIEW ARTICLE

The Genetics, Environment, And Molecular Mechanisms Behind Amyotrophic Lateral Sclerosis and How They Contribute to Frontotemporal Dementia

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ABSTRACT: Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease that affects both the upper and lower motor neuronal systems, located both centrally and peripherally in the cerebral cortex and spinal cord. Despite relating to separate areas of the central nervous system, 50% of ALS patients present with symptoms consistent with frontotemporal dementia (FTD), another neurodegenerative disorder that targets the frontal and temporal lobes of the brain. Currently, the etiology of both conditions is unknown however, over the years both disorders have been linked to various common possible origins such as the C9orf72 gene mutation. This paper reviews what is currently known about the causes and pathogenesis of both disorders, diving into the environmental factors and molecular mechanisms that result in the overall degeneration of neuronal cells.

KEYWORDS: Cellular and molecular biology, Genetics, ALS, FTD, Neurodegeneration.

Introduction

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a neurodegenerative disorder affecting upper and lower motor neurons in the spinal cord, brain stem, and motor cortex which are responsible for voluntary muscle movement. The frequency of ALS cases in Europe and North America is between 1.5-3 per 100,000 per year, with an average age of 55 years at the time of diagnosis.[1] The disorder in its early stages presents with muscle twitching and spasticity, however, as there is no known cure for ALS, all cases eventually result in paralysis and complete loss of organ functioning due to the disease's gradual muscle atrophy. The majority of ALS cases turn fatal 3-5 years after the initial appearance of symptoms due to the loss of neurons responsible for innervating respiratory muscles, causing respiratory failure. The main distinction of ALS from alternative forms of motor neuron disease (MND) such as primary lateral sclerosis or primary muscular atrophy is its influence on both the upper and motor neurons in tandem, hence classifying it as one of the most severe and common forms of MND. Additionally, non-motor-related signs, such as deficits in executive functioning have been discovered in patients with ALS, with around 15% of them developing a full diagnosis of frontotemporal dementia.[2]

Frontotemporal dementia (FTD) is another neurological disorder, characterized by the progressive deterioration of the brain's frontal and temporal lobes, causing them to shrink. Consequently, patients with FTD typically suffer from cognitive impairment, changes in behavior, and language deficits. Although the disorder does present with various subtypes, the behavioral variant of FTD is found to be the most commonly associated with motor neuron disease.[3] Over the years, ALS and FTD have been discovered to have a genetic continuum, with various links between potential mutated gene causes of both disorders, namely the role of the C9orf72 gene expansion, and others such as TARDBP and FUS. However, despite modern research, the etiology of both diseases remains unknown. With approximately 10% of ALS cases being caused by genetic mutations, 90% are categorized as sporadic.[1] In this paper, we holistically look at potential genetic causes of ALS, focusing on the specific genes that progress into FTD as well as the role of environmental factors that can promote this development.

Pathogenesis:

The exact pathophysiology of both ALS and FTD remains a mystery, but over the years, multiple pathways have been theorized by researchers. The typical model of hypothesis includes aspects of prion-like mutant protein aggregation in cells, as well as oxidative stress, an RNA gain of function (or lack of metabolism), and mitochondrial dysfunction. It is unknown which of these are causing, and which are resulting factors, but the appearance of them is a usual biomarker when diagnosing ALS and FTD. Other factors such as neuroinflammation- the reaction of glial (astrocytes, microglia) and immune cells in the context of neurodegeneration -have been proposed, but the lack of success in anti-inflammatory therapies has questioned this concept.

An Italian study found that a group of ALS patients treated using medication known as riluzole had a median extended survival period of about 5.8 months compared to a group of patients not prescribed with any riluzole (18.2 months vs 12.4.).[4] Due to the anti-excitotoxic properties of riluzole, the effectiveness of the drug in the delaying of symptoms proves that ALS may be connected to excitotoxicity. Classical excitotoxicity is when neurons become weakened or die due to increased exposure of neurotransmitters in the synapse, often resulting in an excessive influx of ions into the cell.[5]

During glutamatergic neurotransmission, the presynaptic neuron secretes glutamate, an excitatory neurotransmitter, into

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the synaptic cleft. In classical excitotoxicity, this can happen in one of two ways; 1) there is an elevated amount of glutamate released by the presynaptic neuron, or 2) there is an inefficient reuptake of normal levels of glutamate into astrocytes, due to damaged EAAT2 transporter proteins. In both conditions, high levels of glutamate in the synapse stimulate ionotropic glutamate receptors on the postsynaptic neuron to cause an influx of Na^+ and Ca^{2+} into the cell, resulting in neuronal cell death (Figure 1.) A mild increase in glutamate levels is thought to cause neuronal damage , however full neuronal degeneration is achieved when extracellular glutamate levels increase by around 2-5 μm.[6,7] Riluzole was found to inhibit the release of glutamate by inactivating Na^+ channels on nerve terminals. [8] (Bosch *et al.*) provides a review of the role of excitotoxicity in the progression of ALS.[9]

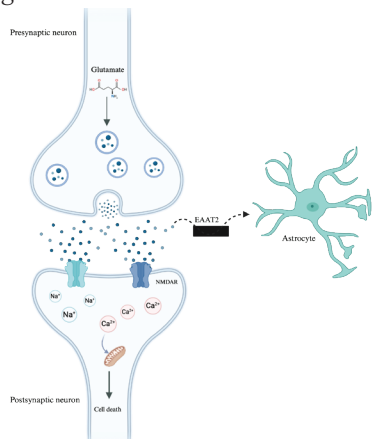

Figure 1: *Created in BioRender. Sp, C. (2024) BioRender.com/t37x209.* Ionotropic receptors are ligand-gated ion channels which enable the entry of ions into the postsynaptic neuron; AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors) are examples of these transmembrane receptors, and primary Na^+ ion channels that mediate excitatory synaptic transmission. NMDA receptors (N-methyl-D-aspartate receptors) are highly permeable Ca^{2+} channels. The excessive presence of Ca^{2+} ions in the postsynaptic neuron due to excitotoxicity can cause mitochondrial dysfunction, and the formation of reactive oxygen species (ROS) that mediate damage to intracellular components and lead to cell death.[10–12]

Death of neuronal cells is typically accompanied by the accumulation of ubiquitinated protein inclusions, which is discussed further in this paper. As neuronal degeneration progresses, eventually, muscle paralysis will spread to various regions of the body. The concept of excitotoxicity is also relevant in the context of FTD; excess glutamate in the synapse has been linked to the occurrence of seizures.[13,14] Seizures are found to appear in the later stages of FTD, suggesting that glutamate-mediated toxicity plays a role somewhere in the pathology of the disorder.

Whilst various starting points of ALS and FTD have been proposed, no clear knowledge on the biological progression and development of the disorders is currently known, impeding the discoveries of a singular cure in the medical field.

Genes:

The incidence of familial ALS makes up around 10% of all cases, proposing the idea that genetic mutations play a key role in the root cause of the disorder. Likewise, the percentage of familial FTD cases is around 10-20%. Multiple genes have been hypothesized as a source of each disease, with some genetic overlap being exhibited within the two disorders.

- ***C9orf72:***

In 2011, it was discovered that a mutation in the chromosome 9 open reading frame 72 gene (C9orf72) could be a leading cause of both ALS and FTD.[15,16] The gene, which is cytogenetically located at locus 9p21.2 contains a series of six nucleotide bases, made up of four guanines and two cytosines (GGGGCC) in the first intron. This is known as a hexanucleotide expansion and normally repeats <20 times in neurologically healthy individuals, however, has been found to repeat up to thousands of times in ALS and FTD patients. (Xi *et al.*) used a 2-step genotyping strategy to investigate the allele frequency of the hexanucleotide repeat expansions in four neurodegenerative disorders, including both ALS and FTD, where they were able to detect the expansion in 9.3% of ALS patients and 5.2% of FTD patients.[17] These results enabled researchers to conclude that the C9orf72 gene mutation is a strong potential cause of both familial ALS and FTD, thus proving the genetic overlap between the two disorders.

Researchers have utilized other repeat expansion disorders of different genes to link back to and investigate the mediated pathways into FTD and ALS from C9orf72. Currently, there are three main proposals on the effects of the C9orf72 repeat expansion: firstly, the idea that the expansion correlates to an RNA gain of function, where the sequestration of RNA binding proteins occurs due to the presence of the mutation transcribed into mRNA, which can result in RNA metabolism and splicing deficits.[18] Secondly, it has been theorized that the expansion induces repeat associated non-AUG (RAN) translation, causing the accumulation of dipeptides in the brain and spinal cord, contributing to neurotoxicity.[19–21] Thirdly, the reduction of regular C9orf72 expression, leading to functioning deficits in cells.

It is still uncertain to researchers what the pathophysiology occurring from this gene mutation is, however, the C9orf72 mutation remains one of the strongest gene advocates for familial ALS and FTD.

- ***TARDBP:***

TAR DNA binding protein 43 (TDP-43) is an RNA/DNA binding protein encoded by the TARDBP gene on chromosome 1. The protein is responsible for many RNA-related metabolic functions, including transcriptional regulation, alternative splicing and therefore gene expression. In 2006, TDP-43 was first identified as a key part of brain and spinal cord inclusions that were found in ALS and FTD patients.[22,23] Mutations in the TARDBP gene most commonly associated with ALS occur on exon 6, which codes for the C-terminal region of the TDP-43 protein, a glycine-rich region heavily involved in protein-protein interactions. These C-terminal mutations specifically were found to increase the intrinsic tendency of TDP-43 to aggregate and lose solubility,[24] leading to a disruption of stress granules. Additionally, the C-terminus was indicated to play a role in cellular localization, as mutations in it resulted in a loss of presence of TDP-43 in the nucleoplasm where it is predominantly localized, and instead caused it to be deposited in cytoplasmic regions in the brain

and spinal cord neurons,[25] causing a loss of TDP-43 function. This accumulation of large, mutant, insoluble TDP-43 protein aggregates in neurons is known to cause cellular toxicity, injury, and eventually death in various neurodegenerative disorders. Interestingly, it was found that 97% of all ALS cases and 45% of FTD cases involve TDP-43 protein aggregation.[26,27]

(White *et al.*) injected mice with mutant TDP-43, finding that the mice then displayed a decline in both motor and cognitive skills, further suggesting that the aggregation of TDP-43 is a key contributing factor to ALS and FTD.[28]

Through modern research and types of DNA sequencing, sufficient evidence has been presented showcasing evident genetic mutations in ALS and FTD patients. It is extremely possible that the disorders can be inherited through a familial link, or that patients may be susceptible to a genetic predisposition of the diseases, through these gene mutations. The two disorders appear to form a sort of genetic continuum, with the ALS phenotype on one side of the spectrum and FTD on the other. Certain genes (TDP-43 and C9orf72) are repeatedly found in both disorders, classifying them in the middle of the ALS-FTD spectrum.

Additionally, the presence of alternative gene mutations such as superoxide dismutase 1 (SOD-1) and FUS are more prevalent in ALS patients, whereas other genes like TAU and PGRN shift more towards the FTD side of the spectrum. While the exact mechanisms of action that results from these gene mutations is unknown, the majority of them seem to be linked to some form of mutant protein aggregates or haploinsufficiency, which ultimately results in neurodegeneration in both disorders

Environmental Factors:

While the role of genetics are crucial in understanding the molecular basis and pathogenesis of 10% of ALS and 25% of FTD cases, the remaining 90% and 75% of cases respectively are categorized as sporadic, meaning it is within reason that the role of the environment in the development and progression of these disorders is also looked at.

- ***Cyanotoxins:***

Cyanotoxins are toxins that are produced by cyanobacteria. Notably, β-Methylamino-L-alanine (BMAA) is a non-proteinogenic amino acid which is produced by cyanobacteria in the genus Nostoc, found in aquatic and terrestrial environments. Elevated levels of BMAA are found in cycad seeds on the island of Guam, which are used to produce the population's dietary flour. Interestingly, the ALS-Parkinson Dementia Complex (ALS-PDC) incidence in Guam was 50-100 times higher than in the United States and worldwide in the 1950's. These statistics enabled the first researchers to hypothesize links between exposure to the neurotoxin BMAA and neurodegeneration.[29] Following this discovery, *in-vivo* experiments were then carried out where 0-81 mmol/kg daily repeated oral administration of BMAA in Macaca fascicularis monkeys exhibited an ALS like phenotype: the primates presented with limb weakness, atrophy, upper extremity tremors, and even behavioral changes.[29] Additionally, human studies were conducted:[30] postmortem brain specimens were taken from 13 sporadic ALS patients in Florida, and BMAA levels were quantified using a fluorescent high performance liquid chromatography (HPLC) technique, where they found similar levels of BMAA in the ALS patients, but not neurologically healthy individuals. This same fluorescent HPLC method was used previously to detect BMAA levels of Chamarro ALS-PDC patients in Guam, where the levels were higher than those in the United States, suggesting that there is a gene-environment interaction in different geographical regions that can cause ALS.

As discussed earlier in the paper, excitotoxicity is a proposed mechanism for neurodegeneration, and developments in research have linked it to cyanotoxins. BMAA reacts with bicarbonate ions (HCO3-) to produce the adduct β-carbamate, which presents structural similarities to the excitatory neurotransmitter, glutamate. β-carbamate binds to ionotropic receptors on the postsynaptic neuron, inducing a significant increase of cellular Ca^{2+}, causing cellular oxidative stress.[31,32] Like previously mentioned, the influx of ions from excitotoxicity leads to multiple mediated pathways that ultimately results in neuronal cell death. In-vivo studies also theorize that BMAA can be incorporated into neuronal proteins, causing aggregation which could also lead to cell death.[33,34]

These collections of findings suggest that cyanotoxins, specifically BMAA, can act as a 'trigger' for the

development of motor neuron degeneration in various different pathways. (Bozzoni *et al.*) and (Sini *et al.*) summarize this. [2,35]

- ***Other environmental factors:***

Electromagnetic fields, specifically extremely low-frequency ones (ELF-EMFs) (ranging from 3-3000 Hz) have been linked to neurodegeneration in ALS.[36,37] Exposure to these could arise occupationally; this includes working near power lines and electrical wiring, meaning people at risk include electricians, train drivers, and electrical equipment repairers. Several studies have found a positive correlation between occupational ELF-EMF exposure and motor neuron disease,[38] and it is speculated that electromagnetic fields cause detrimental effects on the CNS; inducing oxidative stress and neurotransmitter release.

However, it is important to note that there has been conflicting research evidence on the effects of ELFEMF exposure on ALS, [39,40] questioning the reliability of this hypothesis. Additionally, factors such asheavy metals and pesti cides have been linked to ALS.

Similarly to ALS, FTD has been linked to some common environmental factors such as heavy metals like aluminum and pesticides. (Kalkonde *et al.*) assessed the medical and environmental risk factors of FTD in a veteran population and found that the prevalence of traumatic brain injury (TBI) was 9.2% higher in FTD patients compared to non-FTD patients (12.7% vs 3.5%; $P<0.05$.)[41] Severe trauma to the head can damage neurons in the brain, inhibiting neuronal communication which leads to the cognitive deficits present in an FTD phenotype.

A greater understanding of the environmental effects on neuronal degeneration is crucial, but should also be looked at

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in tandem with genetics, considering the possibility of genetic predispositions interacting with these environmental effects when developing ALS and/or FTD.

Conclusion

ALS and FTD remain idiopathic neurological disorders. The absence of knowledge on the distinct cause and pathophysiology of the diseases has obstructed the development of effective enough treatments to which the diseases are converted from fatal to tolerable symptoms. Nevertheless, sufficient evidence supporting the role of many different biological pathways (excitotoxicity, protein aggregation) in the disorders has been found, indicating that both ALS and FTD are multifactorial diseases. The majority of associated factors are usually consistent with the same underlying mechanisms: oxidative stress, TDP-43 protein aggregation, and RNA gain of function. The two diseases likely represent one underlying spectrum of disease, with a variety of common genes being associated with the disorders. Currently, the C9orf72 and TARDBP gene mutations are the most prevalent in both ALS and FTD, with other genes shifting to either side of the ALS-FTD spectrum. Research showcasing the effects of environmental factors such as the cyanotoxin BMAA in the development of ALS promote the idea that the emergence of the disease is a combination of genetics and the environment. It is possible that a genetic predisposition of the diseases can be inherited, and only 'triggered' by exposure to these environmental factors. Emerging therapies and research are vital in understanding the exact pathogenesis of ALS and FTD, and will hopefully clear up the vague links between the two diseases, discovering why a diagnosis of FTD is evident in some ALS patients but not others.

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