BALNEO RESEARCH Balneo and PRM Research Journal
English Edition
e ISSN 2734 - 8458 p ISSN 2734 - 844X ROMANIAN ASSOCIATION OF BALNEOLOGY

Research article

Variants of Amyotrophic lateral sclerosis and rehabilitation: an overview

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Citation: Iluț S., Stan A., Rahovan I., Hapca E., Zmaranda I., Strilciuc S., Muresanu D. – Variants of Amyotrophic lateral sclerosis and rehabilitation: an overview
Balneo and PRM Research Journal
2023, *14(2): 559*

Academic Editor(s):
Constantin Munteanu

Reviewer Officer:
Viorela Bembea

Production Officer:
Camil Filimon

Received: 28.05.2023
Accepted: 15.06.2023
Published: 23.06.2023

Reviewers:
Alisa Tăbîrța
Mariana Rotariu

Publisher's Note: Balneo and PRM Research Journal stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Amyotrophic lateral sclerosis (ALS) represents a progressive neurodegenerative disease that affects motor neurons in the brain and spinal cord leading to the impairment of voluntary muscle control and eventually death. It accounts for about 80%-90% of all motor neuron diseases, and is characterized by a marked variability in terms of clinical forms, genetics, survival rate and diagnostic particularities. A diagnosis of ALS or one of the variants comes with a great burden for the patient and patient's family because of the high morbidity and mortality rate of this disorder. As a consequence, it is mandatory to optimize the accuracy of the diagnostic process of ALS spectrum for providing the best clinical management and quality of life for patients and avoiding diagnostic mistakes. Our review focuses on the general and particular aspects of ALS and its variants in an effort to improve the process of diagnosis, therapy and exclusion of mimics of this group of diseases and to provide the latest findings in this field.

Keywords: amyotrophic lateral sclerosis, rehabilitation in ALS, flail leg, flail arm, progressive muscular atrophy.

1. Introduction

Motor neuron diseases (MND) represent a vast spectrum of progressive degenerative disorders which affect the motor neurons located in the central nervous system. Inherited or sporadic, the MNDs have a wide range of clinical presentations, which vary greatly depending on the involvement of lower and upper motor neurons (1). Upper motor neurons (UMN) originate in the motor cortex and lead the impulses to the lower motor neurons (LMN), which are found in the spinal cord or brainstem (2). Progressive muscle weakness is the central presentation of MNDs and can lead to a timely death through the failure of respiratory muscles (3).

2. Materials and methods

Inclusion criteria was represented of observational studies, experimental studies, randomized control trials and systematic reviews published in English after 1996, focusing on ALS and rehabilitation. Articles published as abstracts were not taken into consideration. Bearing these criteria, a systematic article search was undertaken on the PubMed database between February 1, 2023, and March 31 2023. Additionally, references cited in included

studies and considered relevant were taken into consideration. A systematic review was conceived in accordance to PRISMA-IPD (Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data) guidelines. The results for the search strategy applied for this subject is illustrated in Figure 1.

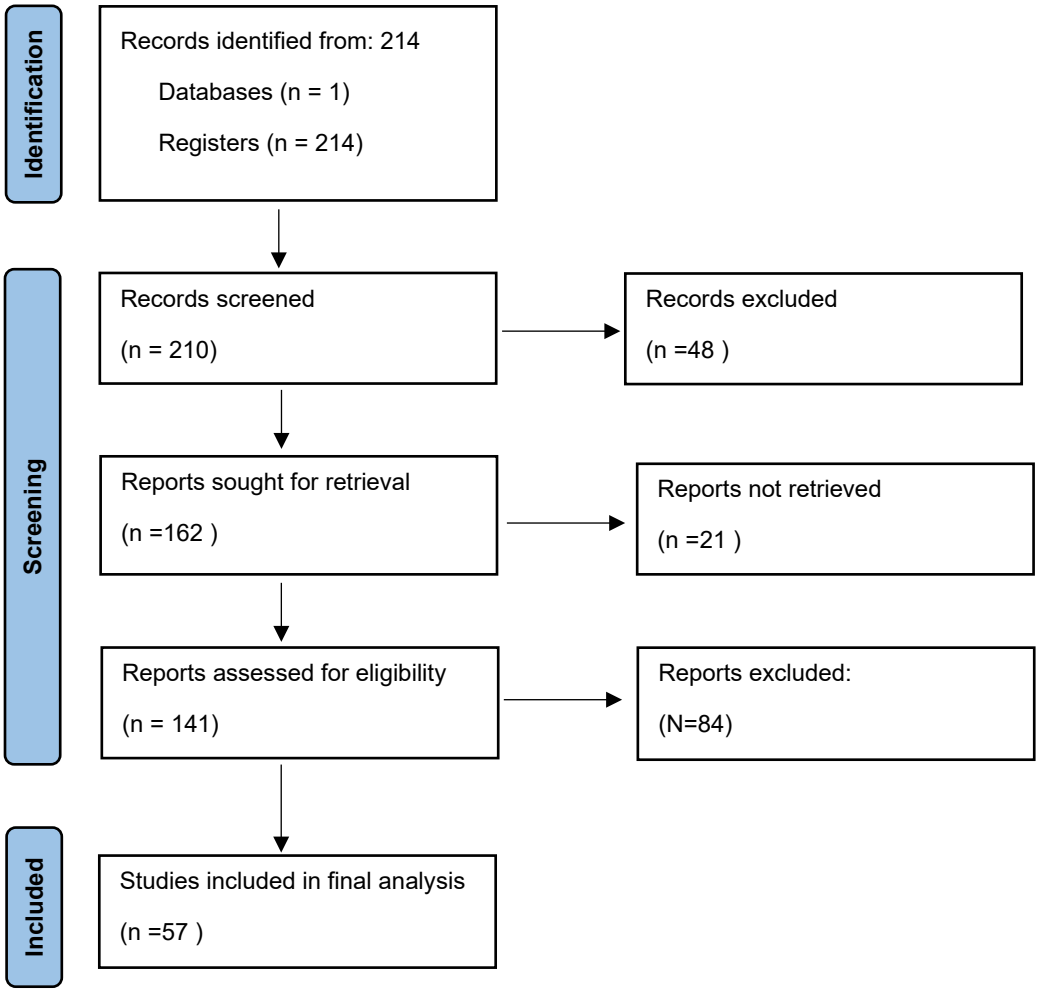

Figure 1. PRISMA diagram for the "ALS and rehabilitation" syntax

3. ALS

Epidemiology

Amyotrophic lateral sclerosis (ALS) and its variants amount to a stunning majority of MNDs (3). Two studies report incidences per 100.000 inhabitants in Europe to be 1,47 and 2,1 respectively (4,5). Incidence increases with old age and is greater in males (4). Although rare, ALS is a serious and fatal disease for which a cure has yet to be found. Median survival is between 2-4 years after diagnosis, but this varies greatly between individuals and is influenced widely by the type of neurons predominately affected, age of onset, physical condition, and mental health (6,7).

Pathophysiology and etiology

Only about 10% of ALS patients suffer from a familial form of the disease. Around 80% have an identifiable mutation as a cause, usually a flawed gene with an autosomal dominant inheritance pattern (8,9). The rest of the cases are considered to be sporadic. However, even sporadic cases of ALS can be subsequently inheritable and can double the risk of first-degree relatives developing ALS (10). The distinction between familial and sporadic forms is difficult because of the 'mutations' variable penetrance (10). The most common mutations in familial ALS are in the SOD1 and C9orf72 genes, together explaining roughly 50% of all familial cases (10). C9orf72 is the most common genetic cause of ALS and can be found in 30% of familial cases and up to 10% of the sporadic forms (11). Another important player is the TARDBP gene, encoding TDP-43 protein, which regulates RNA-expression in cells and is found in the vast majority of cellular inclusions in ALS patients (11). Although it is evident that they play an important role in the development of ALS, environmental factors are hard to identify, and it has been difficult to make definitive statements about the causal relationship to the disease (10,11).

Clinical presentation

In the common form of ALS, both UMNs, namely the pyramidal neurons of the cortex, and LMNs, namely the bulbar neurons in the brainstem or the neurons in the anterior horn of the spinal cord, are involved in the degenerative process (12). Clinical presentation, neurophysiological and neuropathological investigations show clear signs of progressive deterioration in these motor neurons (12). Although there are distinct entities of MNDs that present with either UMN degeneration or LMN degeneration, it is to be taken into account that a portion of them evolve later to affect both types of neurons (10). The degree to which each type of neuron is involved defines the large variety of ALS phenotypes, which will be further presented in our current review. This is also relevant to prognosis, predominant upper motor neuron involvement having the most favorable outcome, compared to, for example, a bulbar or respiratory ALS phenotype, which has much worse survival rates (8).

It is essential to distinguish clinically between UMN and LMN signs. UMN deterioration presented with moderate weakness, hyperreflexia, skeletal muscle spasticity, pathological reflexes, and slowed movements, sometimes accompanied by pseudobulbar symptoms, whereas LMN damage leads to severe weakness and hypotonia hyporeflexia, significant muscle atrophy, muscular cramps, and fasciculations (10,12). Bulbar onset presents with dysphagia, dysarthria, and tongue fasciculations and is more often associated with pseudobulbar symptoms, namely uncontrollable bursts of crying and laughter [8]. Bulbar onset is a strong negative prognosis factor for survival and is found in under one-third of patients, but it is notable that most of the patients with ALS later develop these symptoms in the disease (6,8,10). In addition, the majority of patients experience as a first manifestation a unilateral distal weakness in one limb (10).

Although initially considered a disease of the motor neurons, it is very often observed that cognitive decline is observed in ALS patients, probably through damage that extends to the frontal regions that aid in executive functions and behavior (10). About 10-15% of patients with ALS present frontotemporal dementia, implying that there are indeed reasons

to believe that similar neurodegenerative processes are involved in both pathologies (13). Genetics also plays a role, as patients with mutations in the C9orf72 gene are more likely to have cognitive deficits (10).

Diagnosis

Clinical judgment is usually the most important tool in diagnosing MNDs, as they can be easily diagnosed through specific investigations (2). Although ALS is very variable in initial symptoms, it overlaps with several other neurological disorders that should be excluded before a definitive ALS diagnosis is made (14). Electromyography (EMG) and nerve conduction studies are essential in ruling out other pathologies with similar presentations and must be correlated with the clinical context (14,15). These tests can diagnose an LMN dysfunction and rule out muscular, peripheral nerve, or even associated sensitive nerve abnormalities that would make ALS less likely (2).

Neuroimaging such as magnetic resonance imaging (MRI) of the brain and spinal cord is relevant for excluding alternative differential diagnostics rather than confirming ALS (15). Some significant pathologies to consider are multiple sclerosis, vascular pathologies including stroke, brain or spinal cord tumors, inflammatory or infectious diseases, and traumatic brain injuries, all of which can, to a certain degree, mimic initial symptoms of ALS (2). Additionally, a nerve biopsy can be performed but is rarely thought to be necessary (2).

Treatment

Regarding pharmacological treatment, two drugs show some promising results in slowing the progression of the disease: Riluzole and, more recently with inconclusive results, Edaravone (16,17). Another new therapy is masitinib, 4.5 mg/kg/day suggested a positive effect on the typical disease progression. Early treatment can improve the course of the disease, leading to a slight increase in survival. However, no drug can repair the damage already done (2).

Symptomatic treatment for muscle cramps, spasticity, depression, and other associated pathologies is very relevant in improving the quality of life in ALS patients (17,18). In addition, the aid for communication, be it logopaedic or through electronic devices, should be used whenever necessary as it impacts greatly on the functional performance and psychological well-being of the patients (17,18).

Should not be ignored moderate physical therapy and measures to help integrate ALS patients into the work environment(17,18). Physical therapists should to anticipate the patient's future needs and instruct proper stretching and daily range-of-motion exercises to the patient with ALS and theirs caregivers. From assistive devices, the lightweight ankle-foot orthoses can be used to stabilize weak quadriceps muscles to prevent falls. In a study, Meyer found that individuals evaluated perceived the therapy to be beneficial despite a 3-point decline in the ALS Functional Rating Scale-Revised (ALSFRS-R) and a composite-score reduction of 0.8 in the Measure Yourself Medical Outcome Profile (MYMOP)(19). Finally, nutritional support and maintaining vital functions (e.g., inspiratory muscle training (IMT), lung volume recruitment training (LVRT), and manually assisted coughing (MAC) and ventilation support) are crucial in the more advanced stages of the disease(17).

Speech therapists can provide interventions, like alterations in the taste, consistency, or temperatures of foods. Straws and a certain position of the chin can be used to swallow liquids. In patients with neck extensor weakness are recommend a soft cervical collar to improve positioning during meals.

This review aims to provide an overall picture of the different clinical presentations in ALS, in order to aid clinicians in recognition of some lesser encountered forms of this disease.

4. Clinical forms

The main feature characterizing ALS is a progressive loss of motor neurons, but there is significant heterogeneity in terms of phenotype between cases. Classical ALS is represented by the simultaneous association of upper motor neuron (UMN) and lower motor neuron (LMN) involvement at disease onset. In contrast, atypical forms, like primary lateral sclerosis or progressive muscular atrophy, are present by the early and predominant involvement in the UMN and LMN, respectively. Also, ALS onset can originate in the bulbar region in some patients and the limbs in others. In addition to the site of onset, phenotypic variability also encompasses age at onset, familial occurrence, the extent of extra motor involvement, disease duration, and other important parameters (20). It is important to emphasize that all phenotypic forms are considered variants of ALS because it was observed that, at autopsy, the probability of finding abnormalities in both upper and lower motor neurons is very high. It seems that 10 percent of all cases of ALS are formed by these variants (21). We present the main phenotypic variants of ALS, focusing on the most relevant aspects of these particular forms.

Amyotrophic lateral sclerosis

In patients with the typical form of ALS, symptoms predominate are those of weakness, starting in the hands or legs, or the bulbar manifestation of the disease by slurred speech and dysphagia. Patients almost always present upper and lower motor neuron signs on physical examination. There is a progressive course of the disease, and the survival interval is between three to five years (21).

Two-thirds of patients diagnosed with classical ALS have a spinal form of this disease and present with focal muscle weakness, with symptoms starting either distally or proximally in the upper and lower limbs. There are rare cases when patients may notice focal muscle wasting first, and the weakness is added later. Also, the first presentation may be in the form of a spastic paraparesis. Fasciculations or cramps might precede the onset of wasting or weakness by months or even years, but these are rarely the presenting symptoms. Cold weather might exacerbate weakness (22).

Despite the asymmetry at onset, all limbs develop weakness and wasting sooner or later. Next, most patients progress to develop bulbar symptoms and finally respiratory symptoms (not necessarily in this order). Finally, in evolution, spasticity may develop in the weakened atrophic limbs, with the impairment of gait and manual dexterity (22).

In the case of patients with bulbar onset ALS, dysarthria of speech is the usual presentation. In rare cases, patients may present with dysphagia for liquids or solids before noticing speech disturbances. Limbs symptoms can develop either within 1-2 years after bulbar

symptoms or almost simultaneously. A frequent symptom is sialorrhea caused by difficulty swallowing saliva and a mild UMN type bilateral facial weakness. "Pseudobulbar" symptoms (emotional lability, excessive yawning) are also frequently seen (22).

The fatal evolution of ALS consists of respiratory failure and other pulmonary complications. However, in the case of patients kept alive by tracheostomy-assisted ventilation, the development of a profound state of motor paralysis termed "totally locked-in state" (TLS) arises with all voluntary muscles being paralyzed and some degree of oculomotor impairment(22).

Primary lateral sclerosis

Primary lateral sclerosis (PLS) represents an adult-onset, idiopathic disorder of the upper motor neuron (UMN) system, clinically manifested as slowly progressive, symmetric spinal and bulbar spasticity and pathologically increased reflexes. The distinguishing clinical feature of ALS is the absence of significant lower motor neuron (LMN) signs, demonstrated on electromyography by lack of widespread denervation. Other UMN conditions, such as hereditary spastic paraplegia (HSP), cervical myelopathy, and others, must be excluded (23).

ALS may initially present with UMN signs and develop the LMN signs only later in the disease. For an accurate diagnosis of PLS to be established, the Gordon criteria require an asymptomatic period of 4 years. UMN-predominant presentations that do not meet the disease-duration requirement of the Gordon criteria are termed "early upper motor neuron disease," "pre-PLS," or "pure upper motor neuron disease" (23,24). Traditionally, PLS has been considered a "pure" motor neuron disorder without significant cognitive deficits, and in patients presenting with extra-motor deficits, the term "PLS-plus" is often used (25). One important aspect that defines PLS is that the disease represents only about 3-5% of motor neuron diseases. The prognosis is better, and the survival is longer than the classical form of ALS (26).

Consensus diagnostic criteria for primary lateral sclerosis were established recently (Table 1) to improve the diagnostic accuracy. Clinical signs, laboratory investigations, and electrodiagnosis studies are gathered together, and age is also considered for the optimal and early diagnosis (27).

Core principles	**Diagnostic certainty**
The presence of: - age ≥ 25 years; - symptoms of progressive upper motor neuron (UMN) dysfunction for at least 2 years; - signs of UMN dysfunction* in at least two regions: lower extremity, upper extremity, bulbar.	- The absence of significant active defines probable PLS LMN degeneration 2–4 years from symptom onset. - The absence of significant active defines definite PLS LMN degeneration 4 or more years from symptom onset.
The absence of: - sensory symptoms (unexplained by comorbid condition); - active lower motor neuron (LMN) degeneration†;	* Clinical signs, including spasticity and associated weakness,pathological hyperreflexia (including Hoffman's sign and bilateral extensor toe responses), pseudobulbar affect. Laboratory evidence of UMN dysfunction

from emerging neuroimaging,neurophysiological and neurochemical biomarkers is pending validation.
†Minimally increased insertional activity, and positive sharp waves or fibrillation potentials in extremity muscles are permitted.

Table 1 - Consensus diagnostic criteria for primary lateral sclerosis (PLS)

HSP is a predominantly clinical overlapping disease with the early phase of lower limb-onset PLS. It is essential to mention that both HSP and PLS are mainly clinical syndromes. A significant proportion of patients with an established diagnosis of HSP on clinical criteria will not present a recognized pathological genetic variant. Disorders that mimic PLS are rare, and a high-resolution MRI of the brain and spinal cord will exclude most of these. The duration of a progressive pure UMN syndrome is essential for diminishing the plausibility of many alternative diagnoses (table 2) (27).

Neurodegenerative	**Upper motor neuron-predominant ALS**	**Hereditary spastic paraparesis**	**Alexander disease** Development of clinically progressive lower motor neuron involvement. Family history or relevant genetic variant; symmetrical weakness limited to lower limbs. Focal atrophy and MRI signal change in the medulla, or pathogenic variant in GFAP. Neuroinflammatory	**Primary progressive multiple sclerosis**	**Anti-amphiphysin paraneoplastic syndrome** Inflammatory lesions on MRI of the brain and cord. Positive antibody in context of coincident malignancy
Metabolic	**Adrenomyeloneuropathy** Cerebral MRI white matter abnormalities; raised serum very-long-chain fatty acids; pathogenic variant in ABCD1.				
Infectious	**Tropical spastic paraparesis (Human T-cell lymphotropic virus, HTLV-1 & 2)**		**Syphilis** Positive IgM serology. Positive serology.		
Structural	**Foramen magnum region lesions**		Parafalcine meningioma MRI aspect. MRI aspect.		
Vascular	**Spinal arteriovenous malformation** MRI appearances. MRI aspect.				

Table 2 Differential diagnosis of primary lateral sclerosis

Neuroimaging and neurophysiological investigations have the potential to shape the diagnosis of PLS better and to quantify the UMN lesions better. For example, transcranial magnetic stimulation studies have described a greater central motor conduction time in PLS compared with ALS (28) and also high threshold measures for cortical stimulation, generating relative cortical inexcitability. This characteristic increases the separation of PLS from HSP (29). Regarding EMG, it seems that beta-band EMG has necessary intermuscular coherence as a potential distinguisher of PLS from ALS (30).

New biofluid markers like neurofilaments have the potential to reflect the intensity of neuronal loss in some neurological diseases. It appears that levels tend to be much lower in PLS that in ALS, highlighting the slower progression of the first (31). Also, one important feature observed in some cases of PLS is a focal "knife-edge" atrophy of the precentral gyrus, predominantly absent even in advanced cases of ALS (32). Corticospinal tract fluid-attenuated inversion recovery hyperintensity (FLAIR), involvement of the cerebellum, and iron deposition in the motor cortex have all been observed with increased frequency in PLS (27).

Progressive muscular atrophy

Progressive muscular atrophy (PMA) represents a rare, adult-onset clinically isolated LMN syndrome produced by the progressive degeneration of lower motor neurons, including neuronal cells located in the anterior horn and brainstem motor nuclei. It is clinically defined by progressive flaccid weakness, muscle atrophy, fasciculations, and absent or reduced deep tendon reflexes(33). PMA distinguishes from ALS by the absence of clinical features indicating UMN dysfunction such as spasticity, preserved deep tendon reflexes in atrophic limbs, hyperreflexia, pathologically modified reflexes, and pseudobulbar symptoms. It is important to mention that many patients who had been initially diagnosed with PMA later developed ALS by adding the UMN signs. Also, at autopsy, it is possible to find signs of UMN degeneration despite the absence of clinical UMN findings during lifetime(34).

Patients diagnosed with PMA have been noted to live longer than patients with ALS. Still, recent findings demonstrate that life span is similar in PMA and ALS, supporting the belonging of PMA to the ALS spectrum rather than being an isolated variant of motor neuron disease(35,36).

Currently, the PMA term is used for patients with MND with pure LMN signs on examination to expect the later development of clinically defined UMN signs. Consequently, patients who develop UMN signs are later reconsidered as being diagnosed with ALS(37).

Of motor neuron diseases, 2.5% to 11% of the cases are classified as PMA. It is more prevalent in men (male/female ratio, 3:1-7,5:1), and the incidence is about 0.02 per 100.000. The mean age of onset is 63.4±11.7 years, mostly older than patients with ALS(35,38).

The clinical presentation consists of the LMN as mentioned above features. Weakness and atrophy have an asymmetric development pattern, typically in distal limb muscles, with an extension over months and years. 20% of patients cand present with asymmetric proximal limb weakness, and in 40% of patients, bulbar muscles might be involved later in the disease; between 22% to 35% of individuals with the initial established diagnosis of PMA progress to develop UMN features eventually with a considerable interval of onset ranging from half a month to a decade after the onset of LMN weakness(37).

In patients diagnosed with PMA, the disease evolves during a period of years or decades to months.. The median survival time after onset in individuals diagnosed with PMA is about 12 months longer than in ALS patients (48.3 vs. 36 months)(38). Shorter survival depends on several factors: axial onset, ALSFRS-R less than 38 at the moment of diagnosis, less than 80% of baseline forced vital capacity (FVC), a fast decline in FVC in the first 6 months(36,38).

Diagnosis is established using clinical and electrophysiologic findings of LMN dysfunction in 2 or more different segments (bulbar, cervical, thoracic, and lumbosacral), progression of the disease in time, and the exclusion of mimics. Needle EMG could raise the sensitivity of the accurate diagnosis by showing fasciculations in deep muscles that could miss on examination. PMA must be differentiated from LMN disorders that affect only 1 myotome (flail arm syndrome or flail leg syndrome)(37,39,40). It is a clinical diagnosis and refers to the patients with MND with pure LMN signs that might later develop into UMN signs (LMN onset ALS)(37).

The differential diagnosis between PMA and other LMN syndromes can be very challenging sometimes with diseases such as those affecting motor neurons, nerves, neuromuscular junctions, and muscle fibers.

THE MOST IMPORTANT DIAGNOSES TO EXCLUDE are hereditary LMN diseases such as spinal muscular atrophy (SMA) and spinal-bulbar muscular atrophy. Positive family history can provide valuable information in distinguishing PMA from a hereditary LMN disorder. Both SMA and spinal and bulbar muscular atrophy are different from PMA in terms of phenotype. They are both characterized by symmetric, proximal weakness, in contrast to the asymmetric distal weakness pattern seen in PMA(41). In addition, creatine kinase (CK) levels can be elevated in any chronic MND(42).

Monomeric amyotrophy is another unique MND that must be excluded in the differential diagnosis of PMA. In this case, the weakness and denervation are limited to one limb, usually the arm. The opposite limb might appear clinically unaffected, yet denervation could be demonstrated on needle EMG. Some forms of monomeric amyotrophy represent only an early form of PMA developing in time the typical clinical phenotype(43).

Creutzfeldt-Jakob disease and spinocerebellar ataxias might rarely mimic PMA due to LMN involvement, but other clinical features are helpful in the exclusion of a PMA(44,45,46).

Motor neuropathies are the most challenging differential diagnosis for PMA. Immune-mediated forms, MMN, or hereditary forms are all possible forms of motor neuropathies. MMN usually respects some features that facilitate the differential diagnosis based on clinical, electrodiagnosis, or laboratory findings. Men between 30 and 50 years are affected, and weakness follows a pattern of motor nerve distribution. Conduction block on electrodiagnostic studies represents a definitory feature in MMN along with IgM antibodies against ganglioside-monosialic acid (GM1)(37).

The age of onset can exclude hereditary motor neuropathies, and Charcot-Marie-Tooth disease with purely motor phenotypes often presents subtle sensory disturbances in nerve conduction studies(37).

Other PMA mimics are amyloid neuropathy, porphyria-related neuropathy, and radiculopathies(37).

A minor proportion of individuals with Myasthenia Gravis might have isolated limb weakness and can sometimes be diagnosed with PMA. Electrodiagnostic testing, repetitive nerve stimulation, single-fiber EMG, and myasthenia Gravis's antibodies can help differentiate between atypical Miastenia Gravis forms and PMA(47,48).

Inclusion body myositis (IBM) can mimic PMA in older individuals. Asymmetric proximal and distal weakness and muscle atrophy might guide the physician towards PMA. However, fasciculations are absent in IBM, and needle EMG demonstrates a myopathic process(49).

Management of PMA is similar to the management of ALS(37).

Progressive bulbar palsy

Progressive bulbar palsy (PBP) represents a neurological disorder defined by the selective premature degeneration and death of motor neurons in the lower brainstem, including or not the involvement of the cortico-bulbar tract. Symptoms at presentation are dysarthria, dysphagia, or both. Unless evidence of both upper and lower motor neuron signs is present, PBP patients are not considered probable ALS. However, there are still discussions about whether PBP is part of the motor neuron diseases or an early variant of ALS with the complete phenotype developing in a few months or more(50,51,52,53).

Small studies have shown that almost all patients with PBP evolve into ALS eventually, regardless of the negative or positive findings on EMG studies of the limbs. Also, in patients with PBP demonstrating alterations in EMG parameters of the limbs versus patients without EMG findings, the clinical course is similar(50).

It was observed that this type is prevalent in females, and the first signs of PBP might represent symmetric fasciculations and atrophy of the tongue muscles. Mastication muscles weaken by the degeneration of neurons in the fifth and seventh cranial nuclei. Although muscles of the face and jaws often are affected, the ocular muscles are never involved(54,55).

The diagnosis is established clinically, but electrophysiologic data is always helpful. The progression of bulbar palsy leads to a rapid deterioration of health status, and respiratory weakness might add, along with the increased risk of aspiration pneumonia. Speech therapy might be helpful in patients with mild dysarthria and an adequate nutritional intake with special care to avoid aspiration is mandatory(56).

Patients may also present mood swings with little apparent cause, and the life expectancy of this form of disease ranges between 6 months and 3 years from the onset of symptomatology(57).

Flail arm syndrome

Flail arm syndrome (FAS), also called man-in-the-barrel syndrome or brachial amyotrophic diplegia, represents a variant of motor neuron disease, with the specific features of progressive, predominantly proximal weakness and atrophy of the upper limbs(UL)(58,59,60). It has a relatively slow progression and many forms of presentation, making the differential diagnosis difficult(61).

Patients presenting with FAS have predominantly proximal, progressive, and symmetric wasting and paresis of the UL muscles with spared lower limb (LL) and bulbar muscles(62). Male to female ratio is around 4-9:1, and FAS patients seem to manifest a more prolonged survival than other ALS variants(62).

Studies demonstrated that more than 50% of FAS patients were misdiagnosed. The most common misdiagnoses were MMN, spinal muscular atrophy, carpal tunnel syndrome, and herniated disc(61). Unfortunately, electrodiagnostic studies did not reveal any specific criteria to make a differential diagnosis between FAS and classical ALS. The survival of FAS patients was described in some studies as 20 months longer than in classic ALS, and there is a younger age of onset compared to ALS (mean age of approximately 55 years). Interestingly, it was observed in a large cohort that the first manifestation of the disease was most frequently distal and at the dominant side, a finding that might be useful in the differential diagnosis of FAS(61).

A study comparing a subgroup of 20 patients with the typical features and 357 control ALS patients made some important observations. It was described that patients had wasting in C5 and C6 muscles with lost tendon reflexes in the upper limbs. With the progression of the disease, the motor deficit of the upper limb became bilateral, with the extensor muscles being predominantly affected, resulting in the typical "flail arm syndrome." The cause of death of the majority of patients (75%) was respiratory failure and the progression of the disease from onset of symptoms to time of death was 55.27 ± 35.2 months, with an important difference from the patients in the control ALS population (38 ± 38.3 months)(62).

For an accurate separation of FLS from ALS, some studies compared the two disorders from a multiparameter point of view. A study by Kornitzer et al. used functional, neurophysiological, and pulmonary function parameters to compare FLS and ALS. There are significant differences in vital capacity (VC) and ulnar CMAP (compound muscle action potential) amplitudes between ALS and FLS. It was observed that VC did not decrease in any of the FLS patients by more the 0.65% per month, and the VC did not decrease by less than 4.6% per month in any of the ALS patients. The slower deterioration of pulmonary function in FLS compared to ALS might be because of relative diaphragm sparing. VC has the potential to help distinguish FLS from ALS. Also, the average CMAP amplitude in the ulnar nerve was significantly lower in FLS the in the classic form of ALS, pointing out to a more axonal loss and loss of motor neurons in the lower cervical anterior horn of the group with FLS(63). Another study described neurophysiological differences between FLS and ALS. It was reported that there is an increase in the split hand index (ratio between CMAP amplitude of the ulnar to the median nerve) of 1.24 ± 0.30 versus 2.36 ± 0.32 and in the resting motor threshold in the FLS versus the ALS groups, respectively(64).

Comparisons between flail arm syndrome and upper limb-onset ALS made attempted using clinical and needle electromyography parameters. However, the significant differences observed were only in data regarding the rate of fasciculation and patterns of predominantly affected muscles(65).

Flail leg syndrome

Represents a regional variant of ALS confined to the legs, also known as the pseudopolyneuritic variant of ALS or leg amyotrophic diplegia. It is a relatively rare variant, representing about 3% to 3.5% of all motor neuron disease cases. It affects men predominantly

and mostly LMN and is characterized by a slow progression with survival between 76 to 96 months(19).

The clinical feature representative for FLS is weakness confined to the lumbosacral spinal cord region(43). The symptom onset has a similar mean age to classic ALS (between 55-57 years)(39,40). The onset is mostly asymmetric in half of the patients, but, over time, the weakness affects both lower extremities, and reflexes are absent or diminished; about 25% of patients with FLS progress to the inclusion of a second spinal cord region at 2 years of follow-up. Case series from the literature attempted to formulate a clear definition of this form of ALS. Although some differences exist, there are some common features:

- Insidious onset of weakness isolated to the legs

- Decreased or absent reflexes at presentation

- Symptoms are limited to a single spinal region for 12-24 months

In the absence of sensory symptoms and signs.

A proper diagnosis must include spine MRI and negative GM1 antibody testing.

Nerve conductions studies reveal only reduced CMAP amplitude, without evidence of conduction block or demyelination, and electromyography describes denervating changes, fibrillation potentials, positive sharp waves, and long duration polyphasic motor units.

Serum CK levels may be increased by 100-500 IU/L.

The mean survival was described as between 75.9 – 87 months, better than classical ALS(39,40,43).

ALS-Plus syndrome

Patients with ALS can present some atypical features as some single cases or small series of patients have described in various studies(66), like ocular motility abnormalities, cerebellar and extrapyramidal signs, and autonomic dysfunctions(67). Therefore, consensus criteria for ALS diagnosis include these atypical clinical manifestations in a variant of ALS termed "ALS-Plus syndrome"(68).

In a large cohort of ALS patients, a study identified a great number of individuals with ALS-Plus syndrome (13.6% of ALS patients). It was described that the presence of non-pyramidal features offers many significant details as a poorer prognosis than in other variants of ALS. The bulbar-onset disease was also observed twice as commonly in ALS-Plus than in patients without ALS-Plus. In addition, noted an increased frequency of pathogenic mutations with important clinical implications. Sporadic ALS and familial ALS have been considered clinically identical. Still, an ALS-Plus syndrome could lead to the suspicion that a patient may have an identifiable pathogenic mutation. The conditions identified included nearly 1 in 9 ALS patients with oculomotor abnormalities (gaze abnormalities, horizontal, up-gaze, down-gaze, impersistence, head movements), 1 in 32 patients with extrapyramidal features (resting tremor, bradykinesia, retropulsion, masked face, rigidity, dystonia, apraxia of eye closure or gait apraxia), 1 in 138 ALS patients with cerebellar characteristics (ataxia, limb dysmetria) and 1 in 515 ALS patients with autonomic features (diaphoresis, loss of taste and smell). In addition, pseudobulbar affect observed in 1 in 2 ALS-

Plus patients as opposed to 1 in 4 non-ALS-Plus patients, and cognitive dysfunction was described in 1 in 13 ALS-Plus patients compared with 1 in 34 non-ALS-Plus patients(67).

In another small study, 5 cases of concomitant ALS and parkinsonism were described. The mean age at onset was higher (67 years, range,(65-72)) than the common onset age for ALS patients. Three cases presented signs of motoneuron disease before the onset of parkinsonism. Also, in 3 cases, the parkinsonism consisted of rest tremor and rigidity, while the other 2 presented bradykinesia(69). Some studies reported that ALS is associated with parkinsonism in 5% of cases in the progression of the disease(70).

It is important to mention that autopsy series in the past have demonstrated ALS as a cerebral pathology that involves areas beyond the primary motor cortex. Earlier descriptions of ALS patients demonstrated cognitive impairment and occasional psychosis. A paramount in ALS researchis the shared feature of cytoplasmatic inclusions of the protein TDP-43 in ALS and frontotemporal dementia (FTD). It was observed that FTD manifests in only 10-15% of patients with ALS, most frequently as an early feature. This link between FTD and ALS demonstrates the expansion of ALS to the frontal and temporal lobes(71).

The atypical manifestations in ALS-Plus syndrome support the theory that ALS represents a multisystem neurodegenerative disorder.

Investigations

The diagnosis of amyotrophic lateral sclerosis relies on the medical history, physical examination, electrodiagnostic testing, neuroimaging, and usually some laboratory tests to exclude other causes.

Total diagnostic time, defined as the time from symptom onset to a confirmed diagnosis, has been reported to range from 11 to 15 months. Even after this long period, there is a risk of misdiagnosis due to other diseases that may mimic ALS in the early stages(72).

Electrodiagnosis

EMG is a very important part of the diagnostic procedure because of its specificity, and it can show modifications in clinically unaffected areas. Typical EMG abnormalities in patients with amyotrophic lateral sclerosis are fasciculation/ fibrillation potentials and spontaneous denervation discharges, indicative of reinnervation(73). A correct diagnosis must be made according to the criteria established by the International Federation of Clinical Neurophysiology (table 3)(14). Electrodiagnosis must be made as soon as possible to have an early initiation of the treatment and hence a better outcome.

Table 3 Criteria for detection of neurogenic change by needle EMG in the diagnosis of ALS

1. For the evaluation of LMN disease in ALS in any given body region, clinical and electrophysiological abnormalities have equal diagnostic significance
2. EMG features of chronic neurogenic change must be found, for example:

1. MUPs of increased amplitude and increased duration, usually with an increased number of phases, as assessed by qualitative or quantitative studies.
2. Decreased motor unit recruitment is defined by the rapid firing of a reduced number of motor units. Rapid-firing may not be achieved in limbs affected by clinical features of significant UMN abnormalities.
3. Using a narrow bandpass filter (500 Hz to 5 kHz), unstable and complex MUPs will be observed in most cases of ALS.

3. In ALS, FBS-SW are usually recorded in strong, non-wasted muscles

4. In the presence of chronic neurogenic change on needle EMG in ALS, fasciculation potentials (FPs), preferably of complex morphology, are equivalent to fibrillations and positive sharp waves (fibs-SW) in their clinical significance

MRI

Neuroimaging is often used to evaluate suspected amyotrophic lateral sclerosis to exclude other possible diagnoses like spinal cord injuries, multiple sclerosis, tumors, stroke, or other abnormalities of the central nervous system. Brain MRI should be performed whenever the bulbar disease is present but is also supposed to be useful in finding cortical atrophy in ALS. In addition, spine MRI can be used to evaluate lower motor neuron disease (74). *T2-weighted images* and fluid-attenuated inversion recovery (FLAIR) are the best sequences to detect hyperintensity signal anomalies of the corticospinal tract on both brain and spinal MRI in ALS patients. These changes are identified in up to 96% of patients in some studies and are generally more pronounced in the case of advanced disease (75). However, more studies on MRI changes in ALS patients will guide the goal of personalized diagnostic procedures (76).

Serological and cerebrospinal fluid testing

Serological testing is routinely performed to exclude other pathologies for a correct diagnosis of amyotrophic lateral sclerosis (77). Typical laboratory markers are specified in Table 4.

Ganglioside GM-1 antibodies, Borrelia titers, HIV, and celiac serology should be performed only where clinically indicated. Heavy metal screening is necessary for patients with a potential history of exposure (73).

Occasionally, a lumbar puncture may be required, especially if the individual has unusual features of ALS (78). Cerebrospinal fluid biomarker studies in ALS patients have shown various mechanisms of neurotoxicity, and the existing literature suggests the involvement of both toxic and protective factors that could directly or indirectly influence neuronal degeneration (79).

Genetic testing is sometimes indicated because approximately 5–10% of ALS patients have a family history of ALS (familial ALS) (80). The five most prevalent genes mutated in ALS are *C9orf72*, *SOD1*, *TDP-43*, *FUS*, *and TBK-1* (81).

Table 4 Blood, CSF tests used for the diagnosis of ALS

Full blood count
Erythrocyte sedimentation rate
C-reactive protein

Glucose
Renal function tests
Liver function tests
Electrolytes: Na +, K+, Cl-, Ca 2+
Creatine kinase
Lactate dehydrogenase
Vitamine B12, folate
Serum protein electrophoresis and immunoelectrophoresis
Thyroid function tests: free tri-iodothyronine, free thyroxine, and thyroid-stimulating hormone

Where clinically indicated:

Parathyroid hormone
Heavy metal screening
HIV test
Borrelia IgM and IgG antibodies
Celiac serology

Cerebrospinal fluid tests: glucose, protein, cell count, and, if necessary oligoclonal bands

Genetic testing

Treatment

ALS patients management is multidisciplinary. The treatment is often palliative, and Riluzole (50 mg twice daily) is currently the only disease-modifying treatment approved by the European Food and Drug Administration in 1995, based on two double-blind, placebo-controlled randomized clinical trials (82,83).

Riluzole is a glutamate antagonist, inhibiting presynaptic glutamate release and enhancing glial and neuronal glutamate uptake. It is the only drug shown in clinical trials to increase median survival by 2 to 3 months among patients with amyotrophic lateral sclerosis. However, population studies reveal that the patients tend to have a long-lasting disease with a median survival of 6 to 19 months, mostly because these studies are prospective and include patients in the early stages at the initiation of therapy with Riluzole (84).

Edaravone is an intravenous treatment administered with a dosage of 60mg/day in an alternating cycle of 14 days/month, approved only in some countries (USA, Canada, Japan, South Korea, and Switzerland) after a phase III randomized, double-blind study made in Japan and published in 2017 (85). The latest study of Edaravone efficacy shows no disease-modifying benefit in the progression of patients with ALS, even in a younger and less severely affected subpopulation (86).

A tyrosine kinase inhibitor known under the name of Masitinib, used since 2008 to treat mast cell tumors in dogs, is under investigation as an add-on therapy to Riluzole for patients with amyotrophic lateral sclerosis (87).

Nutrition is an important part of the management of amyotrophic lateral sclerosis patients. Often, they develop dysphagia which leads to malnutrition and worsening of

weakness and fatigue, and eventually, in the late stages, a percutaneous endoscopic gastrostomy may be needed for enteral feeding (88). Therefore, numerous dietary supplements like vitamin A and E and creatine have been studied over the past years. Still, they did not show a significant improvement in the survival rates of patients with amyotrophic lateral sclerosis (89,90).

Respiratory failure due to gradual lung function deterioration is the most common cause of death in ALS patients. However, correct respiratory management lengthens survival. Non-invasive ventilation is the preferred life-prolonging treatment for respiratory insufficiency, but when this method fails, often due to severe bulbar impairment, tracheostomy is recommended (91).

Other symptoms like spasticity, muscle cramps, pain, sialorrhea, dysarthria, dysphagia, constipation, sleep disturbances, emotional lability, depression, and anxiety, can be managed by pharmacological and non-pharmacological interventions. Multidisciplinary care from neurologists, dietitians, and physical and speech therapists is essential to increase survival and quality of life in ALS patients (92).

Conclusions

ALS represents a great burden to both the patients diagnosed with it and the doctors that diagnose them, leading invariably to a timely and unpleasant death. We still lack reliable means to cure the disease, but there is a chance to slow this neurodegenerative process if diagnosed early. Being a rare disease, not every clinician is acquainted to the atypical presentations of the disease, thus slowing down the time between onset of symptoms and definitive diagnosis. The cornerstone of disease management for ALS patients remains multidisciplinary care with dietary changes, speech therapy, physical therapy, occupational therapy and respiratory therapy which has a positive effect on patient satisfaction and outcome. We hope to have provided a comprehensive overview of the subject with focus on the uncommon forms of ALS that will come in hand in the management of this severe illness.

Author Contributions: Conceptualization, I.S. and D.M.; Methodology, S.S.; Software, S.S.; Resources, I.Z..; writing – original draft preparation, I.R., E.H..; writing – reviewing and editing, I.S, S.A.; Supervision, D.M.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Institutional Review Board Statement: Not applicable.

Informed Consent statement: Not applicable

Conflicts of Interest: The authors declare no conflict of interest.

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