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Possible etiology and treatment of amyotrophic lateral sclerosis

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is one of the most dangerous and least understood diseases with a pathophysiology that is still largely unknown. In this article we try to provide a pathophysiological explanation of the etiological, pathogenetic, and clinical aspects of ALS. After a description of the rather complicated classification of the disease, we continue with an evaluation of its clinical presentation.

The bibliography reveals several suspect etiological factors including atherosclerosis, inflammation, tumors, cataracts, diabetes mellitus type 2, aging, and degeneration of the nervous system. One of the more intriguing factors involves changes associated with oxidative damage to both neurons and glial cells. It is known that astrocytes support the development of motor neurons. Oxidative damage is known to lead to the expression of stress sensitive genes, proteins, as well as inflammation of glial cells. Chronic inflammation could be a key factor in ALS since it has been linked to the death of motor neurons.

Pathophysiological research has confirmed the influence of certains proteins on the prognosis of ALS. ALS is typically a proteinopathy in which proteins aggregate in motoneurons. Additionally, glutamate excitotoxicity has also been linked to ALS, with mutated superoxide dismutase (SOD1) having been shown to be responsible for familial ALS.

As concerns the pathogenesis of ALS, we discussed several phenomenon such as increased levels of specific serum compounds, reduced concentrations of myelin, and changes in 5-hydroxytryptamine that could represent key indicators of the pathogenesis, prognosis, and therapy of ALS.

Concerning ALS therapy; treatment with antioxidatives is potentially very important. Exposure to heavy metals is also thought to negatively influence ALS. Evidence also suggests that good nutrition is a very important factor in the treatment of ALS. From a pharmacological perspective, serotonin treatment appears to be a useful therapeutic agent.

MINIREVIEW

INTRODUCTION

Amyotrophic Lateral Sclerosis or Lou Gehrig disease is a terminal, progressive neurodegenerative disease of the brain. It is characterized by degeneration and progressive loss of brain and spinal motoneurons associated with voluntary muscles. Other nerves are not damaged therefore the mental abilities of the patient are preserved. The disease begins with weakness of extremity muscles, followed by muscle atrophy. There are also bulbar symptoms that include dysphagia, dysarthria, voice defects, dysphonia, and breathing difficulties that hamper ventilation. Dysarthria makes many normal activities impossible and thus leads to social isolation (Xie *et al.* 2014). The disease progresses with speech and swallowing difficulties, tongue fasciculation, and slow, difficult swallowing. Nevertheless, sphincter muscles remain functional until late in the disease. Survival, from first symptoms, is approx. 3–4 years, however, in 5% of patients' survival may exceed tens of years (e.g., well-known physicist Stephen Hawkins). Military service, farmers, football players are often considered to be a risky professions.

CLASSIFICATION

The most common is the sporadic form. The familial form (up to 10% of cases) involves an inherited mutation affecting the superoxide dismutase (SOD) enzyme. A third form appeared as an epidemic on the Isle of Guam.

Aggregation of superoxide dismutase and its shift along spinal cord may be the cause of amyotrophic lateral sclerosis development. SOD changes superoxide to hydrogen peroxide, which damages neurons of striated muscles with gradual rise of illness symptoms. Hydrogen peroxide is removed by catalase and glutathione peroxidase. Endocannabinoids increase catalase activity with the possibility of favorable decrease of the toxic peroxide level.

With reduced activity among these enzymes, in the presence of certain metals, such as iron, leads to the formation of free hydroxyl radicals, which are reactive and very dangerous. Mutations of SOD1 are responsible for familial ALS.

Selenium is contained in many antioxidative enzymes as glutathione reductase and glutathione peroxidase, as well as selenium itself can act as antioxidants. Most free radicals are formed intracellularly, with the most important intracellular antioxidants being reduced glutathione (GSH) and thioredoxin reductase (an enzyme containing Se).

CLINICAL FEATURES AND ETIOLOGY

The etiology is unknown. Recently, a theory involving oxidative stress seems to be the most probable. A prevalence of free radicals over antioxidants has been demonstrated in more than 100 conditions and diseases. Examples include, but are not limited to, common diseases such as atherosclerosis, inflammations, tumors, cataracts, and diabetes mellitus type 2, ageing and degenerative neurologic diseases. Astrocytes play an important role since they support motoneurons. Their aging, and thus lower activity, can be compensated for by augmenting old astrocytes with new ones that produce more GDNF factors (glial cell-line-derived neurotrophic factor), which has been shown to prolong motor neuron survival (Das and Svendsen 2015).

Neurons are susceptible to direct oxidative damage, which leads to expression of stress sensitive genes, proteins, and glia inflammations. Direct contact between glia and neurons does not have to be toxic, but immune mediators such as nitric oxide, ROS, anti-inflammatory cytokines, and chemokines released from activated glia cells can act as neurotoxins. Activation of reactive microglia in degenerating areas of ALS patients is a key factor linked to chronic inflammation, which can then lead to death of motor-neurons. Inflammatory cytokines such as tumor necrosis factor (TNF) and interferon-γ participate in microglial activation in ALS. Neurodegeneration occurs in association with angiotensin II and other endogenous factors such as β-amyloid, immunoreaction, and activation of calcium dependent enzymes. Physiological levels of nitric oxide in ALS support surviving motor neurons, but under pathological conditions they may stimulate apoptosis and activation of glia cells (Drechsel *et al.* 2012). ALS is accompanied by higher levels of toxic ROS and RNS (reactive oxygen/nitrogen species) generated both extra- and intracellularly, which can lead to damaged proteins in brain cells and are associated with abnormally aggregated proteins. Recombinant protein has been demonstrated to aggregate in the brain. Pathologically conformed proteins influence progression of the disease. ALS a typical proteinopathy, with aggregated proteins in motor-neurons contributing to neurotoxicity. Prions, auto proliferating infectious agent, are often associated with aggressive neurodegenerative diseases in humans and animals. Dioxin, as well as some other heavy metals containing substances can also have toxic effects on enzymes: cadmium, cobalt, copper.

Glutamate excitotoxicy is also a cause of ALS. Synaptically released L-glutamate, the most important excitatory neurotransmitter in the CNS, is removed from the extracellular space by fast and effective transporters, e.g. astrocytic GLT1. Damage to these transporters causes weight loss and shortens survival time in ALS (Seri *et al.* 2013).

The mechanisms by which singlet oxide causes damage to organisms are similar. Histidine, uric acid, and selenium act against singlet oxide. The neuropeptide galanin is released from nerves, which is followed by deregulation of galanin receptors on carcinoma cells.

Glucocorticoids thus potentiate the neurotoxic effect on TDP-25 by increasing its level and thus signify the

oxidative damage of cells in this disease (Caccammo *et al.* 2013).

PATHOGENESIS

Apart from the clinical condition, it is complicated to follow the improvement or worsening of ALS. Damage and death of motor-neurons, in particular muscle motor-neurons, release certain substances into the blood, with creatine, creatinine, creatine kinase, and myoglobin being among them.

Survival time and blood test parameters were compared.

Serum creatine kinase levels increase in 43.3% of ALS patients, but the differences don't correlate with age, course of the disease, or clinical condition.

Creatine with coenzyme Q10 has even better neuroprotective effects and blocks the creation of alpha synuclein aggregates and prolongs survival time in ALS (Beal 2011).

The concentration of myoglobin as well as myoglobin synthesis is reduced in the muscle cells of ALS patients (Kawai *et al.* 1994).

ALS primarily affects motor-neurons, which means 5-hydroxytryptamine could be a key factor in the pathogenesis and therapy of ALS. The levels of tryptophan, i.e., the serotonin precursor molecule, are reduced in the cerebrospinal fluid in ALS.

THERAPY

Is was several times proved, that antioxidant therapy is very useful in the treatment of ALS. In ALS, it is important that antioxidants also be able to penetrate the hematoencephalic barrier of the brain.

The Earth has a huge number of electrons, therefore contact of human skin with the Earth causes a decrease in the number of free radicals.

Only riluzole (100 mg/day) is recommended as a therapy for ALS. However, it appears to only prolong life by approx. 2–3 months. Patients treated with riluzole have a slight decrease in SOD activity, riluzole improves bulbar and extremity mobility, but does not improve muscle strength. Arimoclomol, a derivate of hydroxylamine has been tested and shown to improve the expression of heat shock protein during cell stress. Its protective effects have been described in ALS, it improves neuromuscular function and prolongs life.

The inhibitor c-Abl (imatinib) prevents death of motor neurons. (Santa-Cruz and Tapia 2014). Also, melatonin is known to be very effective against oxidative stress and neurodegenerative damage in the nervous system of ALS patients.

ALS patients lose weight and strength. Defective energy metabolism and homeostasis contribute to selective vulnerability and degeneration of motor-neurons in ALS. An imbalance in energy metabolism is obviously an important factor both in the progression and possible treatment of ALS.

Quality nutrition greatly helps energy balance and lowers oxidative stress. Insufficient nutrition, cachexia, psychologic stress, and/or breathing disorders can increase oxidative stress in ALS (D´Amico *et al.* 2013).

Other food supplements that can have a positive effect on the course of ALS include virgin olive oil, (Oliván *et al.* 2014), carnitine, turmeric, ferulic acid, and curry. Other possible treatment is by using ursolic acid, lithium carbonate and valproate. Other therapy using cytokine IGF-1, vaccinotherapy, taurine + caffeine: improve the transfer of nerve stimuli, stabilize cellular membranes, maintain blood calcium ion concentrations, accelerates regeneration of tissues. The taurine dose is 1000–2000 mg/day. Daily doses of 5000 mg/day or higher can have side effects (diarrhoea, affecting of CNS, and disorders of short term memory); however, without taurine there is a danger of blindness during treatment. Caffeine strengthens its effects.

Edaravone increases uric acid in the plasma, which then acts as an effective peroxynitrite scavenger, however, it does not decrease the percentage of KoQ10. Edaravone with coenzyme Q10 might be suitable for lowering oxidative stress in ALS. Autologous bone marrow mononuclear cell transplantation, with Riluzole, has been shown to increase survival in ALS (Sharma *et al.* 2015).

CONCLUSION

Amyotrophic lateral sclerosis currently lacks a clear etiology as well as an effective treatment. The most probable explanation for ALS involves oxidative stress and substances that damage motor-neurons, such as aberrant pathologically conformed proteins, certain heavy metals, singlet oxygen, glutamate excitotoxicity, damaged glutamate transporters, and physically demanding work. Prevention seems to be successful (antioxidants, good nutrition) at slowing or delaying the onset of ALS. Regarding therapeutic options, good nutrition seems to be effective at preventing weight loss. Substances that help maintain serotonin levels (blockers of reverse serotonin resorption, i.e., antidepressant (mainly lithium compounds) can be useful. Additionally, other potentially effective and useful substances include: substances that slow motor-neuron death (Imatinib, trolox, and pyruvate (an antioxidant)), substances that protect against peroxides (atorvastatin, reduced glutathione, flavonoids), substances that protect against neurodegenerative diseases (melatonin, resveratrol, creatine, l-carnitine), and angiotensin converting enzyme inhibitors (captopril, ramipril).

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