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