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Familiar Amyotrophic Lateral Sclerosis Linked to SOD1 and VAPB Genes

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Abstract

Introduction: The disease occurs more frequently within certain families, often associated with specific genomic mutations. From the study of f-ALS cases, several mutations in different genes were reported, among them SOD1 (Superoxide dismutase 1) and VAPB (VAMP associated proteins B and C), which were the focus of the present study.

Methodology: This is bibliographic research with a qualitative approach. LILACS, PUBMED, MEDLINE, and Google Scholar databases were used. 218 articles were found, 159 were excluded, and 59 papers were selected. There was a temporal cut from 2002 to 2022.

Results: Increased DNA methylation was observed in whole blood, constituting a marker of epigenetic dysfunction in ALS.27 This high global DNA methylation is also seen in carriers of SOD1 mutations. So far, most individuals affected by ALS8 are Brazilian, Caucasian, and carriers of the same mutation in exon 2 of the VAPB gene (c.166C>T; p.P56S VAPB). A founder effect was then postulated for this mutation.

Conclusion: ALS is, therefore, a multifactorial disease, with no known cause yet, with an inexorable and rapid course, with only palliative treatments that can only increase the patient's survival.

Keywords: Amyotrophic lateral sclerosis; Neurological pathologies; Quality of life

Introduction

Charcot's disease in France, or Lou Gehring's disease in the USA, became known in Brazil by the term Amyotrophic Lateral Sclerosis - ALS. Its first description was made by Jean Martin Charcot, a French neurologist, who, in 1865, carried out anatomical and pathological clinical studies with necropsy material from two patients. Its description was similar, initially, with an analogy to progressive spinal atrophy in adults, which had already been reported by two other scientists, Aran and Duchene, in 1848. The difference between these two was in the faster evolution of ALS's clinical picture [1]. Conceptually, ALS is a progressive neurodegenerative disease characterized by the loss of motor neurons in the spinal cord, brainstem, and motor cortex, drastically reducing the patient's life expectancy [2]. The first description of the disease was made in 1874 by Jean-Martin Charcot (1825-1893), a renowned French physician and scientist [3]. In France, ALS is known as "maladie de Charcot" and in the United States as Lou Gehrig's disease, named after the baseball player who was diagnosed with the disease in 1939 [4]. Pierre Marie (1853-1940), a neurologist who was a disciple of Charcot, was the first to question whether, in addition to motor functions,

there would be impairment of "psychic" functions in ALS [5]. However, cognitive deficits only began to be recognized in European literature in the early 20th century [6]. In 1999, one of the first studies of the prospective characterization of the cognitive profile in ALS was published [7]. Current neuropsychological, genetic, and neuroimaging evidence has supported an overlap between ALS and frontotemporal dementia [6]. The pathophysiological process involved in sporadic ALS is multifactorial and has not yet been fully elucidated. Evidence suggests several mechanisms involved, the main ones being: glutamate-mediated excitotoxicity, mutation of several genes such as SOD1, TARDBP/TDP-43, and FUS, hexanucleotide repeat expansions (GGGGCC) of the C9orf72 gene, abnormalities of neurotrophic factors, neuroinflammation, disorders of the neurofilaments and mitochondrial dysfunction (defects in oxidative phosphorylation, calcium buffering capacity, production of reactive oxygen species and defective mitochondrial dynamics such as aberrant fission and fusion and defective transport of mitochondria to the axon), among others [2-8]. In this sense, the degenerative process of this disease has a complex and multifactorial etiology. Thus, current hypotheses about their underlying pathological mechanisms remain undetermined. However, they suggest that there are interactions between several of them, including Genetic factors; Chemotaxic factors of neutrophils; Oxidative damage; Accumulation of intracellular aggregates; Mitochondrial dysfunction; Axonal transport defects; Glial cell pathology; Environmental factors; Exotocity; Viral Infections and Autoimmunity [2-9]. The disease occurs more frequently within certain families, often associated with specific genomic mutations, while some sporadic cases have been associated with environmental toxins or trauma [8]. Age is one of the most important predictive factors for its occurrence, prevalence is highest between 55 and 75 years. Pathophysiologically, it can be defined as a progressive disorder involving motor system degeneration at different levels: cervical, bulbar, thoracic, and lumbar.

According to genetic aspects, ALS can be classified into:

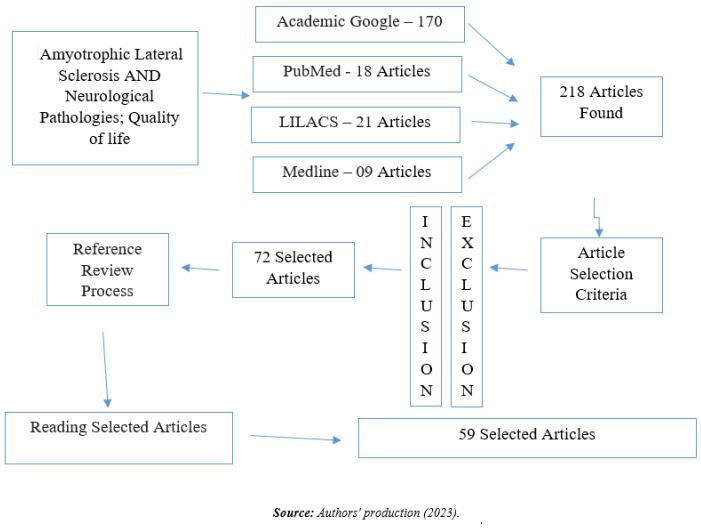
- Familial (ALS-f), that is, with a defined genetic cause (5 - 10% of cases);
- Sporadic (e-ALS), when there is no evidence of a familial inheritance pattern (90-95% of cases) [8-10].

Familial forms of ALS can be transmitted through autosomal dominant, recessive, and X-linked inheritance, with the most common form being adult-onset autosomal dominant. Autosomal recessive is rarer and more frequent in juvenile forms, in primary lateral sclerosis or spastic-like paraplegia. The X-linked dominant form is rarely seen and is seen in families where male patients tend to show more severe phenotypes [11]. The diagnosis of the disease is based on its clinical signs, observing its involvement in upper and lower motor neurons or the brainstem. It must also be differentiated into its various forms: Primary Lateral Sclerosis, Progressive Bulbar Palsy, and Fanca Amyotrophic Lateral Sclerosis [8]. Clinical symptoms, differentiated by their location and origin, associated with diagnostic tests – in general: magnetic resonance imaging, electroneuromyography, and nerve conduction studies – are tabulated to generate a diagnostic algorithm that differentiates the disease into suspected, possible, probable, and definite [12]. From the study of f-ALS cases, several mutations in different genes were reported, among them SOD1 (Superoxide dismutase 1) and VAPB (VAMP associated proteins B and C), which were the focus of the present study [13]. Currently, most cases (50%) of f-ALS are associated with massive expansions of the hexanucleotide GGGGCC (G4C2) in the non-coding region of the C9ORF72 gene, followed by alterations in the genes SOD1 (20% of f-ALS cases), FUS (5%) and TARDBP (5%). Some studies demonstrate population variability regarding the prevalence of these genes associated with ALS. In Brazil, besides the SOD1 and C9ORF72 genes, the VAPB gene is highly prevalent in ALS cases, while in other countries, the SOD1 and C9ORF72 genes are dominant. Concerning VAPB, the first mutation associated with familial ALS was mapped in 2004 in Brazilian patients, in which the exchange of proline for serine at position 56 (P56S) was detected. Due to the phenotypic variability observed in clinical cases associated with ALS, it is relevant to determine which variations are more significant in the Southeast region and associate identified mutations with penetrance age of onset, progression, prognosis, and clinical manifestations [13,14]. Epigenetics are changes (mitotically or meiotically heritable) in gene expression that changes in the DNA sequence cannot explain. In most cases, it acts as an inherited regulation of DNA transcription through the mechanisms of DNA methylation, histone modification, and expression of non-coding RNAs. In addition to the identified genes and loci, epigenetic alterations may be associated with the development of ALS. Based on the problems above, the study aims to describe familial amyotrophic lateral sclerosis linked to SOD1 and VAPB genes.

Methodology

This is bibliographic research with a qualitative approach. It should be noted that bibliographical research is carried out with the aid of material already prepared, consisting mainly of books and scientific articles. However, in most studies, some work of this kind is required; there are researches developed exclusively from bibliographic sources [15]. Regarding the qualitative method, Minayo argues that it is the process applied to the study of biography, the representations and classifications that human beings make about how they live, build their components and themselves, feel, and think [16]. Data were collected from a virtual database. For this, the Virtual Health Library (VHL) was

used in the following information base: Latin American and Caribbean Literature in Health Sciences (LILACS); PUBMED; Online Medical Literature Search and Analysis System (MEDLINE) and Google Scholar from December 2022 to February 2023. The following descriptors were chosen: amyotrophic lateral sclerosis, neurological pathologies, and quality of life found in Health Science Descriptors (DECS). After crossing the descriptors with the keyword, using the Boolean AND operator, the number of texts that met the demands of the study was verified. For sample selection, there was a temporal cut from 2002 to 2022, as the study tried to capture the productions published in the last 20 years. As inclusion criteria were used: to be a scientific article, to be available online, in full for free, and to deal with the researched theme. After associating all descriptors, 218 articles were found, 159 were excluded, and 59 were selected (Figure 1).



Source: *Authors' production (2023).*

Figure 1: *Flowchart of selected references.*

Results and Discussions

Currently, around 58 genes related to ALS have been described. Of these 58 related genes, 32 are considered "main" or "causative" genes; 7 were related as phenotype alterers, and 19 genes were related as susceptibility genes [17,18]. The causative genes' pathways are distinct; some are related to mRNA processing, oxidative stress, endosome traffic, cell signalling (VAPB, protein degradation pathways, AND chromatin remodelling [19]. SOD1 (Superoxide dismutase 1) Nowadays, more than 180 pathogenic mutations in the superoxide dismutase gene (SOD1) have been described in patients with Amyotrophic Lateral Sclerosis [20]. A great diversity of clinical evolution is also observed among these genetic variants. For example, patients with the A4V heterozygous mutation quickly develop an aggressive form of ALS, leading to death within about a year [21]. Other variants, however, appear to have milder phenotypic manifestations, such as the D90A homozygous mutation. This, which causes an autosomal recessive form of ALS, evolves in a slower progression, which can take up to a decade [22].

Some forms of ALS result from a mutation in the gene encoding the antioxidant enzyme Cu+2/Zn+2 superoxide dismutase (SOD1). This gene is located on chromosome 21 (21q22.1), spans 11 kb in length in chromosomal DNA, and consists of 5 exons interrupted by four introns. The exons encode a protein of 153 amino acids [23]. This protein is located in the cytoplasm, nucleus, lysosomes, and mitochondrial intermembrane space. It has the function of capturing copper and zinc ions and forming a homodimer, in which it will carry out the dismutase function, removing dangerous superoxide radicals and metabolizing them into molecules of oxygen and hydrogen peroxide, which are converted into water and oxygen by the enzymes glutathione peroxidase and catalase [24]. The SOD1 protein is highly conserved: horizontal gene transfer is programmed to occur early in eukaryotic evolution. Indeed, the human SOD1 protein is at least 50% homologous with non-human SOD1 proteins from other mammalian species. The three-dimensional structure of the SOD1 protein is very similar to that of immunoglobulin: the folding pattern (Greek key) in SOD1 resembles the hypervariable region (antigen binding) folds present in immunoglobulin [23]. In different populations, the proportions are 12% to 23% of patients diagnosed with Familial ALS and 2% to 7% of sporadic ALS carriers carrying the mutation in the SOD1 gene. Due to the production of altered SOD1 proteins originating from these mutations, the protein encoded by the wild-type allele has regular activity but is reduced in patients with Familial ALS. Mutant SOD1 enzyme activity levels in Familial ALS patients are generally reduced by 25.3% to 93% of the activity compared to normal individuals.

The consequence of this is that the altered protein cannot wholly remove superoxide radicals, and the oxidative stress generated by these superoxide radicals plays a role in the toxic effect on neurons. Ticozzi presents studies that show that mutant SOD1 is prone to incorrect folding and formation of cytoplasmic aggregates, and, in turn, these aggregates can lead to cell death by kidnapping other cytoplasmic proteins essential for neuronal survival by overloading and blocking the system ubquitin/proteasome, by mitochondrial disruption, cytoskeletal disruption or axonal transport [25-26]. Among the gain-of-function theories of how the mutant SOD1 gene contributes to motor neuron death associated with Familial ALS, four main hypotheses have been postulated: hydroxyl radical (OH-) toxicity, nitration toxicity, copper toxicity, and aggregation toxicity [23]. However, the exact mechanism by which SOD1 mutations lead to ALS pathologies is unknown, although numerous hypotheses have been proposed to explain the mediation of mutant SOD1 with toxicity, such as folding protein associated with aggregation,

oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, glutamate excitotoxicity, microglial inflammation and activation, and abnormalities in axonal transport [27]. SOD1 dismutase activity depends on the formation of homodimers associated with Cu+ and Zn2+ ions. Functional studies with proteins carrying pathogenic alterations, such as C6S, N90A, and A89V, demonstrated that their enzymatic activity is preserved in some mutant models. This suggests that the loss of protein function does not play a significant role in the neurodegenerative process of SOD1 in ALS [28]. These mutations are believed to cause a toxic gain of function in the protein. Its progressive accumulation in the cytosol would interfere with several cellular processes, such as vesicle traffic and mitochondrial activity, leading to cell death [29,30]. Initially, the hypothesis arose that the mutations could impair the protein's enzymatic activity, resulting in increased cellular levels of types of reactive oxygen, oxidative stress, and neural death [25]. According to Oliveira and Pereira26, 20% of mutations in Familial ALS in SOD1 cause folding protein and formation of intracellular inclusions. Oxidative stress induces SOD1 normally to monomerize as an intermediate in the aggregate formation process, and it is known that SOD1 does not have this superoxide activity in this way when mutated. Motor neurons are known to be particularly sensitive to oxidative stress, which makes this process potentially more expressed in this cell type. Specific changes in SOD1 messenger RNA half-life and the effect of SOD1 aggregation and monomerization on superoxide activity raise the possibility of decreased SOD1 activity in affected neurons. Six of the SOD1 mutations in patients with familial ALS (A4V; L38V; L106V; I113T; L144F, and V148G) are likely to destabilize the folding loop subunit or contact dimers, changing the structure of standard proteins [23]. The most frequent mutation in the SOD1 gene is D90A. This is an enigmatic mutation because it keeps Cu+2/Zn+2 -SOD1 erythrocytic activity practically every day and has intact specific activity and preserved stability under denaturing conditions. While some cases are heterozygous for the D90A mutation, with dominantly inherited lineages and an aggressive and variable phenotype, all patients are homozygous for the D90A mutation, which in most cases is inherited as a recessive trait, have shown the same phenotypic feature of slow ascending paresis. , starting asymmetrically at the lower extremities. At four years, the first distal symptoms appear in the upper extremities, along with the first bulbar symptoms. Months or even years precede the onset of paresis in the lower extremities. Other atypical features in homozygous D90A patients include bladder abnormality, the urgency to void and difficulty initiating voiding, the periodic feeling of heat, and significantly prolonged central motor latency recorded after transcranial magnetic stimulation [26-31]. The superoxide activity of SOD1 can be measured in two ways: by the intrinsic activity of SOD1, which reflects the enzymatic efficiency of the protein, and by the measure of the recombinant activity of the SOD1 protein normalized for its quantity. This activity is measured in at least eight protein mutations, giving various results ranging from 0 to 150% in the wild-type human allele for SOD1 activity; or by the complete activity within the tissue sample, which can be affected by various factors in the cellular environment, and this is obtained by the regular superoxide activity for the tissue amount. This activity is an unbiased measure that takes into account known and unknown influences on SOD1 enzymatic activity. Intrinsic activity influences the complete training, but only 8 in one of the determinants; the others are any factors that affect the quantity, biological availability, and functionality of SOD1 [24]. SOD1 activity is generally reduced by half in patients with Familial ALS, as measured in red blood cells, lymphoblasts, and fibroblasts. Indirect evidence raises the possibility that a severe reduction may occur in susceptible tissues and specific cell types due to the reduced half-life of the mutant SOD1 messenger RNA in the Central Nervous System and the possible effects of folding and aggregation of the SOD1 protein. SOD1 activity is regular or only slightly reduced in two mutations: D90A in both homozygous and heterozygous patients; and L117V in heterozygous patients, although the measurement of a homozygous patient showed a 67% reduction in SOD1 activity when compared to control subjects [24]. Mutations in SOD1 are characterized by an important variability of interfamilial and interfamilial phenotypes concerning age and place of onset of clinical manifestations and disease duration. An exception is the A4V mutation, which is most often seen in lineages of ALS1 cases and consistently associated with high penetrance, younger ages at onset, the prevalence of lower motor neuron signs, and very rapid disease progression, usually in 12 months [25]. The penetrance of SOD1 mutations is variable, being almost complete for A4V and less than 30% at age 70 for I113T. However, most of the variants described so far are private mutations. Thus, few of them can safely describe the genotype and phenotype correlation. There is no specific therapy for patients with a mutation in the SOD1 gene. Still, there are many ongoing studies to develop new techniques (RNAi, antisense therapy) for the inactivation of this mutation, preventing the cytotoxic synthesis caused by this gene. In the area of immunotherapy, an antibody called SEDI (SOD1-Exposed-Dimer-Interface) was developed, with peptide sequencing corresponding to the dimeric interface of SOD1, which recognizes the enveloping or monomeric SOD1 proteins with this exposed interface [26]. In patients with ALS, regardless of age at disease onset, increased DNA methylation in whole blood was observed, constituting a marker of epigenetic dysfunction in ALS [27]. This high global DNA methylation is also seen in carriers of SOD1 mutations not fully penetrants

(p.Asn65Ser, p.Gly72Ser, p.Gly93Asp, and p.Gly130_Glu133del), contributing to the ALS phenotype [28].

VAPB (Vesicle-associated membrane protein-associated protein B/C)

VAPB consists of a multifunctional protein originating from a family (VAP) of vesicles associated with a protein membrane related to endoplasmic reticulum proteins. VAP proteins (VAPA, VAPB, and VAPC) and their homologs seem to be involved in different cellular processes, such as intracellular traffic and signalling, microtubule organization, mitochondrial localization, calcium homeostasis, lipid metabolism, and tumour proliferation [30]. The VAPB is composed of 3 domains the Major Sperm Protein, the MSP is composed of the first 150 amino acids, and the p56s mutation is found [31]. The VAP proteins are expressed ubiquitously and located between the endoplasmic reticulum region and the Golgi complex. They are involved with several molecular pathways, and some are directly related to the activities of motor neurons. The VAPB Protein has 16 highly conserved amino acids in its MSP domain [17]. The VAPB gene is located on chromosome 20q13.3, covers 57.7 kb in length in genomic DNA and is composed of six exons, and encodes the protein VAMP (Vescicle-associated membrane protein-associated protein B). It is an integral protein of the endoplasmic reticulum membrane, which has several functions, such as in intracellular vesicle trafficking, lipid transport, and protein unfolding response. These proteins are associated with intracellular membranes, including both the endoplasmic reticulum and the Golgi apparatus [25-33]. The VAPB gene encodes a protein located on the outer surface of the endoplasmic reticulum (ER). This comprises two coiled-coil domains, an MSP domain (Major Sperm Domain) and a transmembrane domain, which anchors it in the ER membrane [33]. Interestingly, the VAPB protein has been described as located at sites of contact between the ER. ER and other organelles, especially mitochondria, endosomes, and lipid vesicles. It is through these intersections that different cellular processes take place, such as autophagy, calcium flux regulation, endosome maturation, unfolded protein response, and protein synthesis [34-36]. Mutations in the VAPB gene have been primarily associated with an autosomal dominant familial subtype of Amyotrophic Lateral Sclerosis, ALS8. Patients with this condition presented, in their initial description, two distinct manifestations of ALS, classified as “typical” and “atypical” ALS,” which were distinguished by the presence of tremors only in the atypical form. In addition, manifestations of spinal muscular atrophy were observed among some individuals in the genealogy with a mutation in the VAPB gene. This phenomenon reinforces the tremendous phenotypic variability already described in the phenotypes associated with ALS and suggests that VAPB plays a fundamental role in eminently spinal circuits [31-37]. A mutation that causes the replacement of proline 56 by serine in the MSP domain (P56S) disrupts the three-dimensional structure and favours the aggregation of this protein. Data suggest that this mutation is responsible for a variable form of motor neuron diseases found in several families, mainly in Brazil. Due to the interaction of VAPB with other proteins, the mutation can evolve into a less stable interaction of endoplasmic reticulum proteins with at least two other proteins: tubulin and GAPDH [25-31]. The VAPB gene acts during transport and secretion in the Endoplasmic Reticulum (ER) and the Golgi complex. The P56S mutation may disrupt this function leading to the accumulation of transport intermediates in the form of cytosolic membranous aggregates. However, expression of the mutant form of VAPB does not alter the structure of the ER, and the possibility that alterations in the membrane system of the Golgi complex and ER are occurring in cells that express the altered form of VAPB is not ruled out. Thus, the VAPB mutant protein can compromise intracellular membrane transport and secretion and lead to loss of trophic signals or alteration of intracellular processes resulting in motor neuron death. It is also possible that VAPB is present in distinct structures of the ER membrane and the Golgi complex and that the mutation affects the accumulation of proteins in these sites [31]. ALS8 was subsequently discovered to be caused by this single mutation. Hypotheses suggest that the dominant inheritance of ALS8 is due to the dominant negative effect of the mutant protein. VAPB is ubiquitously expressed, yet the P56S mutation affects motor neurons. This selective vulnerability also occurs with ALS1-SOD1, ALS2-Alsin, and SETX mutations. Different cell types may not require the same amount of VAPB for survival, or VAPB may have another, as yet unknown, specific function in neurons. The P56S mutation can interfere with the stability of the VAPB protein complex, and a failure or gain-of-function mechanism could result in neurotoxicity and, consequently, motor neuron death [31]. Mutations in dominant VAPB lead to VAMP aggregation within immobile clumps in the endoplasmic reticulum (ER), which causes low protein levels, resulting in a diminished endoplasmic reticulum with anchored proteins containing lipid bonds and motor neuron degeneration. After insertion of the protein into the endoplasmic reticulum membrane, the P56S mutation in the VAPB gene causes the rapid assembly to generate paired cisternae in the ER, which give rise to a deeply restructured and non-aggregated domain of cytosolic proteins, which would be normal [33-38]. In addition to the loss of function mechanism, by sequestering potentially functional proteins in inclusion bodies, evidence for a toxic gain of function of mutant VAPB has also been reported. Mutant VAPB inclusions are ubiquitin-positive in transfected cells and motor neurons from transgenic animals. When overexpressed, wild and mutant types have been observed to decrease proteasome activity. This fact suggests that VAPB inclusions can alter proteasomes

and act to alter protein degradation pathways, associated with an important pathogenic mechanism by the toxicity of malformed protein aggregates in both sporadic and familial ALS. Another mechanism involved in inhibiting mitochondrial transport affects the kinesin anterograde motor regulation [26-38]. So far, most individuals affected by ALS8 are Brazilian, Caucasian, and carriers of the same mutation in exon 2 of the VAPB gene (c.166C>T; p.P56S VAPB). A founder effect was then postulated for this mutation in Brazil, which most likely arrived via Portuguese colonization 25 generations ago [31]. Later, other individuals with European ancestry but not carriers of the same VAPB haplotype were described in Germany, suggesting that the P56S mutation also arose independently. Patients in China, the United Kingdom, and the United States have also been reported with the P56S variant. More recently, different mutations in this gene, p.T46I and P56H have also been associated with ALS8. A third mutation (p.V234I) identified in a 43-year-old Dutch patient with joint expansions at C9ORF72 was also recently identified [39-40].

Main limitations arising from Amyotrophic Lateral Sclerosis and therapeutic treatment

It is a disease identified by presenting difficulties in speech; in view of this, as soon as it is diagnosed in the first stages, immediate intervention is necessary in order to soften the evolution of the disease and adapt the treatments to meet the need according to the demand of each patient [41]. Studies claim that the patient's mobility is impaired as the disease progresses, compromising their functional performance and leading them to depend on someone else's care. In this way, living together creates a powerful bond, thus establishing respect for the patient, and therefore physical fatigue does not prevent caring for the patient [42]. The main complications resulting from this pathology are structural and motor, such as weakness, contractures, and spasticity. It courses with impairment of speech, swallowing, and breathing muscles. With its progression, the affected person presents deformities and progressive paralysis, as well as the need for ventilator support, which is the main cause of death [43]. With its rapid progression resulting in a loss of the subject's autonomy in carrying out their simple day-to-day activities, many times they ask for help to complete them, in the future making them unable to carry them out independently, being forced to depend on them the care of another person. And with that, there is a change in the patient's and family's lifestyle and routine [42]. The loss of physical integrity and the absence of a cure bring with it fears about death; this has to do with being aware of how the disease progresses, which causes even more fear and consequently interferes with the patient's quality of life [42]. The emotional function is slightly related to the well-being of the individual, and with the discovery of ALS, several feelings come to appear, among them, sadness and despair are the most common; this has to do with the lack of freedom and independence caused by the rapid disease progression [42]. There are several possibilities of support for the patient with ALS; below are the leading measures adopted in the face of the clinical problem presented.

Sialorrhea: Symptom that causes social embarrassment, and may progress to aspiration pneumonia, the most common cause of death in ALS, after respiratory failure per se. Many patients wear bibs or insert tissues into their mouths to absorb saliva. The American Academy of Neurology recommends non-pharmacological measures, such as aspiration/suction, as well as pharmacological measures, such as anticholinergics, glycopyrrolate, and amitriptyline. The application of botulinum toxin has emerged as a new therapy against sialorrhea in these patients, with satisfactory results. In refractory cases, radiotherapy can be proposed [2-45].

Pseudo-bulbar effects: Affects between 20-50% of carriers, especially those with the bulbar form of the disease. These effects include uncontrollable crying and laughing. Selective serotonin inhibitors, tricyclic antidepressants, and serotonin-epinephrine reuptake inhibitors may be used. A new combination of dextromethorphan and quinidine sulphate was shown to be effective in a multicentre randomized phase 3 trial [2-47].

Sleep disorders: Anxiety and depression are constant conditions in ALS patients. Nocturnal hypoventilation also makes up for this resting difficulty, reducing total sleep time. Postural change and the use of pneumatic mattresses can help the patient. Mirtazapine is especially effective. Other benzodiazepines can also be used, as well as hypnotics such as zolpidem [2-48].

Respiratory Failure: Patients with ALS can progress to frank respiratory failure due to loss of strength and tonus of the diaphragmatic and intercostal muscles, making it necessary for pulmonary assessment of patients with the entity every three months, especially through spirometry. When the volume forced expiratory force exceeds 50% of the expected, non-invasive ventilation should be started [2-53].

Fatigue: Found in 50-80% of carriers and has a multifactorial etiology, including sleep disorders, nocturnal complaints such as nocturia and cramps, nutritional status, vital capacity, depression, and use of medications, including riluzole [2-56]. Modafinil showed significantly significant results when compared to placebo in reducing fatigue in ALS patients [57].

Pain: Symptom described in 60-70% of patients and usually involves extremities, neck, trunk, and back. Anti-inflammatories, non-opiate agents, opiate agents, muscle relaxants, quinine, gabapentin, steroids, botulinum toxin, and physical therapy can be used [2-59].

Spasticity: It can be a limitation of mobility and function for the patient. Studies explicitly investigating spasticity in ALS patients

are scarce. The most commonly used drugs for this symptom include baclofen, tizanidine, benzodiazepines, and dantrolene. Hydrotherapy, cryotherapy, heat, and shock waves can also be used in muscle spasticity [60,61]. Laryngospasm is understood as the sudden feeling that air cannot enter or leave the airways, usually lasting a few seconds and accompanied by inspiratory stridor, audible breaths, and forced rapid contractions of the laryngeal adductor muscles. Non-pharmacological measures can help the patient: change to the orthostatic position, fixation of the arms to stabilize the trunk, nasal breathing, and repeated swallowing. Benzodiazepines can be used as adjuvants in this therapy [2-64].

Constipation and urinary urgency: Symptoms in up to 30% of patients usually involve the genitourinary and digestive tract. Its multifactorial etiology is related to reduced mobility, reduced fluid and solid intake, use of medications, and weakness in the abdominal muscles. Treatment begins with implementing a diet rich in fiber, liquids, and laxative juices. Stimulants and laxatives such as Senna, Cascara Sagrada, and Bisacodyl should be used with care, in low doses, avoiding their chronic use. Lactulose and polyethylene glycol can be used as osmotic agents. Increased urinary frequency is very common in ALS patients [65].

Non-pharmacological measures include: avoiding caffeine and alcohol and use of a Foley catheter. Anticholinergic drugs such as oxybutynin, tolderodine, darifenacin, and solifenacin can be used [2-66]. There is no cure for ALS; therefore, treatment is aimed at minimizing the symptoms, recommending the action of a multidisciplinary team. Among the main medical approaches to managing the disease, the administration of medications and/or surgical approaches are included, whose objective is to minimize the symptoms and limitations imposed by this health condition. Although speech therapy therapeutic strategies are indicated for voice, speech, and swallowing management in patients with ALS, drug and surgical treatments can also impact the mentioned functions [41]. It should also be noted that the definition of palliative care, according to the WHO, is an approach that improves the quality of life of patients (adults and children) and their families who face problems associated with life-threatening illnesses. As well as, according to a consensus-based definition, palliative care is active, holistic care for individuals in all age groups, offering serious health-related suffering resulting from serious illnesses and, above all, those close to the end of life. This type of treatment improves the quality of life of patients, family members, and caregivers. With this, the adoption of palliative care contributes positively to patients with ALS [67]. It should be mentioned that ALS is currently a disease without curative treatment. However, a drug proven to be effective in its treatment (Riluzole) increases the life expectancy of people with the disease. In contrast, other drugs (i.e., tamoxifen and edaravone) are still being studied; further analyses are needed to define their effectiveness. Of these medications [68]. Pharmacological treatment is one of the treatment possibilities for people with ALS. This approach aims to improve the survival of these patients and help maintain functions related to communication and eating, among others. The use of riluzole, for example, can increase the survival of patients with ALS by up to six months. However, the literature does not mention direct and positive effects on voice, speech, and swallowing. Another drug, edaravone, effectively reduces functional limitations in people at the onset of the disease. Nuexdeta had an effect on improving bulbar function in patients with ALS, including the effect on self-perception related to speech and swallowing functions [41]. For the treatment of Riluzole®, it is the only drug approved by the Food and Drug Administration (FDA). It is a benzothiazole capable of reducing the toxic action of glutamate on motor neurons, increasing patient survival by up to 6 months; however, due to unknown factors, it loses its functionality approximately 18 months after starting treatment. Symptomatic treatment is indicated for a variety of symptoms and consists of improving the patient's quality of life [69]. There is no evidence that riluzole reverses already-established neuronal damage. Patients using it should be monitored for possible kidney damage, with an elevation of aminotransferases, nausea and vertigo, granulocytopenia, and asthenia [70]. Finally, palliative therapy is essential for managing patients with ALS, as it helps prevent complications and promotes a better quality of life [68].

Conclusion

Amyotrophic Lateral Sclerosis is, therefore, a multifactorial disease, with no known cause yet, with an inexorable and rapid course, with only palliative treatments that can only increase the patient's survival. A burden for the family and the carrier, which is up to a multidisciplinary team to help share the burden so that it passes in the best possible way until a cure, or something close to it, is found. Finally, palliative therapy is essential for managing patients with ALS, as it helps prevent complications and promotes a better quality of life.

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