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MOTOR NEURON DISEASE: AMYOTROPIC LATERAL SCLEROSIS

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Abstract: Amyotrophic lateral sclerosis (ALS), is an incredibly rare neurological disorder that affects motor neurons, which are nerve cells in the brain and spinal cord that control voluntary muscle movement. The first reported case of ALS was 200 years ago by Charles Bell. There are two kinds of ALS. The etiologic and neuropathologic process of ALS was elucidated. Neuronal degeneration is the major mechanism. Mutation of various genes is its genetic contribution. Risk factors including smoking, diet and balanced weight plays a crucial role in ALS. Symptoms of ALS from the early stage to the life threatening is explained. ALS is diagnosed by diagnostic criteria. The only treatment option in ALS is riluzole and others are symptomatic management.

Index Terms – Amyotropic lateral sclerosis, Etiology, Neuropathology, Risk factors, Treatment

INTRODUCTION

ALS was initially described by French Neurologist Jean-Martin Charcot in 1869.
The illness gained widespread recognition in the US following baseball player Lou Gehrig's 1939 diagnosis. [1]
Amyotrophic lateral sclerosis (ALS), another name for Lou Gehrig's disease, is an incredibly rare neurological disorder that affects motor neurons, which are nerve cells in the brain and spinal cord that control voluntary muscle movement. [2]
A study of American NFL players was conducted a previous report that showed a six-fold rise in the incidence of the deadly neurological disease amyotrophic lateral sclerosis (ALS) in soccer players. [3]
Charles Bell first reported cases of amyotrophic lateral sclerosis (ALS) in 1824. [4]
The disease ALS destroys a person's life within two to three years. [5]
"Amyotrophy" describes the denervation of muscle fibres caused by the degeneration of their corresponding anterior horn cells, which results in the atrophy of the affected muscles and the appearance of fasciculations. When motor neurons in the anterior and lateral corticospinal pathways deteriorate and are replaced by gliosis, the condition known as "lateral sclerosis" occurs. [10]
Once upon a time, ALS was recognised as a distinct clinical syndrome based on the location of the first symptom and the degree of anterior horn cell or corticomotor neuron involvement that initially separated it from other MNDs such as primary lateral sclerosis, primary muscular atrophy, and progressive bulbar palsy. [6]

TYPES OF ALS:

There are two kinds of ALS.
The most prevalent type, sporadic (90–95%), lacks a clear genetically inherited component.
Due to a hereditary dominant inheritance component, familial-type ALS (FALS) accounts for the remaining 5–10% of cases.[1]

While atypical forms of ALS, like primary lateral sclerosis and progressive muscular atrophy, have early and predominant involvement in the UMN and LMN, respectively, typical, or "classical," ALS is associated with simultaneous involvement of both the UMN and LMN at the onset of the disease.[23]

Charcot came to the conclusion that ALS was a brain condition and that a downstream affect was responsible for the lower motor neuron component.

Gowers in particular was adamant that the death of upper and lower motor neurons were separate occurrences, and not all of his colleagues shared this view.[26]

ETIOLOGY:

The fundamental pathogenetic processes of amyotrophic lateral sclerosis are intricate, and little is now known about the precise mechanisms underlying the disease's selective cell death.[7]

The mechanism of neuronal degeneration in motor neuron disease is complex.

The more common sporadic type of the disease is associated with environmental and genetic variables that are poorly understood.

Multiple genetic alterations could be the cause of motor neurone damage in individuals with familial amyotrophic lateral sclerosis.[8]

- Genetic factors
- Excitotoxicity
- Oxidative stress
- Mitochondrial dysfunction
- Impaired axonal transport
- Neurofilament aggregation
- Protein aggregation
- Inflammatory dysfunction and non-neuronal cells
- Deficits in neurotropic factors
- Dysfunction of signalling pathways.[10]

The disease's neuropathological characteristic is motor neuron degeneration, which involves a variety of intraneuronal inclusions of proteinaceous material. Both astrocytes and microglia are involved in the pathogenesis.

In between 30 and 60% of cases, frontotemporal degeneration symptoms are present. Eight to ten percent of cases of amyotrophic lateral sclerosis include a family component, which is caused by mutations in SOD1, TDP-43, FUS/TLS, ANG, and senataxin. There is mounting evidence that alterations in RNA metabolism have harmful effects.[11]

Genetic contribution:

Familial ALS can result from mutations in a variety of genes. The TDP43, FUS, and SOD1 genes are a few of these.

2011 saw the discovery that a particular mutation in the C9ORF72 gene was the most prevalent genetic cause of the illness to date. Familial ALS can result from mutations in a variety of genes.[12]

Excessive fragmentation and malfunctioning of mitochondria in fibroblasts generated from multiple family variants of ALS patients and in motor neurons that express SOD1 mutant in culture.[17]

A "toxic gain of function" occurs when the SOD-1 protein acquires new cytotoxic activity due to mutations in the SOD-1 gene.[25]

The exact mechanisms by which mutations in the SOD1 gene result in the selective death of motor neurons are still unknown, but peroxynitrite, mutant SOD1's altered peroxidase activity, modifications to intracellular copper homeostasis, protein aggregation, and altered glutamate transporter function leading to excitotoxicity are still of interest.

Neurofilaments and peripherin seem to be involved in the degeneration of motor neurons, and mutations in the neurofilament heavy chain gene are sometimes linked to amyotrophic lateral sclerosis.[29]

Glutamate inhibition

There is some evidence that excess glutamate, a neurotransmitter, builds up in the areas around a nerve cell in ALS after the nerve cell has finished its signalling role, producing issues for other nerve cells.

Normally, a transmitting neuron releases glutamate, a chemical messenger that travels between nerve cells, and the neuron docks with the receiving neuron. Glutamate transporter proteins, which are generated by nearby nervous system cells known as astrocytes, swiftly remove it once it has docked.

There could be a problem with this glutamate clearance system in ALS. According to certain research, the glutamate transporter protein EAAT2 may not be as effective in removing glutamate from nerve cells in ALS patients as it should be.

According to other research, this illness may be caused by an overly permeable glutamate receptor, which is a docking place on the surface of motor neurons that accepts glutamate.[13]

There have been reports of reduced glutamate clearance and elevated glutamate levels in the cortex in the SOD-1.[25]

Immune system:

Researchers have seen aberrant immune system hyperactivity in blood samples from ALS patients as well as in animal models of the disease. There is proof that immune system cells termed microglia in the neurological system contribute to their death.[14]

Astrocytes:

Glutamate clearance in ALS patients has been demonstrated to be dysfunctional, most likely due to abnormalities in astrocyte activity. It is still mostly unknown how astrocytes contribute to motor neuron protein aggregation, an ALS clinical characteristic. [12,15]

Recent stem cell investigations on the role of astrocytes in the pathogenesis of ALS have shown that astrocyte malfunction appears to be the initial cause of motor neuron degeneration.[26]

Misfolded proteins:

Normally, cellular proteins only fold in specific patterns soon after they are created. Proteins that are extremely poisonous can be the outcome of improper folding. In 2010, researchers discovered that in at least some cases of sporadic ALS, misfolded SOD1 protein may be detected without the presence of a SOD1 gene mutation.[16]

Similar to prions, cytosolic protein aggregates in ALS induce dysfunction through self-replicating protein misfolding that resembles the specific protein structure linked to the prion protein.

It appears that mutant SOD1 protein aggregates, and reports of this behaviour for RNA protein aggregates are also available.[24]

Mitochondrial factors:

The "energy factories" in cells known as mitochondria malfunction in ALS, though it's unclear precisely where in the sequence of events that this malfunction takes place.

When, mitochondria malfunction, they may be unable to provide the energy that cells require or they may release harmful molecules known as reactive oxygen species, which can cause oxidative stress, a type of poisoning that affects cells.[12]

Growth factor:

A signalling molecule called vascular endothelial growth factor (VEGF) promotes the development of new blood vessels. There is now greater interest in the potential involvement of growth factors in ALS due to evidence that patients with genetic variations in the VEGF gene may be more susceptible to the disease. [12,18]

Apoptosis:

The process of programmed cell death, or apoptosis. Apoptosis, may be a late route for motor neuron degeneration in ALS, according to some data. In a mouse model of ALS, there is evidence that blocking this programmed cell death pathway stopped neuronal loss and avoided axonal degeneration, the onset of symptoms, and paralysis. [12,19,20]

ALS NEUROPATHOLOGY:

The brains of people with ALS usually show no obvious abnormalities. Atrophy of the anterior nerve roots is a common spinal cord condition. Microscopic changes include loss of neurons and axons.

Pathological symptoms of ALS include vacuolization, which leaves large empty spaces next to neurons, and spongiosis, which is marked by tiny holes that resemble sponges.[4]

In ALS patients, 50% of the lower motor neurons in the areas of the spinal cord that cause the limbs to enlarge are frequently found to be defunct at autopsy.[7]

ALS gene mutations is a significant new project. It is consistent with theories of spreading pathology in other neurodegenerative diseases, like Parkinson's, to continue the debate about whether ALS starts in the motor cortex, as suggested by the finding of increased excitability (decreased inhibition) of the motor cortex prior to the onset of symptoms, or simultaneously in various sites in the motor system.

Cortical representations connected to opposable thumb development have been linked to consistent patterns of preferred muscle involvement in ALS, including the lateral hand muscle atrophy known as the "split hand." Reduced motor neuronal excitability is demonstrated by the fasciculation that is so typical in ALS.[24]

The majority of research has shown that cortical hyperexcitability, which is connected to motor neuron degeneration, is an early characteristic of both familial and sporadic ALS.[26]

RISK FACTORS:

The only criteria that have been scientifically proven to be risk factors for the development of ALS sickness are gender, an advantageous family history, and advanced age.

Correlations between environmental, occupational, or physical factors have been attempted, but so far, they have not been successful.

Age is the main risk factor for the onset of ALS, much like other more common neurodegenerative diseases like Alzheimer's and Parkinson's.[5]

Smoking:

Based on a study of evidence-based medicine, smoking is the sole likely risk factor for ALS.[28]

Dietary Factors:

The inverse relationship between a higher intake of antioxidants and a lower risk of ALS is the most researched relationship between dietary variables and ALS. For instance, taking vitamin E pills on a daily basis has been linked to a decreased risk of ALS. [28,31]

Body mass index and physical fitness:

Strong clinical evidence suggests that individuals with ALS are more physically active and have lower body mass indices (BMIs) than the general population.

SYMPTOMS:

The majority of ALS patients need assistance with activities of daily life, and many report feeling fatigued and having a reduced tolerance for exertion.

Dysphagia, which causes hunger and weight loss and is linked to a poor prognosis, affects the majority of ALS patients.

Respiratory compromise, which results in exertional dyspnea, orthopnea, hypoventilation with subsequent hypercapnia, and morning headaches, eventually affects the majority of ALS patients.

When a patient develops dyspnea while at rest, their death is imminent.

The breathing muscles gradually deteriorate and lead to respiratory failure; pneumonia is often the cause of this.[9]

In contemporary practise, "bulbar onset ALS" and "spinal onset ALS" have largely taken the place of the terms PBP and Charcot's ALS.

These symptoms are experienced by most people with bulbar onset ALS in the first two years of the disease. People who have bulbar onset ALS usually have dysphagia (inability to swallow meals or liquids) and dysarthria.

When paralysis worsens and leads to respiratory failure, people with bulbar onset ALS die within two to three years, while those with limb onset ALS die between three to five years.

Lately, ALS has come to be understood as a multi-system illness rather than a condition affecting just motor neurons. Extrapyramidal symptoms such tremor, rigidity, propulsion, and decreased postural reflexes can be present in some ALS patients.[28]

One of the earliest symptoms of ALS is loss of coordination. It's thought to be caused by injury to the nerve pathways that join the brain and spinal cord.

- Loss of motor neurons and inadequate signalling to muscle fibres cause muscular weakness.
- Changes in vocal pitch linked to laryngeal dysfunction. Dysarthria or slurred speech: An excessive movement of the muscles surrounding the mouth is possible.
- Muscle twitches and cramps: This is the result of nerve terminals putting pressure on the muscles.
- Abrupt sobbing and laughing (pseudo bulbar affects): occur when inappropriate inhibition of emotion is caused by nerve degeneration.
- Dysphagia, or difficulty swallowing, is a condition that appears in the latter stages of ALS and is brought on by a loss of muscle control, which is dictated by the nerve cells that control muscle movement.
- Difficulty breathing, including shortness of breath, increased dyspnea, and discomfort during breathing.
- Loss of respiratory muscle control is frequently implicated in deaths. [21]
- Loss of muscle size, strength, or endurance in the lower extremities; • Stumbling, tripping, or clumsiness when running
- Foot drop; some patients describe their gait as "slapping"

The following are some of the initial complaints with upper limb onset:

- Weakness or atrophy of intrinsic hand muscles, cramping, stiffness, and decreased finger dexterity
- Hand drop affecting productivity at work
- Hoarseness, reduced voice, or slurred speech
- Aspiration or choking during eating

The following are some emotional challenges experienced by ALS patients:

- Uncontrollably sobbing or laughing; depression
- Deficit in executive function and further cognitive abnormalities
- Alterations in conduct [27]
- Hoarseness, slurred speech, or a drop in speech volume have all been linked to degeneration in extrapyramidal locations, such as the substantia nigra, thalamus, and globus pallidus.
- Clinically, retropulsion and backward falls may happen at an early stage of ALS. This can indicate engagement outside of the pyramid. [30]

DIAGNOSIS:

The debate over early ALS diagnosis has been reframed by two recent events. The Gold Coast criteria were first proposed by a panel of specialists in order to determine the minimal alterations required in order to diagnose ALS.

By following these criteria, ALS can be identified as a progressive illness if there is no other obvious cause and either

(1) upper and lower motor findings in one body region or
(2) lower motor findings in two body regions.[27]

Second, a group of experts in ALS have proposed the idea of Mild Motor Impairment (MMI), which is based on the phrases "Mild Cognitive Impairment" and "Mild Behavioral Impairment" developed by the cognitive/behavioral neurology community.

This phrase originated from the pre-fALS study, a natural history observational study, which involved the systematic longitudinal observation of pre-symptomatic carriers of autosomal dominant genes for ALS.

The patients' neurological examination was entirely normal during the initial evaluation. A few patients experienced mild motor symptoms during routine reexaminations that did not fit the diagnostic criteria for ALS and that the patient frequently was unaware of. These alterations developed and came about several months or years before the onset of ALS symptoms that might be diagnosed.[27]

A diagnostic algorithm was developed by the World Federation of Neurology (WFN).

The criteria for the diagnostic algorithm were as follows:

- **Clinically definite ALS:** UMN and LMN signs in at least three body segments;
- **Clinically probable ALS:** UMN and LMN signs in at least two body segments with some UMN signs in a segment above the LMN signs; clinically probable, laboratory-supported ALS: UMN and LMN signs in one body segment or UMN signs in one region coupled with LMN signs by electromyography (EMG) in at least two limbs;
- **Clinically possible ALS:** UMN and LMN signs in one body segment, UMN signs alone in at least two segments, or LMN signs in segments above UMN signs;
- **Clinically suspected ALS:** Pure LMN syndrome with other causes of LMN disease adequately ruled out.[27]

TREATMENT:

Developed by the World Federation of Neurology (WFN), a diagnostic for ALS, there are two potential disease-modifying treatments that can delay the disease's development; nevertheless, the majority of patient care is provided by symptomatic treatments, such as speech therapy for dysarthria and muscle relaxants for spasticity.[22]

Guidelines from the American Academy of Neurology for treating ALS patients. All, ALS patients should be prescribed Riluzole to halt the disease's development.

Riluzole:

In a clinical trial, riluzole, the only medication that can prolong survival for ALS patients, was linked to a 35% decrease in death at a dose of 100 mg. [32]

Riluzole is a neuroprotective drug. It blocks glutamatergic neurotransmission in the CNS.

From cultured neuron Riluzole inhibits release of glutamic acid. It is partly due to voltage-dependent channel inactivation on glutaminergic nerve terminals and activation of G protein-dependent signal transduction process. It also blocks some post synaptic

Effects of glutamic acid by NMDA receptors. It has neuroprotective, anti-convulsant and sedative property.[33]

For individuals with impaired oral intake, percutaneous endoscopic gastrostomy (PEG) enteral nutrition should be considered as a means of stabilizing body weight.

In order to increase survival and slow the decline of FVC, noninvasive ventilation (NIV) should be used to treat respiratory insufficiency.

In patients with reduced peak cough flow, particularly during an acute lower respiratory infection, mechanical insufflation or exsufflation may be considered as a means of clearing secretions.

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- Quinidine and dextromethorphan combined to reduce emotional lability (pseudobulbar affect)
- Muscle relaxants to treat spasticity
- Lorazepam for anxiety; mucolytics for thickened secretions; anticholinergics and sympathomimetics for sialorrhea
- For depression, selective serotonin reuptake inhibitors (SSRIs)
- Nonsteroidal anti-inflammatory medications (NSAIDs), transdermal fentanyl, ketorolac (Toradol), tramadol (Ultram), and morphine (immediate or prolonged release) for pain
- Avoid using high-dose vitamin E and creatine [27,31]

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