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Amyotrophic Lateral Sclerosis

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ABSTRACT: The gradual loss of motor neurons in the brain and spinal cord is a hallmark of the neurodegenerative disease amyotrophic lateral sclerosis (ALS). Current ALS management, from diagnosis to prognosis, is still unsatisfactory despite much study. Frontotemporal dementia (FTD) and ALS share pathological characteristics, and many individuals exhibit traits from both conditions. The disease is now known to be caused by a wide variety of genes and pathophysiological mechanisms, and in order to develop successful treatments, it will be essential to comprehend this heterogeneity. Although a fraction of patients has familial disease and contain mutations in genes that play different roles in neuronal function, the processes underlying the development of ALS in the majority of patients are not well known. We discuss every facet of ALS, including its epidemiology, risk factors, causes, clinical manifestations, diagnostic procedures, and treatment. The reader will benefit from having access to a wide variety of disease-related information as a result.

KEYWORDS: Amyotrophic lateral sclerosis, Epidemiology, Diagnosis, Pathophysiology, Clinical features.

I. INTRODUCTION

Lower and upper motor neurons (LMNs) at the spinal or bulbar level gradually disappear in amyotrophic lateral sclerosis (ALS), a deadly motor neuron disease.[1]. In 1869, French neurologist Jean-Martin Charcot published the first description of ALS.[2] Following the baseball player's 1939 diagnosis, it is widely referred to as Lou Gehrig's disease in the United States.[3] Since ALS is a rare disease, the diagnosis is sometimes delayed since more common illnesses are taken into consideration before it.[4] ALS can be divided into two types. The majority (90–95%) are sporadic, meaning they lack a clear hereditary component. FALS, which is connected with a genetic dominant inheritance factor, accounts for the remaining 5–10% of cases.[5]. Typically, symptoms start to appear between the ages of 50 and 65.[6]

• Epidemiology

In Europe and North America, the incidence of sporadic amyotrophic lateral sclerosis (SALS) was uniform in the 1990s, ranging from 1.5 to 2.7 cases per 100,000 people annually (average of 1.89 cases per 100,000). In western nations during the 1990s, the point prevalence ranged from 2.7 to 7.4 per 100,000 (average 5.2 per 100,000) [7]. It is anticipated that 800,000 people who are currently alive will pass away from ALS in the United States alone. In [8] Families account for about 10% of ALS cases, with dominant features typically being inherited. In [9] Sporadic ALS accounts for 90% of all ALS cases, meaning they don't have a familial history.[10]

• Pathophysiology

We still don't fully understand the mechanics behind the neurodegeneration in ALS. Axonal transport, mitochondrial dysfunction, toxic protein aggregation, impaired protein degradation (proteasome and/or autophagy), prion-like spreading, excitotoxicity, lack of neurotrophic support from non-neuronal cells, dysfunction of non-neuronal cells, oxidative stress, hypermetabolism, inflammation, defects in RNA metabolism, RNA toxicity, and many other cellular and molecular processes have been implicated. Each of these mechanisms has a large body of literature that supports it and has been reviewed elsewhere.[11]

II. ETIOLOGY/CAUSES

The following causes are given that are responsible for the development of ALS

- **Genetic causes**

Although hereditary factors have been implicated, sporadic ALS accounts for the majority of ALS cases.[12] Mutations in particular genetic sites cause FALS.[13] The only motor neuron disorders with known etiology are heritable diseases.[14] Five to ten percent of ALS cases are familial, with the other cases thought to be sporadic. Twenty percent of cases of familial ALS are caused by mutations in the gene encoding superoxide dismutase 1 (SOD1), according to a 1993 study by Rosen et al. [15]. Mutations in other genes account for the remaining 80%. SOD1 mutations are also present in 5% of patients with ALS that appears to be spontaneous.[16]

Environmental causes

- **Chemical exposures and metals**

ALS has been linked to exposure to agricultural chemicals, including formaldehyde, pesticides, fertilizers, herbicides, and insecticides.[17] The ALS death rate was more than twice as high in those who had been exposed to formaldehyde over an extended length of time as compared to those who had not.[18] Furthermore, since formaldehyde is a byproduct of cigarette smoke, as was previously indicated, this may be the cause of 10–25% of formaldehyde exposure in indoor air.

Due to the ALS-like symptoms that individuals exposed to high concentrations of lead suffer, lead exposure appears to be the heavy metal that has been investigated the most out of all those that may be linked to the disease.[19] Accordingly, occupations involving lead exposure, such welding, have shown a strong correlation with the development of ALS, with odds ratios (ORs) ranging from 1.9 to 5.7[20].

- **Viral infection and smoking**

Sporadic ALS may be brought on by a persistent viral infection. In the spinal cords of ALS patients, Berger et al. found enterovirus RNA.[21] A tiny percentage of persons with HIV infection have also been documented to have motor neuron disease.[22] Because of oxidative stress, inflammation, and the neurotoxicity of heavy metals included in cigarettes, cigarette smoke has been shown to raise the risk of developing ALS.[23]

- **Clinical presentation and symptoms**

In ALS, the bulbar, cervical, thoracic, and/or lumbar segments are affected by a combination of upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction.[24] With varying clinical manifestations, this results in gradual paralysis of the voluntary skeletal muscles involved in respiratory function, speech (dysarthria), swallowing (dysphagia), and limb movement.[25] There have also been reports of isolated emotional lability, discomfort, stiffness, cramping in the muscles, sialorrhea, and weight loss as early symptoms.[26]

For a few years, patients may experience cramps and fasciculation (defined as involuntary muscle twitching) before weakening appears. Anorexia, mood swings, exhaustion, cognitive symptoms, sensory symptoms, new bladder dysfunction (like urgency of micturition), and multi-system involvement (like dementia, parkinsonism) are some of the symptoms that are occasionally experienced. [27]

III. DIAGNOSING AMYOTROPHIC LATERAL SCLEROSIS

Many of the differential diagnoses of ALS can be ruled out with the use of established criteria and diagnostic testing. A comprehensive patient history, a comprehensive examination, the necessary laboratory, electrodiagnostic, and neuroimaging procedures, as well as genetic testing, are all part of this procedure

- **Neuroimaging**

The most effective neuroimaging method for ALS is magnetic resonance imaging (MRI) of the brain and spinal cord, primarily to rule out disorders that mimic ALS.[28] For instance, a unique pattern of brain shrinkage and neuropathological findings can be used to distinguish new chromosome 9p-linked frontotemporal dementia (FTD)-ALS from classical ALS.[29] In addition to voxel-based morphometry, a neuroimaging analysis method that employs statistical methods, advanced MRI techniques such as diffusion tensor imaging, magnetization transfer, proton magnetic resonance spectroscopy, and resting functional MRI may be helpful in noninvasively identifying specific ALS-associated patterns [30].

- **Laboratory studies**

Cerebrospinal fluid analysis, thyroid function testing, serum calcium and phosphate measures, erythrocyte sedimentation rate measurement, and serum and urine protein electrophoresis should all be part of a routine study for a patient with ALS who appears to be typical. People who may have had exposure in the past should have a strong metal screen. Some ethnic groups have β hexosaminidase deficiency, sometimes known as Tay-Sachs disease, which can mimic ALS. In Ashkenazi Jewish patients, beta hexosaminidase subunits α and β activity should be assessed.[31].

- **Muscle biopsy and neuropathological studies**

Unless a mimic condition (such as inclusion body myositis) needs to be ruled out, skeletal muscle or other tissue biopsies are not necessary for diagnosis. Additionally, when clinical or electrophysiological evidence do not confirm the presence of LMN dysfunction in a particular body location, muscle biopsy may be used to show it. The following histological findings are consistent with an ALS diagnosis: [32]

- Hypertrophied muscle Fibers that are dispersed.
- A moderate number of target or targetoid fibers, at most.
- A slight to moderate degree of fiber type clustering.
- A tiny quantity of necrotic muscle Fibers is present.

- **Genetic testing**

Up to 5% of instances of familial ALS may follow a Mendelian pattern of inheritance, according to a thorough evaluation of all cases; 15 genes and loci have been identified in total [33].Only mutations in SOD1, TARDBP, ANG, VCP, and FUS—out of the 15 genes known to be linked to ALS—are linked to typical ALS; the other genes are linked to odd symptoms or have been identified in a limited number of kindreds.[34] As early data from mice research indicates that passive vaccination techniques can decrease disease progression in the SOD1 model, screening for mutations in these known genes may be beneficial for individuals with familial ALS.[35]

- **Electrodiagnostic tests**

The most important auxiliary technique in the study of ALS is electrodiagnostic research. The hallmark of ALS, the loss of lower motor neurons, can be detected by electromyography [36], which is especially helpful in areas that are clinically unaffected. Fasciculation, spontaneous denervation discharges (fibrillation potentials and positive sharp waves) indicating continuous motor neuron loss, and polyphasic units indicating reinnervation are the most commonly identified abnormalities seen on electromyography. Although the existence of fibrillation potentials and positive sharp waves in clinically normal muscle tissue may help with an early diagnosis, they may not appear until one-third of the motor neurons have been destroyed.[37]

- **Treatment**

It has been proposed that a number of distinct neurological conditions, such as ALS, FTD, and Parkinson's disease, share genetic and environmental vulnerabilities.[38] Patients with dementia, Parkinson's disease, and ALS have all received the same treatment in clinical studies. The evaluations of these therapies may have an impact on additional ALS diagnostic standards.[39] As of right now, riluzole is the only FDA-approved medication that has been shown to improve ALS patients' chances of survival. When compared to controls, two clinical trials showed that the group receiving riluzole had a higher survival rate.[40] Glutamate is known to be released from cerebrocortical nerve terminals as a result of presynaptic inhibition triggered by riluzole.[41] It is an antagonist of the noncompetitive NMDA receptor and inactivates voltage-gated sodium channels.[42] For individuals with definite or suspected ALS for less than five years, an FVC greater than 60%, and no tracheostomy, riluzole at a dose of 50 mg twice daily is recommended.[43] There isn't a new medicine that can extend the life expectancy of people with ALS besides riluzole.[44]

- **Management of ALS**

The treatment of ALS has evolved significantly during the last 20 years. ALS is not incurable, but it is treatable. Treatments and interventions that increase survival have received attention.[45] Although there are no drugs that can stop or reverse the progressive loss of neurons, treatment techniques that maximize quality of life and support the patient's autonomy for as long as possible have gained relevance.[46] To improve health care delivery, prolong survival, and improve quality of life, patients with ALS should be managed by coordinated multidisciplinary care from neurologists, physical therapists, occupational therapists, respiratory therapists, social workers, dietitians, and nursing care managers.[47]

- **Multidisciplinary management**

The way that ALS patients receive medical care has changed in recent years, leading to the emergence of multidisciplinary ALS treatment institutions. These interdisciplinary ALS clinics collect valuable resources and clinical experience by treating just ALS patients, which can help control and offer the best care possible for this degenerative disease.[48] The various problems associated with ALS, including respiratory symptoms, dysphagia, dysarthria, psychosocial disorders, and functional deterioration, can be effectively managed with the help of these multidisciplinary ALS specialty clinics. In order to maximize health care delivery and extend survival, the American Academy of Neurology (AAN) and the European Federation of Neurological Societies advised that, following diagnosis, the patient and caregivers be referred to a multidisciplinary clinic and receive ongoing support from a multidisciplinary care team.[49]

- **Respiratory management**

Respiratory failure, with or without pneumonia, is the leading cause of death in ALS. Reduced breathing is the result of the presenting signs of respiratory muscle weakening brought on by increasing motor neuron degeneration.[50] Dyspnea during exertion or conversation, headaches in the morning, exhaustion, anorexia, sadness, difficulty concentrating, violent nightmares, and nocturia are some of these symptoms. The evaluation and treatment of respiratory function are crucial since respiratory failure is the primary cause of ALS mortality. Examining the patient's FVC is the most popular and accessible method for identifying respiratory deterioration.[51] In order to treat respiratory insufficiency, noninvasive ventilation (NIV) should be taken into consideration, according to the AAN's current guidelines.[52] In patients with ALS, therapeutic use of NIV is believed to increase survival, delay the deterioration of FVC, and enhance quality of life.[53]

- **Nutritional management**

The majority of ALS patients experience dysphagia, which results in weight loss and malnourishment. Weight loss, choking, aspiration, dehydration, and restriction of adequate nutrition are the results of this steady decline. Because of their dysphagia, these patients are more likely to consume inadequate amounts of food and liquids, which might exacerbate their weakness and exhaustion.[54] The first step in nutritional management is to change the consistency of the meal, but eventually enteral feeding may require a percutaneous endoscopic gastrostomy (PEG) or a similar device.[55] The conventional enteral feeding technique, PEG, has been shown to be beneficial in stabilizing the weight loss that is frequently associated with ALS.[56]. Because the procedure's mortality risk increases as respiratory function deteriorates, it is advised that nutritional supplementation with PEG be completed before FVC drops below 50% of expected values.[57]

IV. DIETARY SUPPLEMENTATION

- **Vitamin E and Vitamin A**

Free radical stress is thought to be a major factor in the cell degeneration that causes ALS to develop and progress.[58] Vitamin E supplements slowed the progression of ALS and postponed its commencement in a transgenic mouse study by Gurney et al., but they had no effect on survival rates.[59] Vitamin E consumption only reduced the disease's course when a comparable trial was conducted on humans [60]. Additionally, Michal Freedman et al. demonstrated that patients with lower-than-normal vitamin E levels had a slight protective effect from vitamin E supplements, and that higher-than-normal serum vitamin E levels were linked to a lower risk of ALS.[61] The effectiveness of vitamin A (beta-carotene) supplementation among ALS patients was examined in several studies. According to their findings, beta-carotene does not aid ALS patients delay the disease's course or have any neuroprotective effects.[62]

- **Creatine**

A potential protective effect of dietary creatine supplementation on neurons was demonstrated by Klivenyi et al. in an exploratory study conducted on transgenic mice with ALS. Their findings showed that transgenic mice had better motor function and longer lifespans.[63] According to a follow-up study by Andreassen et al., getting more creatine may help the cellular glutamate transporter, which would stop glutamate excitotoxicity, which is thought to be a mechanism of ALS.[64]

V. CONCLUSION

From epidemiology to the disease's molecular cause and treatment, this study explored a wide spectrum of ALS-related topics. Unfortunately, the prognosis for ALS is only three to five years after symptoms appear, and the disease is thought to be incurable.[65] Numerous antioxidants and supplements have been suggested as an alternate treatment for ALS;

however, the majority of these have not been confirmed by research studies, or studies that have been conducted lack validity or significant evidence in their methodology.[66] Significant progress has been made in our comprehension of the pathophysiology of ALS. It has been determined that ALS is linked to 19 genes and genetic loci.[67] Understanding the molecular mechanisms behind ALS will help develop treatment strategies. Antiapoptotic, anti-aggregation, antioxidant, anti-excitotoxicity, anti-inflammatory, neuroprotective, and neurotrophic growth factor medications are presently undergoing a number of clinical trials.[68] The disease's progression has been slowed down by recent findings of the underlying mechanism of ALS. Therefore, once patients go past their first beginning, future treatments should focus on preventing neuronal damage.

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