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Amyotrophic Lateral Sclerosis (ALS)

Abstract

Amyotrophic lateral sclerosis (ALS) is a motor neuron disorder with a terminal outcome, the pathophysiology of which is not yet clearly understood. There are various subtypes of ALS and factors related both to the environment and to genetics which play a role in the development of the condition. This article will give a general overview of ALS and will specifically discuss some of the different types of ALS, its possible causes, neuropathology, signs and symptoms and its progression. Therapeutic interventions and a brief mention of the future of ALS research will also be outlined.

Keywords

Amyotrophic lateral sclerosis (ALS), motor neuron disease, neurodegeneration, upper andlower motor neurons, frontotemporal dementia

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative condition which is, as yet, incurable. Deterioration of motor neuron occurs in ALS (1,2). Motor neurons have cell bodies which are either present within the motor cortex of the brain, the brainstem or the spinal cord. The axon fibre of motor neurons projects to the spinal cord or to target glands and muscles in order to control them directly or indirectly (3).

Upper motor neurons (UMNs) and lower motor neurons (LMNs) are the two types of motor neurons that exist. LMNs innervate effector muscles directly and their cell bodies are located inside the grey matter of the spinal cord and brain stem. UMNs control LMN activity and form the descending corticospinal and corticobulbar tracts (4). The axons of LMNs are efferent fibres which conduct signals from the

spinal cord to target glands or muscles (5). The motor neuron system is depicted in Figure 1.

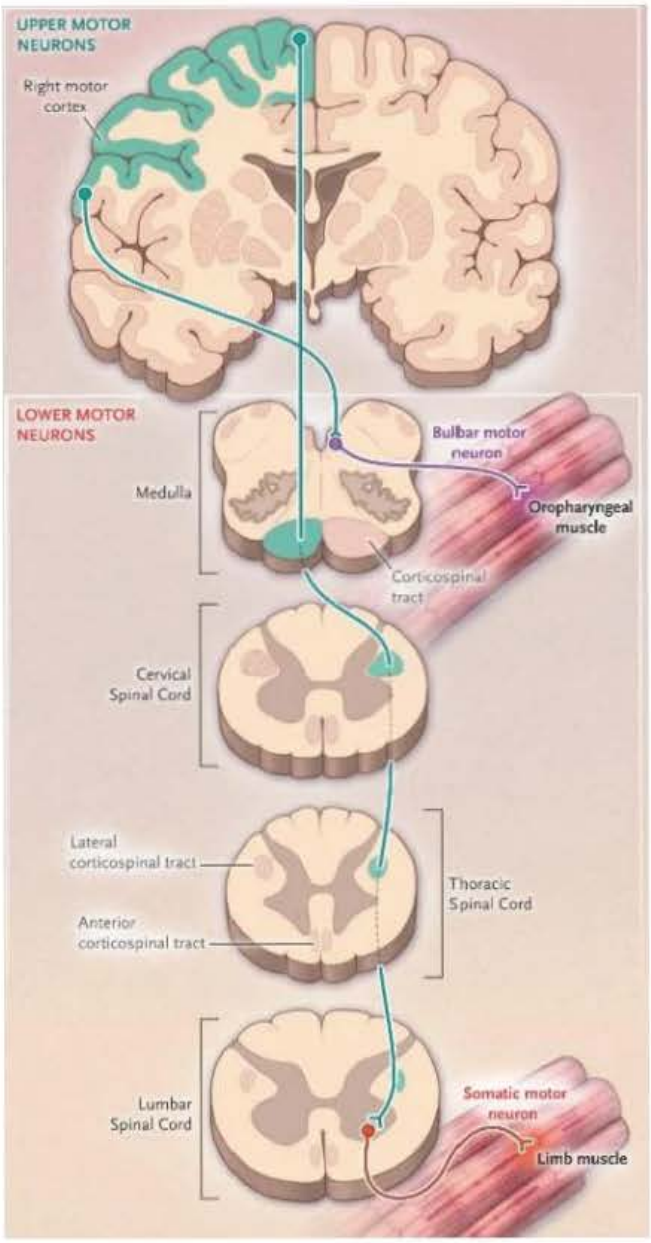

Figure 1 - The motor system showing UMNs and LMNs. Adapted from Brown & Al-Chalabi, 2017

Progressive UMN death along with LMN death takes place throughout the course of this disease, resulting in a variety of symptoms (1,2).

ALS may be familial or sporadic. Familial ALS (fALS) occurs when the diagnosed individual has at least one affected relative, while in sporadic ALS (sALS) there is no known affected relative. The incidence of ALS decreases in people aged 80 years and above (6,7).

Epidemiology

The registry European Amyotrophic lateral sclerosis (EURALS) showed an estimated incidence of ALS of 2.2 per 100,000 person-years (8). Incidence rates of ALS range from 1.1per 100,000 per year to 2.2 per 100,000 per year in difference parts of Europe (9).

fALS is distinguished from sALS as it has an earlier mean age of onset, around 46 years as opposed to 56 years in sALS (10).

The overall male-to-female ratio of ALS is 1.5 - 2:1 making ALS more common in men (11).

Classification of ALS

ALS is classified as being part of a group of MNDs. ALS is the most common MND and it is the predominant MND in adults (12,13).

There are two main forms of classical ALS:

1. Spinal onset ALS, or limb onset ALS and
2. Bulbar onset ALS (14).

Spinal onset ALS presents with upper and lower limb weakness at first, as shown in Figure 2(15). The initial presentation of bulbar onset ALS includes loss of ability to speak, swallow and chew as per Figure 2 (16). A better prognosis is generally seen in spinal onset ALS as is shown in Figure 3 (17)

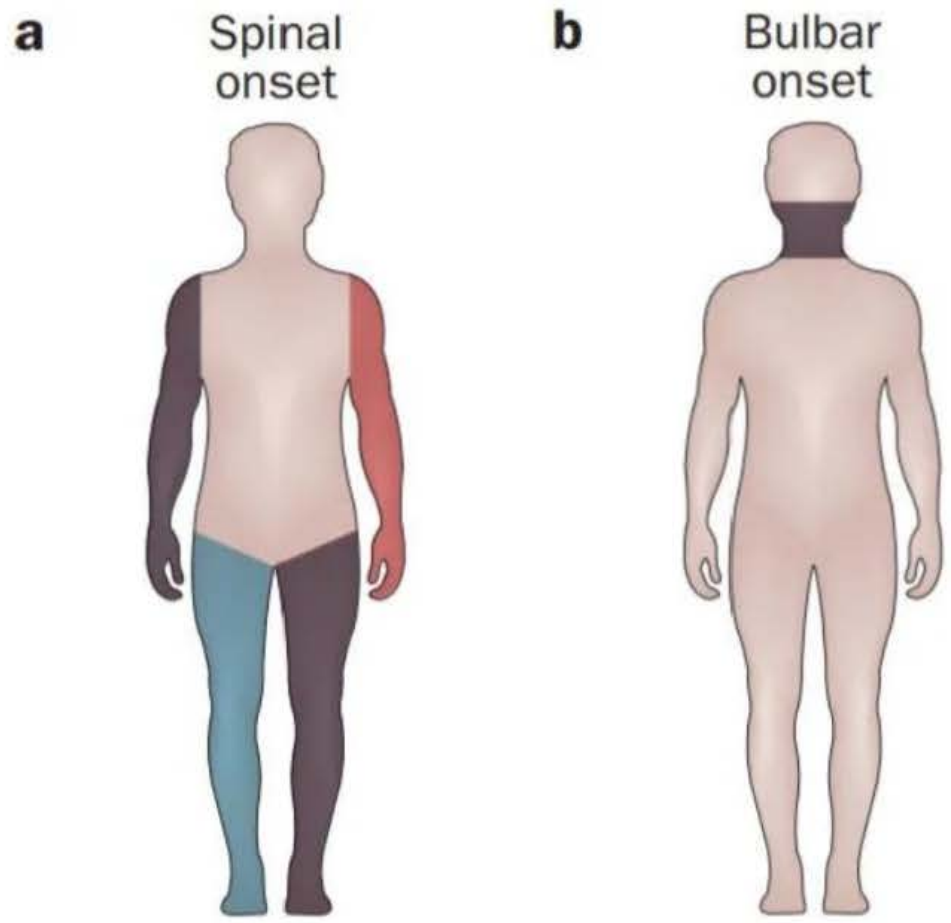

Figure 2 - Patterns of motor involvement in spinal onset ALS vs bulbar onset ALS. More severe involvement is illustrated using darker shading. Adapted from Swinnen & Robberecht, 2014.

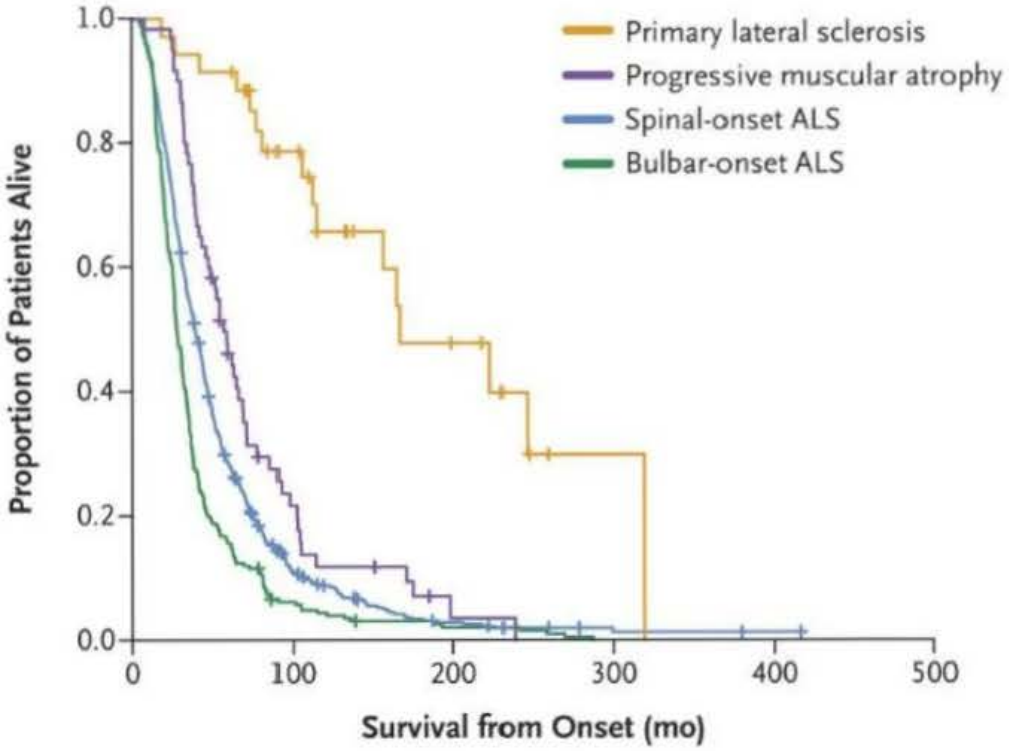

Figure 3 - Graph showing proportion of patients alive against survival from onset (months). Adapted from Brown & Al-Chalabi, 2017.

Regional ALS

When symptoms of ALS affect only one spinal cord region for a year or more, the condition is termed a regional variant of ALS. There is slower progression than classical ALS and survivaltends to be longer (18).

Age of Patient at Onset of ALS

Age at onset can also be used to classify the type of ALS. Approximately 10% of all ALS cases start before patients reach 45 years of age. This is considered young onset ALS. Juvenile ALS occurs in 1% of cases and is said to occur when ALS appears before the age of 25 (6,16). Sudden functional decline and lower longevity are common in late onset ALS, which occurs after the age of 65 (19).

Causes of ALS

Despite the number of genes that are known to be linked with ALS as well as a better understanding of the various cellular processes that contribute to the disease's pathogenesis, the exact cause of ALS remains, as yet, undetermined (20). It is thought that a combination environmental factors such as smoking, body mass index and

metal and pesticide exposure, as well as genetic factors contribute to the incidence of ALS (21).

Genetics of ALS

Around 10% of all ALS cases are familial, (22,23). fALS and sALS cannot be distinguished clinically (22). Recent studies have shown that the burden of ALS-associated genes in sALS appear to be lower than previously estimated (23).

Four specific genes are associated with most cases of fALS:

1. C9orf72 (chromosome 9 open reading frame 72) - 40%
2. SOD1 (Superoxide dismutase [Cu-Zn]) - 20%
3. FUS (fused in sarcoma gene) - 1–5%
4. TARDBP (TAR DNA Binding Protein) - 1–5%

More than one gene must be affected for ALS to occur due to the oligogenic inheritance ofALS. At least 25 genes have been linked to fALS, sALS or both since 1990 (25).

Three main pathways have been identified in which genes associated with ALS cluster:

1. Disturbed RNA metabolism
2. Proteostasis
3. Axonal transport defects (26)

ALS and Frontotemporal Dementia

ALS and frontotemporal dementia (FTD) are better defined as being part of a disease spectrum. This spectrum came about due to the pathological, clinical and genetic similarities between the two diseases. ALS with no cognitive involvement is known as pure ALS while pure FTD excludes any signs of MND. These two conditions are found at opposite poles of the continuum (7).

Neuropathology

A signature feature of ALS is dysfunction of both UMNs and LMNs (27). A pathognomonic feature of ALS is the aggregation of certain proteins within the cytosol of motor neurons. These are termed inclusion bodies (15,28).

TDP-43 protein may aggregate abnormally within the cytoplasm. This occurs in around 97%of ALS cases while it is also seen in up to half of those with FTD (29). The inclusion bodies which deposit in the brain and spinal cord of patients who suffer from ALS and FTD contain hyper-phosphorylated and ubiquitinated TDP-43 aggregates (28). UMN and LMN cell death which follows axonal degeneration and neuromuscular junction loss is a neuropathological signature of ALS (31).

Atrophy of peripheral muscles and of the motor cortex as well as corticobulbar and corticospinal tract sclerosis and hypoglossal nerve thinning are gross pathological features of ALS (15).

Signs and Symptoms

ALS results in muscle atrophy, weakness and spasm which affect the entire body. Both UMN and LMN signs may be present since both are affected in ALS. UMN signs include hyperreflexia, spasticity and slow movements whereas LMN signs include muscle wasting and decreased muscle tone, the presence of fasciculations and hyporeflexia (30). Upper limb onset typically occurs in the dominant hand and seems to preferentially involve the thenar muscles(32). The anterior tibial muscle seems to be the starting point of lower limb onset (33). Muscle weakness often starts in the distal limb muscles (34).

Symptoms of ALS usually only affect one section of the spinal cord initially before progressing to other regions (16). Control of all intentional motor function may be lost (35). The most frequently reported cognitive issues in ALS are problems with language, executive functions, social cognition as well as verbal memory (36).

Most ALS patients experience pain which may be a result of nerve damage (neuropathic),muscle cramps and spasticity. Back, neck, shoulder pain and pressure ulcers also contribute to pain in ALS (37).

Initial symptoms in bulbar onset ALS include dysfunction related to speech and swallowing. Fasciculations and tongue wasting are common in bulbar ALS (6). Some of the observable signs of ALS are shown in Figure 4 and Figure 5.

Diagnosis of ALS

Diagnosis of ALS is made clinically. The presence of UMN and LMN signs are integral to the diagnosis of ALS (30). LMN involvement can be detected by needle electromyography (EMG)before it becomes clinically detectable. This extends the physical examination and allows early diagnosis (38). Positron emission tomography (PET) scanning may detect hypometabolism within frontotemporal lobes of patients with ALS (39).

Although various biomarkers are being explored as potential diagnostic features, none are currently commonly used in medical practice (40, 41). Examples of such biomarkers obtained from cerebrospinal fluid include cystatin C and peptic fragment of the nerve growth factor inducible (VGF) (42).

Therapeutic Interventions

ALS currently has no cure. Treatment is oriented towards easing symptoms and supportive management, the goal being to provide a better quality of life (QoL) and prolonging life (14).

ALS Drug Treatment

A number of medications are used to manage various symptoms in ALS (43). Medications such as riluzole, a glutamate antagonist, slow disease

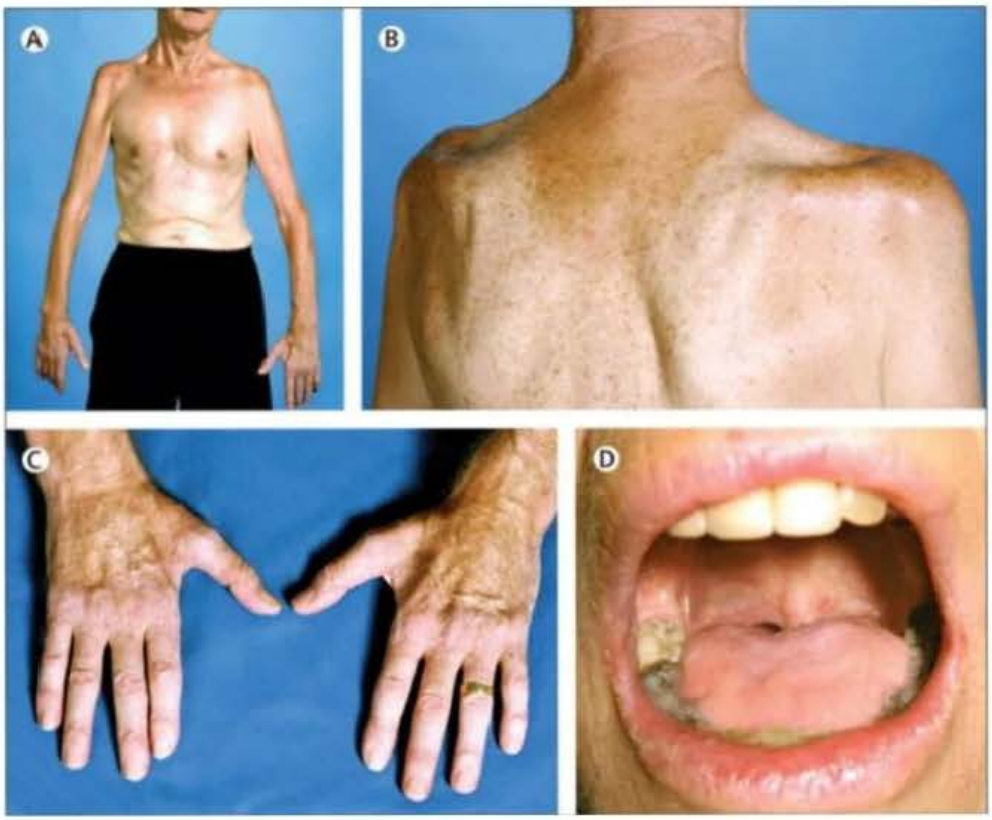

Figure 4
Panel A - Upper limb muscle atrophy typical of flail arm syndrome in ALS
Panel B - Atrophy of infraspinatus, supraspinatus and deltoid in ALS patient
Panel C - Thenar muscle wasting in ALS patient
Panel D - Tongue atrophy in patient with bulbar onset ALS
Adapted from Kiernan et al., 2011

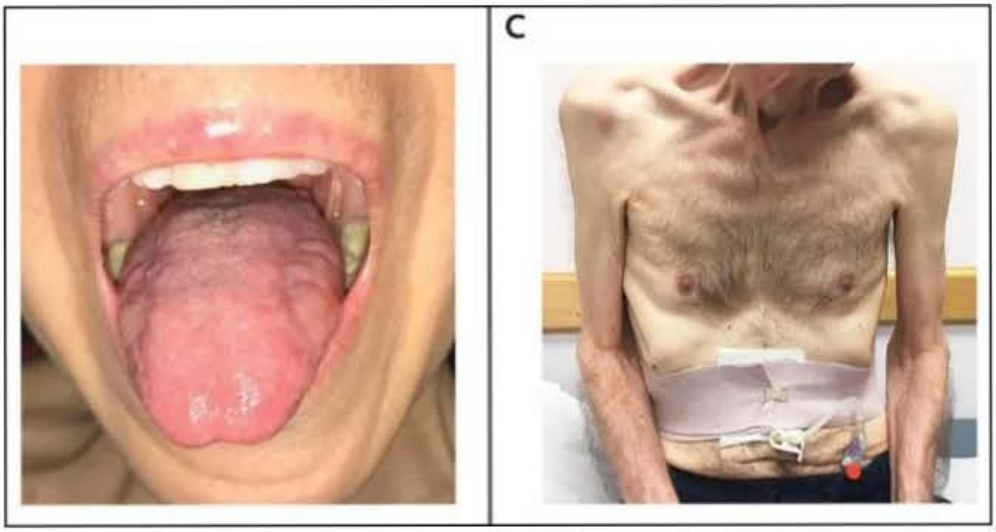

Figure 5
Panel A - Lateral atrophy of the tongue in an ALS patient
Panel B - Atrophied upper limbs in flail arm syndrome in ALS

progression and may prolong survival by two to three months (44,45). The drug edaravone, an antioxidant, may modestly decrease the rate of decline in function in only a very small group of patients who meet very specific criteria (46).

The antispasmodic effects of the oral drugs baclofen and tizanidine are employed to treat muscle spasms (15). Botulinum toxin type A injection (BTX-A) is used to relieve muscle spasticity (47). Muscle cramps can be relieved by gabapentin and carbamezapine (48,49)

Breathing Support

Non-Invasive Ventilation

The main treatment for respiratory depression in ALS is non-invasive ventilation (NIV) and this was the first treatment for ALS which was shown to improve QoL and survival (35,15). NIV has been found to extend survival longer than riluzole and greatly improves QoL (50).

Invasive Ventilation

In advanced ALS, NIV becomes insufficient and invasive ventilation becomes another option(35). Invasive ventilation is inserted past the upper airways by means of a tracheostomy. A tube is then inserted and connected to a ventilator (51).

Palliative Care

Palliative care does not treat the underlying disease but rather, attempts to ease symptoms and increase QoL. This type of care should begin soon after a patient is diagnosed with ALS(52). Discussing end-of-life options with ALS patients allows them time to decide on their preferences and prevents unwanted interventions later on, especially when communication becomes more difficult (53,15).The median survival for ALS is slightly less than 3 years from onset of symptoms (54). Most deaths in patients with ALS are generally due to respiratory failure or pneumonia (6).

Conclusion: The Future of ALS Research

The aetiology of ALS has still not been fully defined and options for treatment are limited (55).This is so because it is difficult to design treatments without knowing the exact pathophysiology of the disease (56). A greater understanding of the genes and biology involved in the pathophysiology of ALS is highly desirable (55).

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