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Amyotrophic Lateral Sclerosis A Mutant Gene Disease - An Overview



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ABSTRACT

Amyotrophic lateral sclerosis (ALS), is a rapidly progressive, invariably fatal neurological disease that attacks the nerve cells responsible for controlling voluntary muscles. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. In 1993 scientists supported by the National Institute of Neurological Disorders and Stroke (NINDS) discovered that mutations in the gene that produces the SOD1 enzyme were associated with some cases of familial ALS. This paper reviews about the genetic causes of ALS in a systematic approach.



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INTRODUCTION

In Amyotrophic lateral sclerosis (ALS), both the upper motor neurons and the lower motor neurons degenerate to die, and stop sending messages to muscles, unable to function the muscles gradually weaken and have very fine fasciculations. Eventually, the ability of the brain to start and control voluntary movement is lost. When muscles in the diaphragm and chest wall fail, people lose the ability to breathe without ventilatory support. ALS usually strikes in late middle age or later, although ALS also affects younger adults and even children, as well as very elderly people. Men are somewhat more likely to develop ALS than are women. ALS is limited to instances of anterior horn cell plus pyramidal tract involvement. There has been an increasing proportion of MND deaths coded to ALS between 1949 and 1977. Death rates from all sources indicate a male preponderance for ALS or MND as a whole, at about 1.5 to 1, male to female. Prevalence rates from outside the Orient range from about 1 to 7 per 100,000 populations for MND and about 2 to 7 for ALS.

Symptoms may include tripping and falling, loss of motor control in hands and arms, difficulty in speaking, swallowing and / or breathing, persistent fatigue, and twitching and muscle cramps and spasms, Spasticity, Constipation, Fatigue, Excessive salivation, Excessive phlegm, Pain, Depression, Sleep problems, Uncontrolled outbursts of laughing and crying.

PATHOPHYSIOLOGY OF ALS

Amyotrophic lateral sclerosis (ALS) is a progressive, degenerative disease of the motor system. Degeneration and loss of large motor neurons in the cerebral cortex, brainstem, and cervical and lumbar spinal cord are characteristic. Marked reduction in the number of large myelinated fibers is notable in the cervical and lumbar ventral roots. Peripheral nerves show reduced numbers of large myelinated fibers, acute axonal degeneration at all levels, and distal axonal atrophy. Motor end-plates reveal small or absent nerve terminals. Subclinical non-motor system involvement includes neuronal loss in Clarke's nucleus and dorsal root ganglia, degeneration of non-motor tracts in the spinal cord, loss of receptors in the dorsal horns of the spinal cord, and myelinated fiber loss with segmental demyelination in sensory and mixed nerves.

DIAGNOSIS & TREATMENT

Electromyography (EMG) may be used to test the health of the muscles and nerves controlling the muscles. This test is very sensitive in detecting lower motor neuron disease. Blood and urine studies including high resolution serum protein electrophoresis, thyroid and parathyroid hormone levels and 24 hours urine collection for heavy metals , Spinal tap , X-rays, including magnetic resonance imaging (MRI), Myelogram of cervical spine, Muscle and /or nerve biopsy, a thorough neurological examination.

The drug Riluzole (RILUTEK) is the only medication approved by the Food and Drug Administration for ALS. Riluzole (2-amino-6-(trifluoromethoxy)benzothiazole) is an agent with complex actions in the nervous system. The dose is 50 mg every 12 hours, taken 1 hour before or 2 hours after a meal. Riluzole may produce hepatic injury with elevations of liver enzymes such as serum transaminases, and periodic monitoring of these is recommended. The most useful agent for the symptomatic treatment of spasticity in ALS is Baclofen (LIORESAL) a GABA-B agonist. Initial doses of 5 – 10 mg are recommended, but the dose can be increased to as much as 200 mg a day if necessary. Tizanidine (ZANFLEX) is an agonist of α_2 -adrenergic receptors in the central nervous system. It reduces muscle spasticity and is assumed to act by increasing presynaptic inhibition of motor neurons. Benzodiazepines such as clonazepam (KLONIPIN) are effective antispasmodics (1,2).

OTHER TREATMENTS

Breathing care

Breathing through mechanical ventilation by inserting a tube in a surgically created hole at the front of the neck and the tube is connected to a respirator.

Physical therapy

Physical therapy includes low- impact exercises to maintain the cardiovascular fitness, muscle strength and range of motion for as long as possible. Regular exercise can also help to improve the sense of well-being. Appropriate stretching can help to prevent pain and help the muscles function at their best.

Occupational therapy

Adaptive equipment can help to continue to perform daily activities such as dressing, grooming, eating and bathing. Equipment (computer) to perform daily activities such as dressing, grooming, eating and bathing can be trained in occupational therapy.

Speech therapy

ALS affects the muscles used to speak, communication becomes an issue as the disease progresses. A speech therapists can also help to explore other methods of communication, such as an alphabet board or simple pen and paper. Later in disease progression, a speech therapist can recommend devices such as tablet computers with text-to-speech applications or computer-based equipment with synthesized speech that may help to communicate (1,2).

PREVALANCE OF ALS BY SOD, ENZYME – MUTATION

Superoxide dismutase (SOD)

It is an enzyme that alternately catalyzes the dismutation (or partitioning) of the superoxide (O_2^-) radical into either ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2). SOD is an important antioxidant defense in nearly all living cells exposed to oxygen. Several common forms of SOD exist: they are proteins whose active site uses copper and zinc, or manganese, iron, or nickel. Thus, there are three major families of superoxide dismutase, depending on the protein fold and the metal cofactor: the Cu/Zn type (which binds both copper and zinc), Fe and Mn types (which bind either iron or manganese), and the Ni type, which binds nickel. Copper and zinc – most commonly used by eukaryotes, including humans. The cytosols of virtually all eukaryotic cells contain an SOD enzyme with copper and zinc (Cu-Zn-SOD). For example, Cu-Zn-SOD available commercially is normally purified from bovine red blood cells. The bovine Cu-Zn enzyme is a homodimer of molecular weight 32,500 (3). New research were conducted using strains of SOD mutation gene in rats both *in vitro* and *in vivo* to predict possible mechanism for ALS, they were as follows,

1. CuZn SOD Gene

Familial amyotrophic lateral sclerosis (FALS) is associated with mutations in SOD, the gene encoding copper/zinc superoxide dismutase (CuZnSOD). Studies reveal that FALS mutant SODs expressed in yeast lacking CuZnSOD are enzymatically active and restore the yeast to the wild-type phenotype. In mammalian neural cells, the overexpression of wild-type SOD inhibits apoptosis induced by serum and growth factor withdrawal or calcium ionophore. In contrast, FALS-associated SOD mutants promote, rather than inhibit, neural apoptosis, in a dominant fashion, despite the fact that these mutants retain enzymatic SOD activity both in yeast and in mammalian neural cells. The results dissociate the SOD activity of FALS-associated mutants from the induction of neural cell death, suggesting that FALS associated with mutations in SOD) may not be simply the result of a decrease in the enzymatic function of CuZnSOD. Furthermore, the results provide an *in vitro* model that may help to define the mechanism by which FALS-associated SOD) mutations lead to neural cell death (4).

2. His46Arg gene

The His46Arg (H46R) mutant of human copper-zinc superoxide dismutase (SOD1) is associated with an unusual, slowly progressing form of familial amyotrophic lateral sclerosis (FALS). The Zn-H46R structure demonstrates a novel zinc coordination that involves only three of the usual four liganding residues, His 63, His 80, and Asp 83 together with a water molecule. In addition, the Asp 124 “secondary bridge” between the copper- and zinc-binding sites is disrupted, and the “electrostatic loop” and “zinc loop” elements are largely disordered. The apo-H46R structure exhibits partial disorder in the electrostatic and zinc loop elements in three of the four dimers in the asymmetric unit, while the fourth has ordered loops due to crystal packing interactions. In both structures, nonnative SOD1–SOD1 interactions lead to the formation of higher-order filamentous arrays. The disordered loop elements may increase the likelihood of protein aggregation *in vivo*, either with other H46R molecules or with other critical cellular components. Importantly, the binding of zinc is not sufficient to prevent the formation of nonnative interactions between pathogenic H46R molecules. The increased tendency to aggregate, even in the presence of Zn, arising from the loss of the secondary bridge is consistent with the observation of an increased abundance of hyaline inclusions in spinal motor neurons and supporting cells in H46R SOD1 transgenic rats (5).

3. RNA-binding protein genes

In RNA dysfunction in amyotrophic lateral sclerosis (ALS) recently aroused upon discovering causative mutations in RNA-binding protein genes. Here, we show that extensive down-regulation of miRNA levels is a common molecular denominator for multiple forms of human ALS. We further demonstrate that pathogenic ALS-causing mutations are sufficient to inhibit miRNA biogenesis at the Dicing step. Abnormalities of the stress response are involved in the pathogenesis of neurodegeneration, including ALS (6).

4. Interleukin-1 β -converting enzyme (ICE)

Amyotrophic lateral sclerosis (ALS) is a progressive age-dependent disease involving degeneration of motor neurons in the brain, brainstem and spinal cord. ALS is universally fatal, with the median survival of patients being five years from diagnosis. In a transgenic mouse model of ALS, we now show that a dominant negative inhibitor of a cell-death gene, the interleukin-1 β -converting enzyme (ICE), significantly slows the symptomatic progression of ALS (7).

CONCLUSION

In this review, we discussed about the pathophysiology of ALS and the few evidences which reveals that ALS is a disease caused by mutations of some genes and still further researchers are needed in this area to prove that ALS caused by mutation of some specific genes.

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