JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

CLINICAL STUDY Open Access

Amyotrophic Lateral Sclerosis: I. Symptomatology and Staging

Dr. Alain L. Fymat*

Professor, International Institute of Medicine & Science, California, USA.

Received date: April 09, 2025, **Accepted date:** April 13, 2025, **Published date:** April 17, 2025.

***Corresponding Author:** Dr. Alain L. Professor, International Institute of Medicine & Science, California, USA.

Abstract

Amyotrophic lateral sclerosis is a relentless progressive and uncurable neurodegenerative disorder that affects the motor neurons in the brain and spinal cord. Clinical symptoms, neuro-radiographic patterns of pathology, and genetics have shed important light on the association between motor neuron diseases, cognition, and behavior. In this article, the signs, symptoms, and staging of the disease and its various types as well as other motor neuron diseases will be presented and discussed.

Abbreviations

ALS: Amyotrophic lateral sclerosis; fALS: familial ALS; FAS: Flail arm syndrome; FLS: Flail leg syndrome; FTD: Fronto-temporal dementia; HD: Hirayama's disease; jALS: juvenile ALS; LMN: Lower motor neuron; MMA: Monomelic atrophy; PDC: Parkinsonism-dementia complex; PLS: Primary lateral sclerosis; PrBP: Progressive bulbar palsy; PrMA: Progressive muscular; PsBP: Pseudobulbar palsy; sALS: sporadic ALS; UMN: Upper motor neuron.

Keywords

Amyotrophic lateral sclerosis; fronto-temporal dementia; monomelic atrophy; motor neuron diseases; neurodegenerative diseases; primary lateral sclerosis; progressive bulbar palsy; progressive muscular atrophy; pseudobulbar palsy.

-oOo-

The term amyotrophic lateral sclerosis (ALS) comes from the Greek language. "A" means no; "myo" refers to muscle; "trophic" means nourishment so, amyotrophic means "no muscle nourishment," and when a muscle has no nourishment, it "atrophies" or wastes away. "Lateral" identifies the areas in a person's spinal cord where portions of the nerve cells that signal and control the muscles are located. As this area

degenerates, it leads to scarring or hardening ("sclerosis") in the region.

ALS is a progressive neurodegenerative disorder that affects the motor neurons in the brain and spinal cord. Although cognitive and behavioral symptoms were documented in patients with ALS-type motor neuron disease in the late 1800's, many were trained that ALS, and motor neuron diseases in general, do not impact thinking and behavior. However, within the last 10 years, there has been a convergence of research on ALS clinical symptoms, neuro-radiographic patterns of pathology, and genetics that have shed important light on the association between motor neuron disease, cognition, and behavior. In this article, after reviewing the various ALS types, the signs and symptoms and the staging of ALS will be discussed. Sidebars will explore in greater details other motor neuron diseases and the ALS functional rating scale.

Types of ALS

When describing ALS, a distinction is usually made between those cases where the disease runs in a family - so-called 'familial' ALS (fALS), and the other cases or 'sporadic'ALS (sALS). However, there are many different sub-types of ALS, which are distinguished by their signs and symptoms and their genetic cause or lack of clear genetic association.

Sporadic ALS

Most people with ALS have a form of the condition that is described as sporadic, meaning it occurs in people with no apparent history of the disorder in their family. This is the most common form of the disease, accounting for approximately 90-95% of people living with ALS. In affected individuals, features of the condition usually first develop in their late fifties or early sixties.

Familial ALS

Individuals with familial ALS (fALS) are the first people in their families known to have the disease. For most of them, lifestyle, environmental or other risk factors may have contributed to the development of the disease. However, about 10% of people with familial ALS have a mutation in a gene that has been linked to ALS.

The signs and symptoms of fALS typically first appear in one's late forties or early fifties. Approximately 5-10% of people living with ALS in the U.S. have family members who have also been diagnosed with the disease, making it probable that a genetic mutation has been inherited. About two-thirds of people with fALS have mutations in known ALS genes, indicating that more genes likely remain to be discovered.

ALS is similar whether it is inherited or appears in a person with no family history of the disease, although people with fALS often start showing symptoms at earlier ages. Regardless of whether the disease is familial or sporadic, the progression of ALS can vary quite a bit from one person to another. Even within families, family members who have been diagnosed with ALS may have different disease courses. Researchers are trying to understand these differences to learn more about how to slow disease progression and treat ALS more effectively.

Other forms of ALS are:

Juvenile ALS

Rarely, people with familial ALS develop symptoms in childhood or their teenage years. These individuals have a rare form of the disorder known as juvenile ALS (jALS).

ALS - Frontotemporal dementia

A small proportion of people with ALS, estimated at 5-10% have a family history of ALS or a related condition called frontotemporal dementia (FTD), which is a progressive brain disorder that affects personality, behavior, and language. The condition also develops in approximately 20% of all individuals with ALS. Here, changes in personality and behavior may make it difficult for affected individuals to interact with others in a socially appropriate manner. Communication skills worsen as the disease progresses. It is unclear how the development of ALS and FTD are related. Individuals who develop both conditions are diagnosed as having ALS-FTD. (For more information on. dementia, see this author's book on the subject).

ALS-Parkinsonism-Dementia complex

A rare form of ALS that often runs in families is known as ALS-parkinsonism-dementia complex (ALS-PDC). This disorder type is characterized by the signs and symptoms of ALS, in addition to a pattern of movement abnormalities known as parkinsonism, and a progressive loss of intellectual function (dementia). Signs of parkinsonism include unusually slow movements (bradykinesia), stiffness, and tremors. Affected members of the same family can have different combinations of signs and symptoms. (For more information on Parkinson's disease and parkinsonism, see this author's book on the subject).

Other motor neuron diseases

ALS is a motor neuron disease, which is a group of neurological disorders that selectively affect motor neurons, the cells that control voluntary muscles of the body. Other motor neuron diseases include:

- Primary lateral sclerosis (PLS);
- Progressive muscular atrophy (PrMA);
- Progressive bulbar palsy (PrBP);
- Pseudobulbar palsy (PsBP); and
- Monomelic atrophy (MMA) also-called Hirayama's disease (HD).

As a disease, ALS itself can be classified in a few different ways:

- By which part of the motor neurons are affected;
- By the parts of the body first affected;
- Whether it is genetic; and
- By the age at which it started.

Each individual diagnosed with the condition will sit at a unique place at the intersection of these complex and overlapping subtypes, which presents a challenge to diagnosis, understanding, and prognosis.

Subtypes of motor neuron diseases

ALS can be classified by the types of motor neurons that are affected. To successfully control any voluntary muscle in the body, a signal must be sent from the motor cortex in the brain down the upper motor neuron (UMN) as it travels down the spinal cord. There, it connects via a synapse to the lower motor neuron (LMN) which connects to the muscle itself. Damage to either the UMN or LMN, as it makes its way from the brain to muscle, causes different types of symptoms. Damage to the UMN typically causes spasticity including stiffness and increased tendon reflexes or clonus, while damage to the LMN typically causes weakness, muscle atrophy, and fasciculation.

Classical ALS

Classical (or classic) ALS involves degeneration to both the UMNs in the brain and the LMNs in the spinal cord. PLS involves degeneration of only the UMNs while PrMA involves only the LMNs. There is a debate over whether PLS and PrMA are separate diseases or simply variants of ALS (Table 1).

Main ALS subtypes	Upper motor neuron degeneration	Lower motor neuron degeneration
Classical ALS	Yes	Yes
Primary lateral sclerosis (PLS)	Yes	No
Progressive muscular atrophy (PrMA)	No	No

Table 1: Classification of the main ALS subtypes

Classical ALS accounts for about 70% of all cases of ALS and can be subdivided into where symptoms first appear as these are usually focused to one region of the body at initial presentation before later spreading. We distinguish between limb-onset ALS (also known as spinal-onset) and bulbar-onset ALS. Limb-onset ALS begins with weakness in the hands, arms, feet, and/or legs and accounts for about two-thirds of all classical ALS cases. Bulbar-onset ALS begins with weakness in the muscles of speech, chewing, and swallowing and accounts for about 25% of classical ALS cases. A rarer type of classical ALS affecting around 3% of patients is respiratory onset, in which the initial symptoms are difficulty breathing (dyspnea) upon exertion, at rest, or while lying flat (orthopnea). (see Tables 2 and 3).

ALS sub-type	Body area and % of occurrence
Limb (or spinal) onset	o Weakness in hands, arms, feet, and/or legs o 66.4% of all cases
Bulbar onset	o Weakness in the muscles of speech, chewing, and swallowing o 25% of all cases
Respiratory onset	o Difficulty breathing (dyspnea) upon exertion, at rest, or while lying flat (orthopnea). o 3% of all cases

Table 2: Sub-types of classical ALS by onset and percentage of occurrence

Primary lateral sclerosis

Primary lateral sclerosis (PLS) is a subtype of the overall ALS category which accounts for about 5% of all cases and only affects the upper motor neurons in the arms, legs, and bulbar region. However, more than 75% of people with apparent PLS go on to later develop lower motor neuron signs within four years of symptom onset, meaning that a definitive diagnosis of PLS cannot be made until several years have passed.

PLS has a better prognosis than classical ALS, as it progresses slower, results in less functional decline, does not affect the ability to breathe, and causes less severe weight loss than classical ALS.

Progressive muscular atrophy

Progressive muscular atrophy (PrMA) is another subtype that accounts for about 5% of the overall ALS category and affects lower motor neurons in the arms, legs, and bulbar region. While PrMA is associated with longer survival on average than classical ALS, it is still progressive over time, eventually leading to respiratory failure and death. As with PLS developing into classical ALS, PrMA can also develop into classical ALS over time if the lower motor neuron involvement progresses to include upper motor neurons, in which case the diagnosis might be changed to classic ALS.

Rare, isolated variants

Isolated variants of ALS have symptoms that are limited to a single region for at least a year; they progress more slowly than classical ALS and are associated with longer survival. These regional variants of ALS can only be considered as a diagnosis should the initial symptoms fail to spread to other spinal cord regions for an extended period (at least 12 months). Variants include:

Flail arm syndrome

Flail arm syndrome (FAS) is characterized by lower motor neuron damage affecting the arm muscles, typically starting with the upper arms symmetrically and progressing downwards to the hands.

Flail leg syndrome

Flail leg syndrome (FLS) is characterized by lower motor neuron damage leading to asymmetrical weakness and wasting in the legs starting around the feet. Isolated bulbar palsy is characterized by upper or lower motor neuron damage in the bulbar region (in the absence of limb symptoms for at least 20 months), leading to gradual onset of difficulty with speech (dysarthria) and swallowing (dysphagia).

ALS sub-type	Body area and % of occurrence
Primary lateral sclerosis (PLS)	o Affects UMNs in the arms, legs, and bulbar region. o 5% of all cases o > 75% of PLS people develop LMNs signs within 4 years o Better diagnosis: Progresses slower, results in less functional decline, does not affect the ability to breathe, and causes less severe weight loss
Progressive muscular atrophy (PrMA)	o Affects LMNs in arms, legs, and bulbar region o 5% of all cases o Longer survival than classical ALS. o Over time, can develop into classical ALS
Rare isolated variants: **o Flail arm syndrome (FAS)** **o Flail leg syndrome (FLS)**	 o LMN damage affecting arm muscles o LMN damage affecting legs

Table 3: Sub-types of classical ALS and percentage of occurrence

Signs and Symptoms

The disease is characterized by symptoms and signs of degeneration of the upper and lower motor neurons, which are specialized nerve cells that control muscle movement. These nerve cells are found in the brain and spinal cord. In ALS, motor neurons die (atrophy) over time, leading to progressive weakness of the bulbar, limb, thoracic and abdominal muscles. Other brain functions, including oculomotor and sphincter function, are relatively spared, but may be involved in some patients. Cognitive dysfunction occurs in 20–50% of cases, and 5–15% develop dementia usually of the frontotemporal type. Death because of respiratory failure follows on average 2–4 years after symptom onset, but 5–10% of patients may survive for a decade or more. The mean age of onset is 43–52 years when the disease runs in a family and 58–63years in other cases. The life-time risk of developing ALS is 1 in 350–500, with male sex, increasing age, and hereditary disposition being the main risk factors.

The first signs and symptoms of ALS may be so subtle that they are overlooked. The earliest symptoms include

muscle twitching, cramping, stiffness, or weakness. Affected individuals may develop slurred speech (dysarthria) and, later, difficulty chewing or swallowing (dysphagia). Many people with ALS experience malnutrition because of reduced food intake due to dysphagia and an increase in their body's energy demands (metabolism) due to prolonged illness. Muscles become weaker as the disease progresses, and arms and legs begin to look thinner as muscle tissue atrophies. Individuals with ALS eventually lose muscle strength and the ability to walk. Affected individuals eventually become wheelchair-dependent and increasingly require help with personal care and other activities of daily living. Over time, muscle weakness causes affected individuals to lose the use of their hands and arms. Breathing becomes difficult because the muscles of the respiratory system weaken. Most people with ALS die from respiratory failure within 2 to 10 years after the signs and symptoms of ALS first appear; however, disease progression varies widely among affected individuals.

Motor symptoms (chorea)

The disorder causes muscle weakness, atrophy, and muscle spasms throughout the body due to the degeneration of the upper motor and lower motor neurons. Sensory nerves and the autonomic nervous system are generally unaffected, meaning the majority of people with ALS maintain hearing, sight, touch, smell, and taste.

We can distinguish between five different motor symptoms, as further succinctly described:

Initial-onset symptoms

The start of ALS may be so subtle that the symptoms are overlooked. The earliest symptoms of ALS are muscle weakness or muscle atrophy, typically on one side of the body. Other presenting symptoms include trouble swallowing or breathing, cramping, or stiffness of affected muscles; muscle weakness affecting an arm or a leg; or slurred and nasal speech. The parts of the body affected by early symptoms of ALS depend on which motor neurons in the body are damaged first.

Limb-onset symptoms

In limb-onset ALS, the first symptoms are in the arms or the legs. If the legs are affected first, people may experience awkwardness, tripping, or stumbling when walking or running; this is often marked by walking with a "dropped foot" that drags gently on the ground. If the arms are affected first, they may experience difficulty with tasks requiring manual dexterity, such as buttoning a shirt, writing, or turning a key in a lock.

Bulbar-onset symptoms

In bulbar-onset ALS, the first symptoms are difficulty speaking or swallowing. Speech may become slurred, nasal in character, or quieter. There may be difficulty with swallowing and loss of tongue mobility.

Respiratory-onset symptoms

A small proportion of people experience "respiratory-onset" ALS, where the intercostal muscles that support breathing are affected first.

Upper- and lower-motor neuron symptoms

Over time, people experience increasing difficulty moving, swallowing (dysphagia), and speaking or forming words (dysarthria). Symptoms of upper motor neuron involvement include tight and stiff muscles (spasticity) and exaggerated reflexes (hyperreflexia), including an overactive gag reflex. While the disease does not cause pain directly, pain is a symptom experienced by most people with ALS caused by reduced mobility. Symptoms of lower motor neuron degeneration include muscle weakness and atrophy, muscle cramps, and fleeting twitches of muscles that

can be seen under the skin (fasciculations).

Cognitive, emotional, and behavioral symptoms

Cognitive impairment or behavioral dysfunction is present in 30–50% of individuals with ALS and can appear more frequently in later stages of the disease. Language dysfunction, executive dysfunction, and troubles with social cognition and verbal memory are the most commonly reported cognitive symptoms in ALS.

Cognitive impairment is found more frequently in patients with C9orf72 gene repeat expansions, bulbar onset, bulbar symptoms, family history of ALS, and/or a predominantly upper motor neuron phenotype.

Emotional lability is a symptom in which patients cry, smile, yawn, or laugh, either in the absence of emotional stimuli, or when they are feeling the opposite emotion to that being expressed. It is experienced by about half of ALS patients and is more common in those with bulbar-onset ALS. While relatively benign relative to other symptoms, it can cause increased stigma and social isolation as people around the patient struggle to react appropriately to what can be frequent and inappropriate outbursts in public.

In addition to mild changes in cognition that may only emerge during neuropsychological testing, around 10–15% of individuals have signs of frontotemporal dementia (FTD). Repeating phrases or gestures, apathy, and loss of inhibition are the most frequently reported behavioral features of ALS. ALS and FTD are now considered to be part of a common disease spectrum (ALS–FTD) because of genetic, clinical, and pathological similarities. Genetically, repeat expansions in the C9orf72 gene account for about 40% of genetic ALS and 25% of genetic FTD.

Cognitive and behavioral issues are associated with a poorer prognosis as they may reduce adherence to medical advice, and deficits in empathy and social cognition which may increase caregiver burden.

Stages

The stages of ALS can vary from person to person, but the disease typically progresses in a predictable way through different stages as outlined below.

Early stage (mild symptoms)

• **Initial symptoms:** The early stage of ALS may present with mild initial symptoms, such as:
o Muscle weakness or twitching (fasciculations).
o Difficulty with fine motor skills (e.g., buttoning a shirt or writing).
o Slurred speech or difficulty swallowing (dysphagia).
o Mild muscle cramps or stiffness (spasticity).
o Unexplained falls or stumbling.
• **Impact:** The symptoms are usually localized to one part of the body, such as the hands, arms, or legs. Many people can still carry out most of their daily activities with little difficulty.

Middle stage (progressive weakness)

As the disease spreads, many muscles weaken and start to stiffen. Range of motion exercises will likely be recommended by physical therapists to help keep muscles loose and prevent the formation of contractures and muscle pain. Breathing may become affected. A BiPAP machine or a phrenic pacer might be suggested, particularly to help improve sleeping. A feeding tube might be recommended to help meet nutritional needs. Medications might be also recommended to help control pseudobulbar effect (uncontrolled laughing or crying) or to help reduce muscle spasms.

People with bulbar-onset ALS often work with a speech therapist to keep their ability to speak for longer. Those with limb-onset ALS may rely on a cane, walker, or wheelchair due to difficulties walking and maintaining

balance. To summarize, middle stage symptoms involve:

• **Increased weakness:** The muscle weakness and atrophy (muscle wasting) begin to spread to other areas of the body, including:
o Difficulty with walking, standing, or using the arms and hands.
o More noticeable speech problems (e.g., difficulty articulating words).
o Increased difficulty swallowing and breathing.

• Loss of mobility: Patients may need assistive devices like a walker or wheelchair.
• Loss of independence: As motor function declines, individuals may require help with daily activities like dressing, feeding, and bathing.

Late stage (severe disability)

As ALS progresses and a person's muscles become paralyzed, they may lose the ability to move and speak. Many people with ALS may require a wheelchair to get around. Some may communicate through assistive devices like an eye-tracking device or a letter board. Others may choose to undergo a tracheostomy, a procedure in which a tube is surgically inserted into the throat, to help them breathe. People with late-stage ALS are often cared for at home or in a hospice. To summarize, late-stage symptoms involve:

• **Severe weakness:** Muscle weakness becomes severe, and most voluntary muscles lose function, including:
o Loss of the ability to move arms, legs, or head.
o Complete loss of speech and swallowing ability.
o Respiratory difficulties as the muscles responsible for breathing become weak.

• **Complete paralysis:** In the later stages, patients are often paralyzed and may require a ventilator to assist with breathing.

• **Cognitive changes:** While ALS mainly affects motor neurons, some people may experience cognitive changes, such as difficulties with memory, problem-solving, and decision-making (this is known as frontotemporal dementia in some ALS patients).

• **Total dependence:** Patients become completely dependent on caregivers for all daily activities.

Late-stage disease management

Difficulties with chewing and swallowing make eating very difficult (dysphagia) and increase the risk of choking or of aspirating food into the lungs. In later stages of the disorder, aspiration pneumonia can develop. Maintaining a healthy weight can become a significant problem that may require the insertion of a feeding tube. As the diaphragm and intercostal muscles of the rib cage that support breathing weaken, measures of lung function such as vital and inspiratory pressure diminish. In respiratory-onset ALS, this may occur before significant limb weakness is apparent. Individuals affected by the disorder may ultimately lose the ability to initiate and control all voluntary movement, known as locked-in syndrome. Bladder and bowel function are usually spared, meaning urinary and fecal incontinence are uncommon, although trouble getting to a toilet can lead to difficulties. The extraocular responsible for eye movement are usually spared, meaning the use of eye tracking technology to support augmentative communication is often feasible, albeit slow, and needs may change over time. Despite these challenges, many people in an advanced state of disease report satisfactory wellbeing and quality of life.

End-stage (terminal phase)

• **Respiratory failure:** In the final stage of ALS, respiratory failure occurs due to the weakening of the respiratory muscles. Most individuals with ALS die from complications related to respiratory failure, such as pneumonia, or from respiratory insufficiency.

• **Death:** This stage typically occurs 2 to 5 years after the initial onset of symptoms with one in ten people surviving for at least 10 years. Some individuals may survive longer with the help of life-sustaining interventions such as mechanical ventilation.

It is important to note that the progression of ALS can vary significantly between individuals, and some people may experience a more rapid decline, while others may have a slower progression. Early intervention with medical care, including respiratory support and physical therapy, can help manage symptoms and improve the quality of life.

Progression

Although the initial site of symptoms and the subsequent rate of disability progression vary from person to person, the initially affected body region is usually the most affected over time, and symptoms usually spread to a neighboring body region. For example, symptoms starting in one arm usually spread next to either the opposite arm or to the leg on the same side. Bulbar-onset patients most typically get their next symptoms in their arms rather than legs. Arm-onset patients typically spread to the legs before the bulbar region, and leg-onset patients typically spread to the arms rather than the bulbar region. Over time, regardless of where symptoms began, most people eventually lose the ability to walk or use their hands and arms independently. Less consistently, they may lose the ability to speak and to swallow food. It is the eventual development of weakness of the respiratory muscles, with the loss of ability to cough and to breathe without support, that is ultimately life-shortening in ALS.

Functional rating scale

The rate of progression can be measured using the ALS Functional Rating Scale - Revised (ALSFRS-R), a 12-item instrument survey administered as a clinical interview or self-reported questionnaire that produces a score between 48 (normal function) and 0 (severe disability). The ALSFRS-R is the most frequently used outcome measure in clinical trials and is used to track disease progression (see Sidebar2). Though the degree of variability is high, and a small percentage of people have a much slower progression, on average, people with ALS lose about 1 ALSFRS-R point per month. Brief periods of stabilization ("plateaus") and even small reversals in ALSFRS-R score are not uncommon, since the tool is subjective, can be affected by medication, and different forms of compensation for changes in function. However, it is rare (<1%) for these improvements to be large (i.e. greater than 4 ALSFRS-R points) or sustained (i.e. greater than 12 months). A survey-based study among clinicians showed that they rated a 20% change in the slope of the ALSFRS-R as being clinically meaningful, which is the most common threshold used to determine whether a new treatment is working in clinical trials.

Prognosis, Staging, and Survival

Although respiratory support using non-invasive can ease problems with breathing and prolong survival, it does not affect the progression rate of ALS. Most people with ALS die between two and four years after the diagnosis. Around 50% of people with ALS die within 30 months of their symptoms beginning, about 20% live between five and ten years, and about 10% survive for 10 years or longer.

The most common cause of death among people with ALS is respiratory failure, often accelerated by pneumonia. Most ALS patients die at home after a period of worsening difficulty breathing, a decline in their nutritional status, or a rapid worsening of symptoms. Sudden death or acute respiratory distress are uncommon. Access to palliative care is recommended from an early stage to explore options, ensure psychosocial support for the patient and

caregivers, and to discuss advance healthcare directives.

As with cancer staging, ALS has staging systems numbered between 1 and 4 that are used for research purposes in clinical trials. Two very similar staging systems emerged around a similar time, the King's staging system (KSS) and the Milano-Torino (MiToS) functional staging (see Tables 4 and 5, respectively):

	Stage 1	Stage 2	Stage 3	Stage 4
Stage description	Symptom-onset involvement of the first region	2A: Diagnosis 2B; Involvement of the second region	Involvement of the third region	4A: Need for a feeding tube 4B: Need for non-invasive ventilation
Median time in stage	13.5 months	17.7 months	23.3 months	4A: 17.7 months 4B: 30.3 months

Table 4: King's ALS staging system and prognosis at each stage

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Stage description	No loss of afunctional domain	Loss of 1 functional domain	Loss of 2 functional domains	Loss of 3 functional domains	Loss of 4 functional domains	Death
Probability of death at each stage	7%	26%	33%	33%	86%	100%

Table 5: Mitos ALS staging system and prognosis at each stage

Providing individual patients with a precise prognosis is not currently possible, though research is underway to provide statistical models on the basis of prognostic factors including age at onset, progression rate, site of onset, and presence of frontotemporal dementia.

Those with a bulbar onset have a worse prognosis than limb-onset ALS; a population-based study found that bulbar-onset ALS patients had a median survival of 2.0 years and a 10-year survival rate of 3%, while limb-onset ALS patients had a median survival of 2.6 years and a 10-year survival rate of 13%.

Those with respiratory-onset ALS had a shorter median survival of 1.4 years and 0% survival at 10 years. While astrophysicist Stephen Hawking lived for 55 more years following his diagnosis, his was an exceptional case.

Conclusions and take-aways

- ALS is a progressive neurodegenerative disorder that affects the motor neurons in the brain and spinal cord. However, within the last 10 years, there has been a convergence of research on ALS clinical symptoms, neuro-radiographic patterns of pathology, and genetics that have shed important light on the association between motor neuron disease, cognition, and behavior.

- Motor symptoms (chorea) include muscle weakness, atrophy, and muscle spasms throughout the body due to the degeneration of the upper motor and lower motor neurons.

Sensory nerves and the autonomic nervous system are generally unaffected, meaning the majority of people with ALS maintain hearing, sight, touch, smell, and taste.

- Five different motor symptoms can be categorized as: Initial-onset symptoms, limb-onset symptoms, bulbar-onset symptoms, respiratory-onset symptoms, and upper- and lower-motor neuron symptoms.

- Symptoms of cognitive impairment or behavioral dysfunction are present in 30–50% of individuals with ALS and can appear more frequently in later stages of the disease. Language dysfunction, executive dysfunction, and troubles with social cognition and verbal memory are the most commonly reported cognitive symptoms.

- In addition to mild changes in cognition, around 10–15% of individuals have signs of frontotemporal dementia (FTD). Indeed, ALS and FTD are now considered to be part of a common disease spectrum because of genetic, clinical, and pathological similarities.

- Cognitive and behavioral issues are associated with a poorer prognosis as they may reduce adherence to medical advice, and deficits in empathy and social cognition which may increase caregiver burden.

- The stages of ALS can vary from person to person, but the disease typically progresses in a predictable way through different stages from early stage (mild symptoms) to middle stage (progressive weakness), to late stage (severe disability), to end stage (terminal phase).

- It is important to note that the progression of ALS can vary significantly between individuals, and some people may experience a more rapid decline, while others may have a slower progression.

- Early intervention with medical care, including respiratory support and physical therapy, can help manage symptoms and improve the quality of life.

- Although the initial site of symptoms and the subsequent rate of disability progression vary from person to person, the initially affected body region is usually the most affected over time, and symptoms usually spread to a neighboring body region.

- The rate of progression can be measured using the ALS Functional Rating Scale - Revised (ALSFRS-R), a 12-item instrument survey administered as a clinical interview or self-reported questionnaire that produces a score between 48 (normal function) and 0 (severe disability) as detailed in the Sidebar.

Sidebar - The ALS Functional Rating Scale

The ALS Functional Rating Scale - Revised (ALSFRS-R), a 12-item instrument survey (three of which are newer items) administered as a clinical interview or self-reported questionnaire. It devolves as follows:

Criteria

ALSFRS-R includes 12 questions that can have a score of 0 to 4. A score of 0 on a question would indicate no function while a score of 4 would indicate full function. This scale has been useful for doctors in diagnosing patients, measuring disease progression and for researchers when selecting patients for a study and measuring the potential effects of a clinical trial.

The ALSFRS-R scale has some limitations though since it is not useful to compare scores of people who present with different onset. In ALS, the main type of onset is bulbar followed by limb-onset, which describes the region of motor neurons first affected. Individuals may also present with respiratory-onset ALS, but this occurs very rarely. Since there are three different types of ALS, ALSFRS-R scores are often grouped in categories depending on the type of onset.

Since there are three main pathways of progression, the questions are also divided in relation to the types of onsets. Questions 1 to 3 are related to bulbar onset, questions 4 to 9 are related to limb onset and questions 10 to 12 are related to respiratory onset. Further developments of the ALSFRS-R include an extended version (ALSFRS-EX) to mitigate the floor effect and a version with explanatory notes, which is particularly suitable for self-assessment (ALSFRS-R-SE, self-explanatory).

Progression

ALSFRS-R scores calculated at diagnosis can be compared to scores throughout time to determine the speed of progression. The rate of change, called the ALSFRS-R slope can be used as a prognostic indicator.

Relating the ALSFRS-R score to staging criteria is also useful in determining prognosis. The King's system (KS) relies on the clinical spread of disease as a measure of progression while the Milano-Torino Staging (MiToS) utilizes the sub scores produced by the ALSFRS-R to define stages.

Questions

The questions used to determine an individual's ALSFRS-R score are listed in Table 6 below:

Question	4	3	2	1	0
1. Speech	Normal processes	Detectable disturbance	Intelligible with repeating	Combined with nonvocal communication	Loss of useful speech
2. Salivation	Normal	Slight but definite excess of saliva in mouth; may have nighttime drooling	Moderately excessive saliva; may have minimal drooling	Marked excess of saliva with some drooling	Marked drooling; requires constant tissue or handkerchief
3. Swallowing	Normal eating habits	Early eating problems; occasional choking	Dietary consistency changes	Needs supplemental tube feeding	NPO (exclusively parenteral or enteral feeding)
4. Handwriting	Normal	Slow or sloppy: all words are legible	Not all words are legible	Able to grip pen but unable to write	Unable to grip pen
5a. Cutting food & handling utensils (patients w/o gastrostomy)	Normal	Somewhat slow and clumsy, but no help needed	Can cut most foods, although clumsy and slow; some help needed	Food must be cut by someone but can still feed slowly	Needs to be fed
5b. Cutting food & handling utensils (patients with gastrostomy)	Normal	Clumsy but able to perform all manipulations independently	Some help needed with closures and fasteners	Provides minimal assistance to caregiver.	Unable to perform any aspect of task
6. Dressing and hygiene	Normal function	Independent and complete	Intermittent assistance or	Needs attendant for self-care	Total dependence

		self-care with effort or decreased efficiency	substitute methods		
7. Turning in bed and adjusting bed clothes	Normal	Somewhat slow and clumsy, but no help needed	Can turn alone or adjust sheets, but with great difficulty	Can initiate but not turn or adjust sheets alone	Helpless
8. Walking	Normal	Early ambulation difficulties	Walks with assistance	Non-ambulatory functional movement	No purposeful leg movement
9. Climbing stairs	Normal	Slow	Mild unsteadiness or fatigue	Needs assistance	Cannot do
10. Dyspnea (new)	None	Occurs when walking	Occurs with one or more of the following: eating, bathing, dressing (ADL)	Occurs at rest, difficulty breathing when either sitting or lying	Significant difficulty, considering using mechanical respiratory support
11. Orthopnea (new)	None	Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows.	Needs extra pillows in order to sleep (more than two)	Can only sleep sitting-up	Unable to sleep
12. Respiratory insufficiency (new)	None	Intermittent use of BiPAP (Bilevel Positive Airway Pressure)	Continuous use of BiPAP during the night	Continuous use of BiPAP during the night and day.	Invasive mechanical ventilation by intubation or tracheostomy

Table 6: Questions used in the ALS Functioning Rating Scale

References

1. American Speech Language-Hearing Association (2012). "Amyotrophic Lateral Sclerosis (ALS)", Rockville, MD.
2. American Speech Language-Hearing Association (2016). "Amyotrophic lateral sclerosis (ALS)", Rockville, MD.
3. (The) Amyotrophic Lateral Sclerosis (ALS) Association (2020). "Understanding ALS".
4. (The) Amyotrophic Lateral Sclerosis (ALS) Association (2022). "Who Gets ALS?".
5. (The) Amyotrophic Lateral Sclerosis (ALS) Association (2023). "FDA-approved drugs for treating ALS".
6. (Canada) Amyotrophic Lateral Sclerosis (ALS) Society of Canada (2017). "About ALS".
7. Andersen PM (2006). "Amyotrophic lateral sclerosis associated with mutations in the CuZn superoxide dismutase gene", Curr Neurol Neurosci Rep. 6(1):37-46. doi:10.1007/s11910-996-0008-9.

8. Andersen PM and Al-Chalabi A (2011). ". Clinical genetics of amyotrophic lateral sclerosis: What do we really know?", Nat Rev Neurol. 11;7(11):603-15. doi: 10.1038/nrneurol.2011.150.
9. Bede P, Elamin M, Byrne S, McLaughlin RL, Kenna K, Vajda A, et al. (2013). "Basal ganglia involvement in amyotrophic lateral sclerosis", Neurology 81(24):2107–15. doi: 10.1212/01.wnl.0000437313.80913.2c.
10. Beeldman E, Raaphorst J, Klein Twennaar M, de Visser M, Schmand BA, and de Haan RJ (2016). "The cognitive profile of ALS: a systematic review and meta-analysis update". Journal of Neurology, Neurosurgery, and Psychiatry 87 (6): 611–19. doi:10.1136/jnnp-2015-310734.
11. Bigio EH, Weintraub S, Rademakers R, Baker M, Ahmadian SS, Rademaker A, et al. (2013). "Frontotemporal lobar degeneration with TDP-43 proteinopathy and chromosome 9p repeat expansion in C9ORF72: clinicopathologic correlation", Neuropathology 33(2):122–33. doi: 10.1111/j.1440-1789.2012.01332.x.
12. Boddy SL, Giovannelli I, Sassani M, Cooper-Knock J, Snyder MP, Segal E, et al. (2021). "The gut microbiome: A key player in the complexity of amyotrophic lateral sclerosis (ALS)", BMC Med. 19(1):13. doi: 10.1186/s12916-020-01885-3.
13. Bonifacino T, Zerbo RA, Balbi M, Torazza C, Frumento G, Fedele E, et al. (2021). "Nearly 30 Years of animal models to study amyotrophic lateral sclerosis: A historical overview and future perspectives", Int. J. Mol. Sci. 22(22). doi: 10.3390/ijms222212236.
14. Bos van den MAJ, Higashihara M, Geevasinga N, Menon P, Kiernan MC, and Vucic S (2018). "Imbalance of cortical facilitatory and inhibitory circuits underlies hyperexcitability in ALS", Neurology 91(18):e1669–e76. doi: 10.1212/WNL.0000000000006438.
15. Bos van den MAJ, Higashihara M, Geevasinga N, Menon P, Kiernan MC, and Vucic S (2021). "Pathophysiological associations of transcallosal dysfunction in ALS", Eur. J. Neurol. 28(4):1172–80. doi: 10.1111/ene.14653.
16. Braak H, Brettschneider J, Ludolph AC, Lee VM, Trojanowski JQ, and Tredici KD (2013). "Amyotrophic lateral sclerosis: A model of corticofugal axonal spread", Nat. Rev. Neurol. 9(12):708–14. doi: 10.1038/nrneurol.2013.221.
17. Braak H, Ludolph AC, Neumann M, Ravits J, and Tredici del K (2017). "Pathological TDP-43 changes in Betz cells differ from those in bulbar and spinal alpha-motoneurons in sporadic amyotrophic lateral sclerosis", Acta Neuropathol. 133(1):79–90. doi:10.1007/s00401-016-1633-2.
18. Brown RH and Al-Chalabi A (2017). "Amyotrophic Lateral Sclerosis". The New England Journal of Medicine. 377 (2): 162–72. doi:10.1056/NEJMra1603471.
19. Cappellari A, Ciammola A, and Silani V (2008). "The pseudopolyneuritic form of amyotrophic lateral sclerosis (Patrikios' disease) [La forme pseudopolyneuritique de la sclérose latérale amyotrophique (maladie de Patrikios)], Electromyogr Clin Neurophysiol. 48(2)75-81.
20. Castelnovo V, Canu E, Mattei de F, Filippi M, and Agosta F (2023). "Basal ganglia alterations in amyotrophic lateral sclerosis", Front. Neurosci. 17:1133758. doi: 10.3389/fnins.2023.1133758.
21. Chapman M.C, Jelsone-Swain L, Fling BW, Johnson TD, Gruis K, and Welsh RC (2012). "Corpus callosum area in amyotrophic lateral sclerosis", Amyotroph. Lateral Scler. 13(6):589–91. doi: 10.3109/17482968.2012.708935.
22. Chen H, Qian K, Du Z, Cao J, Petersen A, Liu H, et al. (2014). "Modeling ALS with iPSCs

reveals that mutant SOD1 misregulates neurofilament balance in motor neurons". Stem Cell 14(6):796–809. doi: 10.1016/j.stem.2014.02.004.

23. Chio A, Borghero G, Restagno G, Mora G, Drepper C, Traynor BJ, Sendtner M, et al. (2012). "Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of C9ORF72", Brain 135(Pt 3):784-93. doi: 10.1093/brain/awr366.
24. Chiò A, Mora G and Lauria G (2017). "Pain in amyotrophic lateral sclerosis". The Lancet. Neurolog. 16 (2): 144–57. arXiv:1607.02870. doi:10.1016/S1474-4422(16)30358-1.
25. Christensen J, Yamakawa GR, Shultz SR, and Mychasiuk R (2021). "Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties", Prog. Neurobiol. 198:101917. doi: 10.1016/j.pneurobio.2020.101917.
26. Couratier P, Corcia P, Lautrette G, Nicol M, and Marin B (2017). "ALS and frontotemporal dementia belong to a common disease spectrum". Revue Neurologique. 173 (5): 273–9. doi:10.1016/j.neurol.2017.04.001.
27. Cykowski MD, Takei H, Schulz PE, Appel SH, and Powell SZ (2014). "TDP-43 pathology in the basal forebrain and hypothalamus of patients with amyotrophic lateral sclerosis", Acta Neuropathol. Commun. 2:171. doi: 10.1186/s40478-014-0171-1.
28. Dilliott AA, Kwon S, Rouleau GA, Iqbal S, and Farhan SMK (2023). "Characterizing proteomic and transcriptomic features of missense variants in amyotrophic lateral sclerosis genes", Brain doi: 10.1093/brain/awad224.
29. Duchenne GB and Poore GV (1883). "Selections from the clinical works by Duchenne (de Boulogne)" xxii:472.
30. Eisen A, Kim S, and Pant B (1992). "Amyotrophic lateral sclerosis (ALS): A phylogenetic disease of the corticomotoneuron"?, Muscle Nerve 15(2):219–24. doi: 10.1002/mus.880150215.
31. Eisen A and Kuwabara S (2012). "The split hand syndrome in amyotrophic lateral sclerosis", J. Neurol. Neurosurg. Psychiatry 83(4):399–403. doi: 10.1136/jnnp-2011-301456.
32. Eisen A, Kiernan M, Mitsumoto H, and Swash M (2014). "Amyotrophic lateral sclerosis: A long preclinical period?", J. Neurol. Neurosurg. Psychiatry. 85(11):1232–8. doi: 10.1136/jnnp-2013-307135.
33. Eisen A, Braak H, Tredici del K, Lemon R, Ludolph AC, and Kiernan MC. (2017). "Cortical influences drive amyotrophic lateral sclerosis", J. Neurol. Neurosurg. Psychiatry 88(11):917–24. doi: 10.1136/jnnp-2017-315573.
34. Eisen A (2021). "The dying forward hypothesis of ALS: Tracing its history", Brain Sci. 11(3):300. doi:10.3390/brainsci11030300.
35. Eisen A and Bede P (2021). "The strength of corticomotoneuronal drive underlies ALS split phenotypes and reflects early upper motor neuron dysfunction", Brain Behav. 11(12):e2403. doi: 10.1002/brb3.2403.
36. Eisen A and Lemon R (2021). "The motor deficit of ALS reflects failure to generate muscle synergies for complex motor tasks, not just muscle strength", Neurosci. Lett. 762:136171. doi: 10.1016/j.neulet.2021.136171.
37. Es van MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, et al. (2017). "Amyotrophic lateral sclerosis". Lancet. 390 (10107): 2084–98. doi:10.1016/S0140-6736(17)31287-4.
38. Farg MA, Sundaramoorthy V, Sultana JM,

Yang S, Atkinson RA, Levina V, Halloran MA, Gleeson PA, Blair IP, Soo KY, King AE, and Atkin JD (2014). “C9ORF72, implicated in amyotrophic lateral sclerosis and frontotemporal dementia, regulates endosomal trafficking”, Hum Mol Genet. 23(13):3579-95. doi: 10.1093/hmg/ddu068. Erratum In: Hum Mol Genet. 26(20):4093-4. doi: 10.1093/hmg/ddx309.

39. Fecto F and Siddique T (2011). “Making connections: Pathology and genetics link amyotrophic lateral sclerosis with frontotemporal lobe dementia”, J Mol Neurosci. 45(3):663-75. doi: 10.1007/s12031-011-9637-9.
40. Ferraiuolo L, Kirby J, Grierson AJ, Sendtner M, and Shaw PJ (2011). “Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis”, Nat Rev Neurol. 7(11):616-30. doi: 10.1038/nrneurol.2011.152.
41. Filippini N, Douaud G, Mackay C.E, Knight S, Talbot K, and Turner MR (2010). “Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis”, Neurology 75(18):1645–52. doi: 10.1212/WNL.0b013e3181fb84d1.
42. Gabery S, Ahmed RM, Caga J, Kiernan MC, Halliday GM, and Petersen A (2021). “Loss of the metabolism and sleep regulating neuronal populations expressing orexin and oxytocin in the hypothalamus in amyotrophic lateral sclerosis”, J. Neuropathol. Appl. Neurobiol. 47(7):979–89. doi: 10.1111/nan.12709.
43. Gan L, Cookson MR, Petrucelli L, and Spada la AR (2018). “Converging pathways in neurodegeneration, from genetics to mechanisms”, Nat. Neurosci. 21(10):1300–9. doi: 10.1038/s41593-018-0237-7.
44. Goetz CG (2000). "Amyotrophic lateral sclerosis: Early contributions of Jean-Martin Charcot". Muscle & Nerve 23 (3): 336–43. doi:10.1002/(SICI)1097-4598(200003)23:3<336:AID-MUS4>3.0.CO;2-L.
45. Goldstein LH and Abrahams S (2013). “Changes in cognition and behavior in amyotrophic lateral sclerosis: Nature of impairment and implications for assessment”, Lancet Neurol. 12(4):368–80. doi: 10.1016/S1474-4422(13)70026-7.
46. Gordon P (2006). “History of ALS”. In: New York. Mitsumoto H., Przedborski S., Gordon P.H., editors. Taylor & Francis; London: 2006.
47. Gordon PH (2006). "Chapter 1: History of ALS". In Mitsumoto H, Przedborski S, Gordon PH (eds.). Amyotrophic Lateral Sclerosis. CRC Press. p. 9. ISBN 978-0824729240.
48. Gordon PH (2013). “Amyotrophic lateral sclerosis: An update for 2013 clinical features, pathophysiology, management and therapeutic trials”, Aging and Disease 4(5):295–310. doi:10.14336/AD.2013.0400295.
49. Grad LI, Rouleau GA, Ravits J, and Cashman NR (2017). “Clinical spectrum of amyotrophic aateral sclerosis (ALS)”, Cold Spring Harb. Perspect. Med. 7(8). doi: 10.1101/cshperspect.a024117.
50. Grossman AB, Levin BE, and Bradley WG (2006). "Premorbid personality characteristics of patients with ALS". Amyotrophic Lateral Sclerosis. 7 (1): 27–31. doi:10.1080/14660820510012004.
51. Gunes ZI, Kan VWY, Ye X, and Liebscher S (2020). “Exciting complexity: The role of motor circuit Elements in ALS pathophysiology”, Front. Neurosci. 14:573. doi: 10.3389/fnins.2020.00573.
52. Gunes ZI, Kan VWY, Jiang S, Logunov E, Ye XQ, and Liebscher S (2022). “Cortical Hyperexcitability in the Driver’s Seat in ALS”, Clin Transl Neurosci. 5:1–19.
53. Hablitz LM and Nedergaard M (2021). “The glymphatic system: A novel component of fundamental neurobiology”, J. Neurosci.

41(37):7698–711.
doi: 10.1523/JNEUROSCI.0619-21.2021.

54. Hablitz LM and Nedergaard M (2021). “The glymphatic system”, Curr. Biol. 31(20):R1371–5.
doi: 10.1016/j.cub.2021.08.026.
55. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. (2017). "Amyotrophic lateral sclerosis". Nature Reviews. Disease Primers. 3 (17071):17071. doi:10.1038/nrdp.2017.71.
56. Hardiman O, Al-Chalabi A, Brayne C, Beghi E, van den Berg LH, Chio A, et al. (2017). “The changing picture of amyotrophic lateral sclerosis.: Lessons from European registers”, Journal of Neurology, Neurosurgery, and Psychiatry 88(7):557–63. doi:10.1136/jnnp-2016-314495. hdl:2318/1633611.
57. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. (2020). “Amyotrophic lateral sclerosis”, Nature Reviews Disease Primers 3(17071): doi:10.1038/nrdp.2017.71.
58. Hawrot J, Imhof S, and Wainger BJ (2022). “Modeling cell-autonomous motor neuron phenotypes in ALS using iPSCs”, Neurobiol. Dis. 134. doi: 10.1016/j.nbd.2019.104680.
59. Hertzberg VS, Singh H, Fournier CN, Moustafa A, Polak M, Kuelbs CA, et al. (2022). “Gut microbiome differences between amyotrophic lateral sclerosis patients and spouse controls”, Amyotroph. Lateral Scler. Frontotemporal Degener. 23(1–2):91–9. doi: 10.1080/21678421.2021.1904994.
60. He J, Mangelsdorf M, Fan D, Bartlett P, and Brown MA (2015). “Amyotrophic lateral sclerosis genetic studies: From genome-wide association mapping to genome sequencing”, The Neuroscientist 21(6): 599–615. doi:10.1177/1073858414555404.
61. Hudson AJ (1981). “Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: A review”, Brain 104(2):217–47. doi: 10.1093/brain/104.2.217.
62. Jessen NA, Munk AS, Lundgaard I, and Nedergaard M (2015). “The glymphatic system: A beginner's guide”, Neurochem. Res. 40(12):2583–99. doi: 10.1007/s11064-015-1581-6.
63. Katz JS, Dimachkie MM, and Barohn RJ (2015). “Amyotrophic lateral sclerosis: A historical perspective” [Sclérose latérale amyotrophique: une perspective historique]. Neurol Clin. 33(4):727-34.
doi:10.1016/j.ncl.2015.07.013
64. Khalaf R, Martin S, Ellis C, Burman R, Sreedharan J, Shaw C, et al. (2019). “Relative preservation of triceps over biceps strength in upper limb-onset ALS: The 'split elbow'.”, J. Neurol. Neurosurg. Psychiatry 90(7):730–3. doi: 10.1136/jnnp-2018-319894.
65. Kiernan C (2012). “Amyotrophic lateral sclerosis and frontotemporal dementia”. J. Neurol. Neurosurg. Psychiatry 83(4):355. doi: 10.1136/jnnp-2012-302357.
66. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, et al. (2011). “Amyotrophic lateral sclerosis”, Lancet 377(9769):942–55. doi: 10.1016/S0140-6736(10)61156-7.
67. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC (2011). “Amyotrophic lateral sclerosis”, Lancet 377(9769):942-55. doi: 10.1016/S0140-6736(10)61156-7.
68. Kiernan MC and Park SB (2023). “Hyperexcitability, neurodegeneration, and disease progression in amyotrophic lateral sclerosis”, Muscle Nerve. doi: 10.1002/mus.27843.
69. Kilb W (2012). “Development of the GABAergic system from birth to adolescence”, Neuroscientist 18(6):613–30.

doi: 10.1177/1073858411422114.

70. Kuzma-Kozakiewicz M, Andersen PM, Ciecwierska K, Vázquez C, Helczyk O, Loose M, et al. (2019). "An observational study on quality of life and preferences to sustain life in locked-in state". Neurology. 93(10):e938 – e945. doi:10.1212/WNL.0000000000008064.
71. Kwan J and Vullaganti M (2022). "Amyotrophic lateral sclerosis mimics". Muscle & Nerve 66 (3): 240–52. doi:10.1002/mus.27567.
72. Landau E (2009). "Stephen Hawking serves as role model for ALS patients". CNN.
73. Masrori P and Van Damme P (2020). "Amyotrophic lateral sclerosis: A clinical review". European Journal of Neurology. 27(10):1918–29. doi:10.1111/ene.14393.
74. Lemon RN and Griffiths J. (2005). "Comparing the function of the corticospinal system in different species: or organizational differences for motor specialization?", Muscle Nerve 32(3):261–79. doi: 10.1002/mus.20333.
75. Lemon RN (2008). "Descending pathways in motor control", Annu. Rev. Neurosci. 31:195–218. doi:10.1146/annurev.neuro.31.060407.125547.
76. Lillo P. and Hodges JR (2009). "Frontotemporal dementia and motor neurone disease: Overlapping clinical-pathological disorders", J. Clin. Neurosci. 16:(9)1131–5. doi: 10.1016/j.jocn.2009.03.005.
77. Lucia D, McCombe PA, Henderson RD, and Ngo ST (2021). "Disorders of sleep and wakefulness in amyotrophic latera sclerosis (ALS): A systematic review", Amyotroph. Lateral Scler. Frontotemporal Degener. 22(3–4):161–9. doi: 10.1080/21678421.2020.1844755.
78. Ludolph AC, Emilian S, Dreyhaupt J, Rosenbohm A, Kraskov, Lemon RN, et al. (2020). "Pattern of paresis in ALS is consistent with the physiology of the corticomotoneuronal projections to different muscle groups", J. Neurol. Neurosurg. Psychiatry. 91(9):991–8. doi: 10.1136/jnnp-2020-323331.
79. Lynch E.M, Robertson S, FitzGibbons C, Reilly M, Switalski C, Eckardt A, et al. (2021). "Transcriptome analysis using patient iPSC-derived skeletal myocytes: Bet1L as a new molecule possibly linked to neuromuscular junction degeneration in ALS", Exp. Neurol. 345. doi: 10.1016/j.expneurol.2021.113815.
80. Martin S., Battistini C, and Sun J (2022). "A gut feeling in amyotrophic lateral sclerosis: Microbime of mice and men", Front. Cell. Infect. Microbiol. 12. doi: 10.3389/fcimb.2022.839526.
81. Masuda M, Senda J, Watanabe H, Epifanio B, Tanaka Y, Imai K, et al. (2016). "Involvement of the caudate nucleus head and its networks in sporadic amyotrophic lateral sclerosis-frontotemporal dementia continuum", Amyotroph. Lateral Scler. Frontotemporal Degener. 17(7–8):571–9. doi: 10.1080/21678421.2016.1211151.
82. Masrori P and Van Damme P (2020). "Amyotrophic lateral sclerosis: a clinical review", European Journal of Neurology 27(10):1918-29. doi:10.1111/ene.14393.
83. MedlinePlus Genetics (2023). "Amyotrophic lateral sclerosis".
84. McIntosh J, Mekrouda I, Dashti M, Giuraniuc CV, Banks RW, Miles GB, Bewick GS (2023). "Development of abnormalities at the neuromuscular junction in the SOD1-G93A mouse model of ALS: dysfunction then disruption of postsynaptic structure precedes overt motor symptoms", Front. Mol. Neurosci. 16:1169075. doi: 10.3389/fnmol.2023.1169075.
85. MedlinePlus Genetics (2023). "Amyotrophic lateral sclerosis".
86. Mehl T, Jordan B, and Zierz S (2017).

"Patients with amyotrophic lateral sclerosis (ALS) are usually nice persons"-How physicians experienced in ALS see the personality characteristics of their patients". Brain and Behavior. 7 (1): e00599. doi:10.1002/brb3.599.

87. Mehta PR, Brown AL, Ward ME, and Fratta P (2023). "The era of cryptic exons: Implications for ALS-FTD", Molecular Neurodegeneration 18(1):16. doi:10.1186/s13024-023-00608-5.
88. Menon P, Bae JS, Mioshi E, Kiernan MC, and Vucic S (2013). "Split-hand plus sign in ALS: differential involvement of the flexor pollicis longus and intrinsic hand muscles", Amyotroph. Lateral Scler. Frontotemporal Degener. 14(4):315–8. doi: 10.3109/21678421.2012.734521.
89. Menon P, Kiernan MC, and Vucic S (2014). "Cortical excitability differences in hand muscles follow a split-hand pattern in healthy controls", Muscle Nerve 49(6):836–44. doi: 10.1002/mus.24072.
90. Mestre H, Mori Y, and Nedergaard M (2020). "The brain's glymphatic system: Current controversies. Trends", Neurosci. 43(7):458–466. doi: 10.1016/j.tins.2020.04.003.
91. Meyer BU, Roricht S, Einsiedel von GH, Kruggel F, and Weindl A (1995). "Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum", Brain 118(Pt 2):429–440. doi: 10.1093/brain/118.2.429.
92. Mills KR (2010). "Characteristics of fasciculations in amyotrophic lateral sclerosis and the benign fasciculation syndrome". Brain. 133 (11): 3458–69. doi:10.1093/brain/awq290.
93. Min YG, Choi SJ, Hong YH, Kim SM, Shin JY, and Sung JJ (2020). "Dissociated leg muscle atrophy in amyotrophic lateral sclerosis/motor neuron disease: the 'split-leg' sign", Sci. Rep. 10(1):15661. doi: 10.1038/s41598-020-72887-7.
94. Mitsumoto, H, Chad, DA, and Pioro, EP. (1998). "History, definition, and classicification of ALS". In: Mitsumoto, H., Chad, D.A., Pioro, E.P. (Eds.), "Amyotrophic lateral sclerosis. contemporary neurology series". 49 ed. Oxford Press, New York. pp. 3–17.
95. Muscular Dystrophy Association. (2015). "ALS: Amyotrophic Lateral Sclerosis".
96. Nakazumi Y and Watanabe Y (1992). "F-wave elicited during voluntary contraction as a monitor of upper motor neuron disorder", Electromyogr. Clin. Neurophysiol. 32(12):631–5.
97. (U.K.) National Health Service (NHS) (2018)."Motor neurone disease".
98. (U.S.) National Institute of Health (2018). "Patient with amyotrophic lateral sclerosis (ALS)" (case, Open-i) openi.nlm.nih.gov.
99. (U.S.) National Institute of Neurological Disorders and Stroke (NINDS) (2017). "Amyotrophic lateral sclerosis" Fact Sheet.
100. (U.S.) National Institute of Neurological Disorders and Stroke (NINDS) (2020). "Motor Neuron Diseases Fact Sheet". www.ninds.nih.gov.
101. Nedergaard M and Goldman SA (2030). "Glymphatic failure as a final common pathway to dementia", Science 370(6512):50–6. doi: 10.1126/science.abb8739.
102. Neumann M, Sampathu DM, Kwong LK., Truax AC, Micsenyi MC, Chou TT, et al. (2006). "Ubiquitinated TDP-43 in frontotempora lobar degeneration and amyotrophic lateral sclerosis". Science 314(5796):130–3. doi: 10.1126/science.1134108.
103. Ng Kee Kwong KC, Mehta AR, Nedergaard M, and Chandran S (2020). "Defining novel functions for cerebrospinal fluid in ALS pathophysiology", Acta Neuropathol.

Commun. 8(1):140. doi: 10.1186/s40478-020-01018-0.

104. Oiwa K, Watanabe S, Onodera K, Iguchi Y, Kinoshita Y, Komine O. et al. (2023). “Monomerization of TDP-43 is a key determinant for inducing TDP-43 pathology in amyotrophic lateral sclerosis”, Sci. Adv. 9(31). doi: 10.1126/sciadv.adf6895.

105. Okamoto K, Mizuno Y, and Fujita Y (2008). "Bunina bodies in amyotrophic lateral sclerosis". Neuropathology. 28 (2): 109–15. doi:10.1111/j.1440-1789.2007.00873.x.

106. Parkin Kullmann JA, Hayes S, and Pamphlett R (2018). "Are people with amyotrophic lateral sclerosis (ALS) particularly nice? An international online case-control study of the Big Five personality factors". Brain and Behavior 8 (10): e01119. doi:10.1002/brb3.1119.

107. Peggion C, Scalcon V, Massimino ML, Nies K, Lopreiato R, Rigobello MP, and Bertoli A (2023). “SOD1 in ALS: Taking stock in pathogenic mechanisms and the role of glial and muscle cells. Antioxidants” (Basel)11(4). doi: 10.3390/antiox11040614.

108. Pickles S and Petrucelli L (2018). “CRISPR expands insight into the mechanisms of ALS and FTD”, Nat. Rev. Neurol. 14(6):321–3. doi: 10.1038/s41582-018-0005-z.

109. Pillai JA and Leverenz JB (2017). “Sleep and neurodegeneration: A critical appraisal”, Chest 151(6):1375–86. doi: 10.1016/j.chest.2017.01.002.

110. Plog BA and Nedergaard M (2018). “The glymphatic system in central nervous system health and disease: Past, present, and future”, Annu. Rev. Pathol. 13:379–94. doi: 10.1146/annurev-pathol-051217-111018.

111. Raaphorst J, Beeldman E, De Visser M, De Haan RJ, and Schmand B (2012). "A systematic review of behavioral changes in motor neuron disease". Amyotrophic Lateral Sclerosis. 13 (6): 493–501. doi:10.3109/17482968.2012.656652.

112. Ramamoorthi K and Lin Y (2011). “The contribution of GABAergic dysfunction to neurodevelopmental disorders”, Trends Mol. Med. 17(8):452–62. doi: 10.1016/j.molmed.2011.03.003.

113. Rasmussen M.K, Mestre H, and Nedergaard M (2018). “The glymphatic pathway in neurological disorders”, Lancet Neurol. 17(11):1016–24. doi: 10.1016/S1474-4422(18)30318-1.

114. Ravits J.M and Spada La AR (2009). “ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration”, Neurology 73(10):805–11. doi: 10.1212/WNL.0b013e3181b6bbbd.

115. Reale LA, Dyer MS, Perry SE, Young KM, Dickson TC, Woodhouse A, and Blizzard CA (2023). “Pathologically mislocalized TDP-43 in upper motor neurons causes a die-forward spread of ALS-like pathogenic changes throughout the mouse corticomotor system”, Prog. Neurobiol. 226:102449. doi: 10.1016/j.pneurobio.2023.102449.

116. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, et al. (2011). “A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD”, Neuron. 72(2):257–68. doi: 10.1016/j.neuron.2011.09.010.

117. Renton AE, Chio A, and Traynor BJ (2013). “State of play in amyotrophic lateral sclerosis genetics”, Nat Neurosci. 17(1):17-23. doi: 10.1038/nn.3584.

118. Renton AE, Chiò A, and Traynor BJ (2014). "State of play in amyotrophic lateral sclerosis genetics". Nature Neuroscience. 17 (1): 17–23. doi:10.1038/nn.3584. hdl:2318/156177.

119. Robberecht W and Philips T (2013). "The changing scene of amyotrophic lateral sclerosis". Nature Reviews. Neuroscience. 14

(4): 248–64. doi:10.1038/nrn3430.

120. Rowland LP (2001). “How amyotrophic lateral sclerosis got its name: The clinical-pathologic genius of Jean-Martin Charcot”, Arch. Neurol. 58(3):512–5. doi: 10.1001/archneur.58.3.512.

121. Rowland LP and Shneider NA (2001). “Amyotrophic lateral sclerosis”, N. Engl. J. Med. 344(22):1688–700. doi: 10.1056/NEJM200105313442207.

122. Scekic-Zahirovic J, Fischer M, Stuart-Lopez G, Burg T, Gilet J, Dirrig-Grosch S, et al. (2021). “Evidence that corticofugal propagation of ALS pathology is not mediated by prion-like mechanism”, Prog. Neurobiol. 200:101972. doi: 10.1016/j.pneurobio.2020.101972.

123. Shefner JM, Musaro A, Ngo ST, Lunetta C, Steyn FJ, Robitaille R, et al. (2023). “Skeletal muscle in amyotrophic lateral sclerosis”, Brain. doi: 10.1093/brain/awad202.

124. Shojaie A. Rota S, Al Khleifat A, Ray Chaudhuri K, and Al-Chalabi A (2023). “Non-motor symptoms in amyotrophic lateral sclerosis: lessons from Parkinson's disease”, Amyotroph. Lateral Scler. Frontotemporal Degener. 1–10. doi: 10.1080/21678421.2023.2220748.

125. Siddique N and Siddique T (2001). “Amyotrophic lateral sclerosis overview”, In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews(R) [Internet], Seattle (WA): University of Washington, Seattle.

126. Siddique T and Ajroud-Driss S (2011). “Familial amyotrophic lateral sclerosis: A historical perspective [Sclérose latérale amyotrophique familiale,: Une perspective historique]”, Acta myologica : myopathies and cardiomyopathies (official journal of the Mediterranean Society of Myology) 30(2):117-20.

127. Silani V, Ludolph A, and Fornai F (2017), “The emerging picture of ALS: a multisystem, not only a motor neuron disease”, Arch. Ital. Biol. 155(4):99–109. doi: 10.12871/00039829201741.

128. Simon NG, Lee M, Bae JS, Mioshi E, Lin CS, Pfluger CM, et al. (2015). “Dissociated lower limb muscle involvement in amyotrophic lateral sclerosis. J. Neurol. 262(6):1424–32. doi: 10.1007/s00415-015-7721-8.

129. Snowden JS, Harris J, Richardson A, Rollinson S, Thompson JC, and Neary D (2013). “Frontotemporal dementia with amyotrophic lateral sclerosis: A clinical comparison of patients with and without repeat expansions in C9orf72”, Amyotroph. Lateral Scler. Frontotemporal Degener.14:172–6. doi: 10.3109/21678421.2013.765485.

130. Sonnenburg JL and Sonnenburg E.D (2019). “Vulnerability of the industrialized microbiota”. Science 366:6464. doi: 10.1126/science.aaw9255.

131. Stefani A and Hogl B (2021). “A step forward in understanding the role of sleep and its link to neurodegeneration”, Brain 144(3):700–2. doi: 10.1093/brain/awab047.

132. Sun J, Huang T, Debelius JW, and Fang F (2021). “Gut microbiome and amyotrophic lateral sclerosis: A systematic review of current evidence”, J. Intern. Med. 290(4):758–88. doi: 10.1111/joim.13336.

133. Swash M (2012). “Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis?”, J. Neurol. Neurosurg. Psychiatry 83(6):659–62. doi: 10.1136/jnnp-2012-302315.

134. Talbot K (2011). “Familial versus sporadic amyotrophic lateral sclerosis: A false dichotomy? [Sclérose latérale amyotrophique familiale versus sporadique: Une fausse dichotomie?”, Brain 134(12):3429–34, https://doi.org/10.1093/brain/awr296

135. Tamaki Y, Ross JP, Alipour P, Castonguay CE,

Li B, Catoire H, et al. (2023). “Spinal cord extracts of amyotrophic lateral sclerosis spread TDP-43 pathology in cerebral organoids”, PLoS Genet. 19(2). doi: 10.1371/journal.pgen.1010606.

136. Teive HA, Lima PM, Germiniani FM, and Munhoz RP (2016). "What's in a name? Problems, facts and controversies regarding neurological eponyms". Arquivos de Neuro-Psiquiatria. 74(5):423–5. doi:10.1590/0004-282X20160040.
137. Thakore NJ, Drawert BJ, Lapin BR, and Pioro EP (2021). “Progressive arm muscle weakness in ALS follows the same sequence regardless of onset site: Use of TOMS, a novel analytic method to track limb strength”, Amyotroph. Lateral Scler. Frontotemporal Degener. 1–8. doi: 10.1080/21678421.2021.1889000.
138. Timmins HC, Vucic S, and Kiernan MC (2023). “Cortical hyperexcitability in amyotrophic lateral sclerosis: From pathogenesis to diagnosis”, Curr. Opin. Neurol. doi: 10.1097/WCO.0000000000001162.
139. Tsuboguchi S, Nakamura Y, Ishihara T, Kato T, Sato T, Koyama A, et al. (2023). “TDP-43 differentially propagates to induce antero- and retrograde degeneration in the corticospinal circuits in mouse focal ALS models”, Acta Neuropathol. doi: 10.1007/s00401-023-02615-8.
140. Turner MR, Swash M, and Ebers GC (2010). “Lockhart Clarke's contribution to the description of amyotrophic lateral sclerosis “, Brain 133(11):3470–9. doi: 10.1093/brain/awq097.
141. Turner BJ and Talbot K (2008). “Transgenics, toxicity and therapeutics in rodent models of mutant SOD1-mediated familial ALS”, Prog. Neurobiol. 85(1):94–134. doi:10.1016/j.pneurobio.2008.01.001. https://doi.org/S0301-0082(08)00002-6 [pii]
142. Turner MR and Swash M (2015). “The expanding syndrome of amyotrophic lateral sclerosis: A clinical and molecular odyssey [Le syndrome en expansion de la sclérose latérale amyotrophique: une odyssée clinique et moléculaire]. Journal of Neurology, Neurosurgery, and Psychiatry 86(6): 667-73. doi:10.1136/jnnp-2014-308946.
143. Vasques JF, Mendez-Otero R, and Gubert F (2020). “Modeling ALS using iPSCs: Is it possible to reproduce the phenotypic variations observed in patients in vitro?”, Regen. Med. 15(7):1919–33. doi: 10.2217/rme-2020-0067.
144. Vance C, Rogelj B, Hortobagyi T, De Vos KJ, Nishimura AL, Sreedharan J, et al. (2009). “Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6”, Science 323(5918):1208-11. doi: 10.1126/science.1165942.
145. Veltema AN (1975). “The case of the saltimbanque Prosper Lecomte: A contribution to the study of the history of progressive muscular atrophy (Aran-Duchenne) and amyotrophic lateral sclerosis (Charcot)”, Clin. Neurol. Neurosurg. 78(3):204–9. doi: 10.1016/s0303-8467(75)80050-3.
146. Visser J, de Jong JM, and Visser de M (2008). "The history of progressive muscular atrophy: syndrome or disease?". Neurology 70 (9): 723–7. doi:10.1212/01.wnl.0000302187.20239.93.
147. Vucic S and Kiernan MC (2006). “Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of motor neuron disease”, Brain 129(Pt 9):2436–46. doi: 10.1093/brain/awl172.
148. Wainberg M, Andrews SJ, and Tripathy SJ (2023). “Shared genetic risk loci between Alzheimer's disease and related dementias, Parkinson's disease, and amyotrophic lateral sclerosis”, Alzheimer’s Res. Ther. 15(1):113. doi: 10.1186/s13195-023-01244-3.

149. Wang ZL, Cui L, Liu M, Zhang K, Liu S, and Ding Q (2019). “Split-hand syndrome in amyotrophic lateral sclerosis: Differences in dysfunction of the FDI and ADM spinal motoneurons”, Front. Neurosci. 13:371. doi: 10.3389/fnins.2019.00371.

150. Wang ZL, Cui L, Liu M, Zhang K, Liu S, Ding Q, and Hu Y (2019). “Reassessment of split-leg signs in amyotrophic lateral sclerosis: Differential involvement of the extensor digitorum brevis and abductor hallucis muscles”, Front. Neurol. 10:565. doi: 10.3389/fneur.2019.00565.

151. Wang ZL, Liu M, Ding Q, Hu Y, and Cui L (2019). “Split-hand index in amyotrophic lateral sclerosis: An F-wave study”, Amyotroph. Lateral Scler. Frontotemporal Degener. 20(7–8):562–7. doi: 10.1080/21678421.2019.1646770.

152. Weber M, Eisen A, Stewart H, Hirota N (2000). “The split hand in ALS has a cortical basis”, J. Neurol. Sci. 1801–2):66–70. doi: 10.1016/s0022-510x(00)00430-5.

153. Wicks P (2007). "Excessive yawning is common in the bulbar-onset form of ALS". Acta Psychiatrica Scandinavica. 116 (1): 76, author reply 76–76, author reply 77. doi:10.1111/j.1600-0447.2007.01025.x.

154. Wijesekera LC and Leigh PN (2009). "Amyotrophic lateral sclerosis". Orphanet Journal of Rare Diseases. 4(4):3. doi:10.1186/1750-1172-4-3.

155. Wilbourn AJ (2000). “The “split hand syndrome”, Muscle Nerve 23(1):138. doi: 10.1002/(sici)1097–4598(200001)23:1<138:aid-mus22>3.0.co;2–7.

156. Wingo TS, Cutler DJ, Yarab N, Kelly CM, and Glass JD (2011). "The heritability of amyotrophic lateral sclerosis in a clinically ascertained United States research registry". PLOS ONE. 6(11): e27985. doi: 10.1371/journal.pone.0027985.

157. Wittstock M, Wolters A, and Benecke R (2007). “Transcallosal inhibition in amyotrophic lateral sclerosis”, Clin. Neurophysiol. 118(2):301–7. doi: 10.1016/j.clinph.2006.09.026.

158. Woolley SC and Strong MJ (2015). “Frontotemporal dysfunction and dementia in amyotrophic lateral sclerosis”, Neurol. Clin. 33:(4)787–805. doi: 10.1016/j.ncl.2015.07.011.

159. World Health Organization (2018). "8B60 Motor neuron disease". ICD-11 for Mortality and Morbidity Statistics.

160. Ye S, Luo Y, Jin P, Wang Y, Zhang N, Zhang G, et al. (2021). “MRI volumetric analysis of the thalamus and hypothalamus in amyotrophic lateral sclerosis”, Front. Aging Neurosci. 13:610332. doi: 10.3389/fnagi.2021.610332.

Diseases of the nervous system:

161. Barohn RJ and Amato AA (2013). “Pattern-recognition approach to neuropathy and neuropathy”. Neurologic Clinics 31(2):343-61. doi: 10.1016/j.ncl.2013.02.001.

162. Blumenfeld H (2002). “Neuroanatomy through clinical cases”. Sunderland, Mass.: Sinauer. ISBN 087893060-4.

163. Cooper-Knock J, Jenkins T, and Shaw PJ (2013). “Clinical and molecular aspects of motor neuron disease". San Rafael, California. ISBN 978-1-61504-429-0.

164. Emos MC and Agarwal S (2022). “Neuroanatomy, upper motor neuron lesion. StatPearls Publishing.

165. Foster LA and Salajegheh MK (2019). "Motor neuron disease: Pathophysiology, diagnosis, and management". The American Journal of Medicine 132 (1): 32–37. doi: 10.1016/j.amjmed.2018.07.012.

166. Fymat AL (2021). “The Human Brain: Wonders and Disorders”, Tellwell Talent Publishers, pp 500, 29 March 2021. ISBN: 978-0-2288-4885-1 (Hardcover); 978-0-2288-4884-4 (Paperback).
167. Fymat AL (2023). “Tourette: The Self-Under-Siege Neurodevelopmental and Neuropsychiatric Motor Syndrome”, Tellwell Talent Publishers, pp. 466, August 2023, ISBN: 978-1-7794-1027-6 (Hardcover); 978-1-7794-1026-6 (Paperback). https://portal.tellwell.ca/Tellwell/Design/256783.
168. Fymat AL (2023). “Memory: The Enchanted Loom's Property in Search of Self”, Tellwell Talent Publishers, 2023 Tellwell Talent Publishers, pp 684, 30 December 2023, ISBN: 10-1779415281 (Hardcover); 10-978-1779415288 (Paperback).
169. Fymat AL (2024). “Aging: From Evolution to Modern Biology to Anti-Aging”, Tellwell Talent Publishers, pp 600, 12 August 2024, ISBN-10: 1773705121; ISBN-13: 978-1773705125.
170. Healthdirect Australia (2020). "Motor neurone disease (MND)". healthdirect.gov.au.
171. Ince PG, Clark B, Holton J, Revesz T, and Wharton SB (2008). Chapter 13 “Diseases of movement and system degeneration”. In Greenfield JG, Love S, Louis DN, Ellison DW (eds.). Greenfield's neuropathology. Vol. 1 (8th ed.). London: Hodder Arnold. p. 947. ISBN 978-0=3440-90681-1.
172. Javed K and Daly DT (2022). “Neuroanatomy, lower motor neuron lesion”. StatPearls Publishing.
173. Mitra J, Guerrero EN, Hegde PM, Liachko NF, Wang H, Vasquez V, et al. (2019). “Motor neuron disease-associated loss of nuclear TDP-43 is linked to DNA double-strand break repair defects”, Proceedings of the U.S. National Academy of Sciences 116 (10):4696 – 705. doi: 10.1073/pnas.1818415116.
174. (UK) Motor Neurone Disease Association (2015). “An introduction to motor neurone disease”.
175. (Irish) Motor Neurone Disease Association (2018). “Different types of MND”.
176. (U.S.) National Health Institutes (NIH) (2018). “Motor neuron disease”.
177. (U.S.) National Institute of Neurological Disorders and Stroke (NINDS) (2014, 2022). “Motor neuron diseases: Fact sheet”. ninds.nih.gov.
178. Schapira AH, Wszolek ZK, Dawson TM, and Wood NW (2017). “Neurodegeneration.” Chichester, West Sussex. ISBN 978-1-118-66191-8.
179. Science Direct Topics (2022). “Progressive muscular atrophy – An overview”. sciencedirect.com.
180. Shaw PJ (2005). “Molecular and cellular pathways of neurodegeneration in motor neurone disease”. Journal of Neurology, Neurosurgery, and Psychiatry 76(8):1046-57. doi:10.1136/jnnp.2004.048652.
181. Statland JM, Barohn RJ, McVey AL, Katz JS, and Dimachkie MM (2015). “Patterns pf weakness, classification of motor neuron disease, and clinical diagnosis of sporadic amyotrophic lateral sclerosis”. Neurologic Clinics 33(4):735-48. doi:10.1016/j.ncl.2015.07.006.

Neurodegenerative diseases:

182. Al-Kuraishy HM, Abdulhadi MH, Hussien NR, Al-Niemi MS, Rasheed HA, and Al-Gareeb AI (2020). “Involvement of orexinergic system in psychiatric and neurodegenerative disorders: A scoping review”, Brain Circ 6(2):70–80. doi: 10.4103/bc.4219.
183. Arora RD and Khan YS (2023). "Motor Neuron Disease". StatPearls. Treasure Island

(FL): StatPearls Publishing.

184. Burrell JR, Kiernan MC, Vucic S, and Hodges JR (2011). “Motor neuron dysfunction in frontotemporal dementia”, Brain 134(Pt 9):2582–94. doi: 10.1093/brain/awr195.

185. Burrell JR, Halliday GM, Kril JJ, Ittner LM, Gotz J, Kiernan MC, and Hodges JR (2016). “The frontotemporal dementia-motor neuron disease continuum”, Lancet 388(10047):919–31. doi: 10.1016/S0140-6736(16)00737-6.

186. Calderon-Garciduenas L, Torres-Jardon R, Greenough GP, Kulesza R, Gonzalez-Maciel A, Reynoso-Robles R, et al. (2023). “Sleep matters: Neurodegeneration spectrum heterogeneity, combustion and friction ultrafine particles, industrial nanoparticle pollution, and sleep disorders-Denial is not an option”, Front. Neurol. 14:1117695–701. doi: 10.3389/fneur.2023.1117695.

187. Checkoway H, Lundin JI, and Kelada SN (2011). "Chapter 22: Neurodegenerative diseases". In Rothman N, Hainaut P, Schulte P, Smith M, Boffetta P, Perera F (eds.). Molecular Epidemiology: Principles and Practices. International Agency for Research on Cancer pp. 408–9. ISBN 978-9283221630.

188. Christidi F, Karavasilis E, Rentzos M, Kelekis N, Evdokimidis I, and Bede P (2018). “Clinical and radiological markers of extra-motor deficits in amyotrophic lateral sclerosis”, Front. Neurol. 9:1005. doi: 10.3389/fneur.2018.01005.

189. Drory VE, Neufeld MY, and Korczyn AD (1993). “F-wave characteristics following acute and upper motor neuron lesions”, Electromyogr. Clin. Neurophysiol. 33(7):441–46.

190. Fymat AL (2019). “Alzhei … Who? Demystifying the Disease and What You Can Do About it”, Tellwell Talent Publishers, pp 236, 23 December 2019. ISBN: 978-0-2288-2420-6 (Hardcover); 978-0-2288-2419-0 (Paperback).

191. Fymat AL (2020). “Parkin... ss..oo..nn: Elucidating the Disease... and What You Can Do About it”, Tellwell Talent Publishers, pp 258, 6 April 2020. ISBN: 978-0-2288-2874-7 (Hardcover); 978-0-2228-2875-4 (Paperback).

192. Fymat AL (2020). “Dementia: Fending off the Menacing Disease... and What You Can Do About it”, Tellwell Talent Publishers, pp 488, 21 September 2020. ISBN: 978-0-2288-4146-3 (Hardcover); 978-0-2288-4145-6 (Paperback).

193. Fymat AL (2023). “Multiple Sclerosis: The Progressive Demyelinating Autoimmune Disease”, Tellwell Talent Publishers pp 504, 30 March 2023. ISBN: 978-0-2288.

194. Fymat AL (2023). “Multiple System Atrophy: The Chronic, Progressive, Neurodegenerative Synucleopathic Disease”, Tellwell Talent Publishers, pp. 302, May 17, 2023. ISBN: 978-0-2288-9493-8 (Hardcover); 978-0-2288-9492-1 (Paperback). https://portal.tellwell.ca/Tellwell/Design/256783.

195. Fymat AL (2024). “Huntington: The Neurodegenerative, Neuropsychiatric, and Hyperkinetic Disease”, Tellwell Talent Publishers, pp 570, 2024, ISBN-978-1-7796-2659-2; ISBH: 978=1-7796-2658-2.

196. Gowers WR (1870). “An Address on some aspects of diseases of the nervous system and their study”, Br. Med. J. 1896(2):1310–2. doi: 10.1136/bmj.2.1870.1310.

197. Gowers WR (1893). “A manual of diseases of the nervous system”, London.

198. Grossman M (2019). “Amyotrophic lateral sclerosis - a multisystem neurodegenerative disorder”, Nat. Rev. Neurol. 15(1):5–6. doi: 10.1038/s41582-018-0103-y.

199. Hudson AJ and Kiernan JN (1988). “Preservation of certain voluntary muscles in motoneurone disease”, Lancet 1(8586):652–3.

doi: 10.1016/s0140-6736(88)91455-9.

200. Marques C, Burg T, Scekic-Zahirovic J, Fischer M, and Rouaux C (2021). “Upper and lower motor neuron degenerations are somatotopically related and temporally ordered in the SOD1 mouse model of amyotrophic lateral sclerosis”, Brain Sci. 11(3). doi: 10.3390/brainsci11030369.
201. Morris JC (2013). “Neurodegenerative disorders of aging: The down side of rising longevity”. Mo. Med. 110(5):393–4.
202. (UK) National Health Service (2014). “Motor neurone disease”.
203. Wijesekera LC, Mathers S, Talman P, Galtrey C, Parkinson MH, Ganesalingam J, et al. (2009). “Natural history and clinical features of the flail arm and flail leg ALS variants”, Neurology 72(12):1087–94. doi:10.1212/01.wnl.0000345041.83406.a.
204. World Health Organization (2018). “8B60 motor neuron disease”. ICD-11 for Mortality and Morbidity Statistics.

Signs & symptoms:

205. Ahmed RM, Newcombe RE, Piper AJ, Lewis SJ, Yee BJ, Kiernan MC, et al. (2016). "Sleep disorders and respiratory function in amyotrophic lateral sclerosis", Sleep Medicine Reviews 26:33–42. doi:10.1016/j.smrv.2015.05.007.
206. Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, van den Berg LH (2016). "Amyotrophic lateral sclerosis: moving towards a new classification system", The Lancet Neurology 15(11): 1182–94. doi:10.1016/S1474-4422(16)30199-5 hdl:2318/1636249.
207. Bedlack RS, Vaughan T, Wicks P, Heywood J, Sinani E, Selsov R, et al. (2016). “How common are ALS plateaus and reversals”. Neurology 86(9):80812.812. doi:10.1212/WNL.0000000000002251.
208. Beeldman E, Raaphorst J, Klein Twennaar M, de Visser M, Schmand BA, and de Haan RJ (2016). "The cognitive profile of ALS: a systematic review and meta-analysis update", Journal of Neurology, Neurosurgery, and Psychiatry 87(6):611–9. doi:10.1136/jnnp-2015-310734.
209. Castrillo-Viguera C, Grasso DL, Simpson E, Shefner J, and Cudkowicz ME (2010). "Clinical significance in the change of decline in ALSFRS-R", Amyotrophic Lateral Sclerosis Journal 11(1–2):178–80. doi:10.3109/17482960903093710.
210. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. (1999). "The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III)", Journal of the Neurological Sciences 169(1–2):13–21. doi:10.1016/s0022-510x(99)00210-5.
211. Chiò A, Mora G, and Lauria G (2017). "Pain in amyotrophic lateral sclerosis", The Lancet Neurology 16(2):144–57. arXiv:1607.02870. doi:10.1016/S1474-4422(16)30358-1.
212. Couratier P, Corcia P, Lautrette G, Nicol M, and Marin B (2017). "ALS and frontotemporal dementia belong to a common disease spectrum", Revue Neurologique 173(5): 273–79. doi:10.1016/j.neurol.2017.04.001.
213. Crockford C, Newton J, Lonergan K, Chiwera T, Booth T, Chandran S, et al. (2018). “ALS-specific cognitive and behavioral changes associated with advancing disease stage in ALS”, Neurology 91(15): e1370 – e1380. doi:10.1212/WNL.0000000000006317.
214. Duan QQ, Jiang Z, Su WM, Gu XJ, Wang H, Cheng YF, et al. (2023). “Risk factors of amyotrophic lateral sclerosis: A global meta-summary”, Front. Neurosci. 17:1177431. doi: 10.3389/fnins.2023.1177431.

215. Gautier G, Verschueren A, Monnier A, Attarian S, Salort-Campana E, and Pouget J (2010). "ALS with respiratory onset: clinical features and effects of non-invasive ventilation on the prognosis". Amyotrophic Lateral Sclerosis 11(4):379–82. doi:10.3109/17482960903426543.

216. Grad LI, Rouleau GA, Ravits J, and Cashman NR (2017). "Clinical spectrum of amyotrophic lateral sclerosis (ALS", Cold Spring Harbor Perspectives in Medicine 7(8): a024117. doi:10.1101/cshperspect.a024117.

217. Gromicho M, Figueiral M, Uysal H, Grosskreutz J, Kuzma-Kozakiewicz M, Pinto S, et al. (2020). "Spreading in ALS: The relative impact of upper and lower motor neuron involvement", Annals of Clinical and Translational Neurology 7(7):1181-92. doi:10.1002/acn3.51098.

218. Jawdat O, Statland JM, Barohn RJ, Katz JS, and Dimachkie MM (2015). "Amyotrophic lateral sclerosis regional variants (brachial amyotrophic diplegia, leg amyotrophic diplegia and isolated bulbar amyotrophic lateral sclerosis", Neurological Clinics 33(4): 775–85. doi:10.1016/j.ncl.2015.07.003.

219. Kwan J, and Vullaganti M (2022). "Amyotrophic lateral sclerosis mimics". Muscle & Nerve 66(3):240–52. doi:10.1002/mus.27567.

220. Landau E (2009). "Stephen Hawking serves as a role. Model for ALS patients", CNN

221. Mayo Clinic (2022). "Amyotrophic lateral sclerosis - Symptoms and causes".

222. McNeill A, Amador MD, Bekker H, Clarke A, Crook A, Cummings C, et al. (2022). "Predictive genetic testing for motor neuron disease: Time for a guideline", European Journal of Human Genetics 30(6): 635–6. doi:10.1038/s41431-022-01093-y.

223. Raaphorst J, Beeldman E, De Visser M, De Haan RJ, and Schmand B (2012). "A systematic review of behavioral changes in motor neuron disease", Amyotrophic Lateral Sclerosis 13(6):493–501. doi:10.3109/17482968.2012.656652.

224. Ravits J, Appel S, Baloh RH, Barohn R, Brooks BR, Elman L, et al. (2013). "Deciphering amyotrophic lateral sclerosis: What phenotype, neuropathology, and genetics are telling us about pathology", Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration 14(Suppl 1):5–18. doi:10.3109/21678421.2013.778548.

225. Renton AE, Chiò A, and Traynor BJ (2014). "State of play in amyotrophic lateral sclerosis", Nature Neuroscience 17(1):17–23. doi:10.1038/nn.3584.

226. Sauvé WM (2016). "Recognizing and treating pseudobulbar affect", CNS Spectrums 21(S1):34–44. doi:10.1017/S1092852916000791.

227. Swinnen B and Robberecht W (2014). "The phenotype variability of amyotrophic lateral sclerosis", Nature Reviews Neurology 10(11):661–70. 670. doi:10.1038/nrneurol.2014.184.

228. Tard C, Defebvre L, Moreau C, Devos D, and Danel-Brunaud V (2017). "Clinical features of amyotrophic lateral sclerosis and their prognostic value", Revue Neurologique 173(5):263–72. doi:10.1016/j.neurol.2017.03.029.

229. Wicks P (2007). "Excessive yawning is common in the bulbar-onset form of ALS", Acta Psychiatrica Scandinavica 116(1):76, author reply 76, 77. doi:10.1111/j.1600-0447.2007.01025.x.

230. Wingo TS, Cutler DJ, Yarab N, Kelly CM, and Glass JD (2011). "The heritability of amyotrophic lateral sclerosis in a clinically ascertained United States research registry", PLoS One 6(11): e2798. doi:10.1371/journal.pone.0027985.

231. Yunusova Y, Plowman EK, Green JR, Barnett C, and Bede P (2019). “Clinical measures of bulbar dysfunction in ALS”, Frontiers in Neurology 10:106. doi: 10.3389/fneur.2019.00106.

232. Zhang H, Chen L, Tian J, and Fan D (2021). “Disease duration of progression is helpful in identifying isolated bulbar palsy of amyotrophic lateral sclerosis”, BMC Neurology 21(1): 405. doi:10.1186/s12883-021-02438-8.

Risks:

233. Andrew AS, Bradley WG, Peipert D, Butt T, Amoako K, and Pioro EP, et al. (2021). “Risk factors for amyotrophic lateral sclerosis: A regional United States case-control study”. Muscle Nerve 63(1):52–9. doi:10.1002/mus.27085.

234. Beaudin M, Salachas F, Pradat P.F, and Dupre N (2022). “Environmental risk factors for amyotrophic lateral sclerosis: A case-control study in Canada and France”, Amyotroph. Lateral Scler. Frontotemporal Degener. 23(7–8):592–600. doi:10.1080/21678421.2022.2028167.

235. Koretsky MJ, Alvarado C, Makarious MB, Vitale D, Levine K, Bandres-Ciga S, et al. (2023). “Genetic risk factor clustering within and across neurodegenerative diseases”, Brain. doi: 10.1093/brain/awad161.

236. Ryan M, Heverin M, McLaughlin RL, and Hardiman O (2019). "Lifetime Risk and Heritability of Amyotrophic Lateral Sclerosis". JAMA Neurology. 76 (11): 1367–74. doi:10.1001/jamaneurol.2019.2044.

237. Vitturi BK, Montecucco A, Rahmani A, Dini G, and Durando P (2023). Occupational risk for multiple sclerosis: A systematic review with meta-analysis”, Frontiers in Public Health 1 (2023): doi:10.3389/fpubh.2023.1285103.

238. Wang MD, Little J, Gomes J, Cashman NR, and Krewski D (2017). “Identification of risk factors associated wirth onset and progression of amyotrophic lateral sclerosis using systematic review and mewta-analysis”, Neurotoxicology 61:101–30. doi:.10.1016/j.neuro.2016.06.015.

239. Yang T, Hou Y, Li C, Cao B, Cheng Y, Wei Q, et al. (2021). "Risk factors for cognitive impairment in amyotrophic lateral sclerosis: a systematic review and meta-analysis". Journal of Neurology, Neurosurgery, and Psychiatry. 92 (7):688–93. doi:10.1136/jnnp-2020-325701.

240. Zhu Q, Zhou J, Zhang Y, Huang H, Han J, Cao B, et al. (2023). “Risk factors associated with amyotrophic lateral sclerosis based on the observational study: AS systematic review and meta-analysis”, Front. Neurosci. 17:1196722. doi: 10.3389/fnins.2023.1196722.

Staging:

241. Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, and Berg van den LH (2016). "Amyotrophic lateral sclerosis: Moving towards a new classification system". The Lancet. Neurology. 15(11):1182–94. doi:10.1016/S1474-4422(16)30199-5.

242. Bergner M, Bobbitt RA, Carter WB, and Gilson BS (1981). "The sickness impact profile: Development and final revision of a health status measure", Medical Care 19(8):787–805. doi:10.1097/00005650-198108000-00001.

243. Brettschneider J, Tredici del K, Toledo JB, Robinson JL, Irwin DJ, Grossman M, et al. (2013). “Stages of pTDP-43 pathology in amyotrophic lateral sclerosis”, Ann. Neurol. 74(1):20–38. doi: 10.1002/ana.23937.

244. Cedarbaum JM, Stmbler N, Malta E, Fuller C, Hilt D, Thurmond B, and Nakanishi A (1999).

"The ALSFRS-R: A revised ALS functional rating scale that incorporates assessments of respiratory function", Journal of the Neurological Science 169(1–2):13–21. doi:10.1016/s0022-510x(99)00210-5.

245. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. (1999). "The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III)". Journal of the Neurological Sciences 169(1–2):13–21. doi:10.1016/s0022-510x(99)00210-5.

246. Chiò A, Hammond E, Mora G, Bonito V, Filippini, and Graziella (2015). "Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis", Journal of Neurology, Neurosurgery, and Psychiatry 86(1):38–44. doi:10.1136/jnnp-2013-306589. hdl:2318/153858.

247. Fang T, Al Khleifat A, Stahl DR, Lazo La Torre C, Murphy C, Young C, et al. (2017). "Comparison of the King's and MiToS staging systems for ALS". Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration. 18(3–4):227–32. doi:10.1080/21678421.2016.1265565.

248. Kimur F, Fujimura C, Ishida S, Nakajima H, Furutama D, Uehara H, Shinoda K, Sugino M, and Hanafusa T (2006). "Progression and rate of ALSFRS-R at time of diagnosis predicts survival time in ALS", Neurology 66(2):265–7. doi:10.1212/01.wnl.0000194316.91908.8a.

249. Maier A; Boentert M; Reilich P; Witzel S; Petri S; Großkreutz J; Metelmann M; Lingor P; Cordts I; Dorst J; Zeller D; Günther R; Hagenacker T; Grehl T; Spittel S; Schuster J; Ludolph A, Meyer T 2022). "ALSFRS-R: An adapted annotated and self-explanatory version of the revised amyotrophic lateral sclerosis functional rating scale", Neurological Research & Practice 4(1): 60. doi:10.1186/s42466-022-00224-6.

250. Roche JC, Rojas-Garcia R, Scott KM, Ellis CE, Burman R, Wijesekera L, Turner MR, and Leigh PN (2012). "A proposed staging system for amyotrophic lateral sclerosis", Brain: A Journal of Neurology 135(Pt 3): 847–52. doi:10.1093/brain/awr351.