

Research Progress in Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic Lateral Sclerosis is a chronic progressive neurodegenerative disorder. Because of its low incidence, people also have a limited understanding of its onset and treatment. The patient with this disease has a motor nerve that causes the muscles of the body to become weak. About 20% of Amyotrophic Lateral Sclerosis patients are genetically ill. Some studies have shown that the excitatory amino acid neurotransmitter glutamate may also be involved in pathogenesis. At the same time, researchers at the University of Michigan found that persistent environmental pollutants measured in the blood were significantly associated with Amyotrophic Lateral Sclerosis and may also be indicative of disease risk factors for Amyotrophic Lateral Sclerosis. However, the cause of the disease has not yet been determined, and the medical profession has not found a way to cure the disease. The average survival rate of patients with Amyotrophic Lateral Sclerosis after diagnosis was 3-5 years. The Amyotrophic Lateral Sclerosis specific drug is being developed. The anticoagulant riluzole appears to slow the progression of amyotrophic lateral sclerosis and may improve the survival rate of patients with cancer, and edaravone also shows modest efficacy.

1. Introduction

Amyotrophic Lateral Sclerosis(ALS) is also known as Motor Neuron Disease (MND), Charcot's disease, and Lou Gehrig's disease [1]. The MND was first described by several neurologists in the mid-19th century. A few years later, the French neurologist Shakko defined the disease entity "muscular atrophic lateral sclerosis"[2]. At present, MND is understood as a series of different neurodegenerative syndromes with progressive deterioration of motor neurons, including "classic" amyotrophic lateral sclerosis, progressive bulbar palsy (PBP), and progressive muscular atrophy (PMA), primary lateral sclerosis (PLS), etc [3].

Clinically, the diagnosis of ALS is mainly based on the standard catalogue of the EI escoria, defined by the World Federation of Neurology in 1994[4]. It was revised in 1998 [5] and called the "Avery House" standard. In 2006, based on electromyography and nerve conduction measurement, it was reached a new standard for the diagnosis of amyotrophic lateral sclerosis by the meeting held in Awaji Island [6], including the following clinical symptoms:

- 1) Signs of lower motor neuron (LMN) are present in both limbs: myasthenia, amyotrophia, fasciitis, hyporeflexia, hypotonia, muscular flaccidity or spasm.
- 2) At least one region (medulla oblongata, neck or lumbosacral portion) has upper motor neuron (UMN) signs, such as extensor plantar response, spasm, or pathologic hyperreflexes.
- 3) Progressive exacerbation of symptoms, including signs and symptoms of damage to an old lesion or new area [7].

2. Neuropathological character of ALS

Motor neuron degeneration The pathophysiology of motor neuron degeneration in ALS includes

the dysfunction of mitochondrial and superoxide dismutase 1 (SOD1), impaired axonal transport, apoptosis and cell death, and the aggregation of neurofilament and protein, such as TDP-43 Protein lesions, neurotrophic factor deficiency and/or dysfunction, and so on. In the end, disease progresses into the outcome of motor neuron degeneration. It has been established two databases related to ALS: the ALSOD database and the ALSGene database. The ALSOD database contains detailed information on pathophysiological related genes, and the ALSGene database lists inheritance associated studies. [8]

Currently, according to ALS's neuropathological mechanism, the aim of ALS treatment is improving the survival and functional stability of motor neurons[9][10], which includes the following types of drugs:

Anti-excitotoxic drugs: Excitotoxicity is primarily regulated by glutamate release, which leads to acute toxicity. The relative typical molecules including NMDA, AMPA receptor and glial glutamate transporter like excitatory amino acid type 2 (EAAT2) regulate the concentrations of most extracellular glutamate.

Anti-aggregation drugs: The aggregates of protein exist in the neuron cell bodies of ALS patients, such as the buninari. Preventing these endocellular aggregates can increase the survival of motor neurons. The subcellular component involved in the degradation of aggregates is the endoplasmic reticulum. Functional defects of endoplasmic reticulum may contribute to the formation of protein aggregates and inhibition of the proteasome.

Cellular energy suppliers: Mitochondrial dysfunction leads to a lack of cellular energy in ALS, thus preventing neuronal energy loss is beneficial to increase and prolong neuronal survival.

Antioxidants: The production of reactive oxygen species (ROS), such as H₂O₂, will damage neurons. At the same time, there are mechanisms to prevent cell damage caused by oxidation reactions in the cell, such as superoxide dismutase 1 (SOD1). The mutation of SOD1 can induce ALS.

SOD1 reducing agent: Removal of mutant and dysfunctional SOD1 proteins may be beneficial for the survival of motor neurons.

Anti-inflammatory compounds: Neuroinflammation plays an important role in the chronic damage processes of neurons' microenvironment.

Neuroprotective drugs: Since neurodegeneration is a general mechanism of ALS's progression, neuroprotective drugs can prevent or retard the breakdown of neurons.

Anti-apoptotic agents: Apoptosis finally leads to cell death. Therefore, compounds that prevent apoptosis may contribute to the improvement of the survival rate of motor neurons.

Growth factor: Growth factors such as granulocyte colony-stimulating factor (G-CSF), vascular endothelial growth factor (VEGF) and glial cell line-derived neurotrophic factor (GDNF), etc. can stimulate the growth of new neurons and the repair of damaged neurons. Even in an environment where motor neurons degenerate, muscles also can be strengthened to maintain motor function.

Gene therapy: Researchers at Hopkins University directly injected the adenovirus-associated virus (AAV) vector carrying insulin-like growth factor 1 (IGF-1) into the muscles of the mice limbs, and found that it effectively delayed the progression of the disease, significantly prolonged the survival of mice, even in those mice with obviously ALS-like symptoms. The key point of this study was the use of the AAV vector, which has a "reverse transport" function from the muscle to the motor neurons of the spinal cord, bypassing the blood brain barrier (BBB) and directly transferring IGF-1 to the affected neurons.

3. Noology of ALS

Recently, the neuropsychiatric findings of ALS still limited. On the one hand, it is difficult to demonstrate that the behavioral and psychiatric abnormalities of ALS are inherent or unique to the disease; on the other hand, the link between the cause and the disease remains unknown. Witgert et al. proposed that approximately 40-60% of patients with ALS have cognitive impairment and frontal dysfunction [11]; Zago and colleagues classified ALS with frontotemporal dementia [12].

3.1 Sleep Disorders

Sleep disorders are a common problem in patients with ALS. The reason of sleep disorders, along side anxiety, may be caused by problems such as decreased mobility, muscle spasm or dysphagia [13].

3.2 Fatigue

Fatigue is another symptom in ALS patients, which is not only a physical fatigue, but rather a pathological mental state [14].

3.3 Depressed and Anxiety

ALS prone to develops depressed and anxiety as well. After diagnosis, faced the “incurable” disease, accompany with the decrease of the quality and time of living, ALS patients easily arise those negative emotions. It is reported that the incidence of depressed in patients with ALS is approximately 44%, and the prevalence of mania is around 30% [15]. Based on the DSM-IV criteria, another survey showed the prevalence of depression is about 11% [16]. The incidences of depression and anxiety were not as high as expected [17], which suggests that the quality of patient’s living depends not only on the residual life but also on the mental and psychological status. It has been reported that schizophrenia is also associated with ALS [18], but the pathophysiology is still unclear.

4. Relationship between ALS and intestinal microorganism

The total number of microorganisms in the human body is as high as 100 trillion, and the gross weight of intestinal microorganism is about 1.5 kg [19], which weights nearly the same as the brain, and the number of microorganism is 150 times that of human cells [20]. The diversity of gut microbiota interacts with the brain through various pathways such as nerve, endocrine, immune, and metabolism to form a “microbial-intestinal-brain axis” channel. It is known that the channel also plays an important role in the development of obesity, inflammation, tumor and neurological disease [21]. The gut microbiota is a source of biologically active metabolites in many central nervous system diseases, which intertwines with the pathogenesis of neurological diseases, myelination and complicated host behavior by affecting the transmission of neurons and the plasticity of synapse [22-24]. In the past few years, it has been shown that gut microbiota disorders associated with the pathogenesis of depressed, Parkinson's disease (PD), Alzheimer's disease (AD), and so on [25] [26]. Recent studies have reported the discovery of a relationship between gut microbes and ALS.

The SOD1 mutant mice are often used as animal disease models of ALS. In 2015, Wu group [28] found that the number and function of Paneth cells were abnormal in the intestine of SOD1 mutant mice, the levels of inflammatory factors such as IL-17 in the intestine were increased, while the number of butyrovibrio fibrisolvens was decreased by sequencing, which can produce butyrate. It is suggested that gut microbiota are associated with ALS. Subsequently, the same group reported that the diversity of intestinal flora from four ALS patient were reduced, the ratio of *B. faecalis* and *Bacteroides* was decreased in three patients, and the levels of SCFAs in feces of two patients also reduced during conducting a fecal microbiota analysis in four ALS patients and 96 healthy controls in 2017 [29]. These experimental results suggest that the diversity of intestinal flora is associated with motor neuron disease.

The Blacher team showed that a symptom similar to ALS worsened after clearing away major of microbial strains by using wide-spectrum antibiotics in SOD1 mutations mouse models in 2019. The species and quantity of the host microbial strain community were changed by supplementing butyric acid to partially rectify the status. At the same time, it can improve the intestinal barrier function and biological flora structure disorder. In addition, this study also found that a strain called *Akkermansia Muciniphila* that can significantly slowed the disease progression and prolonged the survival of mice by increasing the concentration of nicotinamide content (NAM) in blood and

cerebrospinal fluid[30].

Although the studies of gut microbiota diversity and ALS are relatively limited, existed results have suggested that the gut microbiota may regulate the progress of ALS, and one of its regulatory mechanisms may be related to nicotinamide. Which provides a new idea for further exploring the pathophysiological mechanism of ALS and developing new microbial therapeutic targets[31].

5. Future Prospect of ALS

Hawking's death and the “ice bucket plan” made us realize that ALS is such a complicated disease of human beings. Due to the limited patients' number and the poorly understood about it, ALS still obscured to us. The reasons are related to the insufficiency of clinical model, the obvious difference of individuals, the mismatch between animal models and clinical cases, and the unclearness between the exact etiology and pathogenic mechanism, and so on. Establishing proper animal models, increasing investment to explore its exact pathogenesis, and how to translate animal experiment results into clinical individualized treatment are all worthwhile future efforts.

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