

# ALS Mimics



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## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease. Most patients die within 2–5 years of symptom onset due to the lack of effective therapy options. A diagnostic delay is encountered quite often, since disease progression as well as site and speed of onset may vary significantly. Some diseases can mimic features of ALS, especially in early stages. It is very important to differentiate those mimics from ALS as potentially treatable conditions might be missed otherwise. ALS typically affects the upper as well as the lower motor neuron, which implies that diseases sharing at least one of these clinical features have to be considered in the differential diagnosis. The

following conditions should be taken into account as a differential diagnosis for ALS with predominant affection of the lower motor neuron: Immune mediated neuropathies such as multifocal motor neuropathy (MMN) with pronounced distal paresis without striking atrophy signs and conduction blocks in electroneurography, and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with common signs of sensibility disturbances, areflexia and cytoalbuminologic dissociation in the cerebrospinal fluid (CSF). Sporadic inclusion body myositis (sIBM) with typical biopsy findings and clinically predominant affection of the finger flexors. Spinal and bulbar muscular atrophy (SBMA), in which androgen receptor (AR-)gene testing and clinical signs of androgen insensitivity will help to differentiate the disease from ALS. Hirayama disease shows cold paresis; a cervical MRI scan and a normal neurography will help to confirm the diagnosis. In benign fasciculation syndrome, there is no muscle paresis or atrophy, and acute denervation cannot be detected in the EMG. In spinal muscular atrophy (SMA), testing for the SMN gene will help to differentiate the condition from ALS; furthermore, SMA is a very rare disease in adults. As a differential diagnosis for ALS with both clinical affection of the upper and lower motor neuron e. g. metabolic diseases such as adrenoleukodystrophy, metachromatic leukodystrophy and Tay-Sachs disease should be taken into account. Here, laboratory tests are the most important steps for a correct diagnosis. Cervical myelopathy is also capable of affecting the upper and lower motor neuron, but can easily be differentiated by a cervical MRI scan. As a differential diagnosis of ALS with predominant affection of the upper motor neuron, we discuss hereditary spastic paraparesis (HSP) which presents with a symmetric spasticity of the legs. The MRI often shows atrophy of the spinal cord, and SPG gene testing is done to differentiate HSP from ALS.

## ABBREVIATIONS

<b>ALS</b>	Amyotrophic Lateral Sclerosis
<b>AR gene</b>	Androgen Receptor Gene
<b>BFS</b>	Benign Fasciculation Syndrome
<b>CAG</b>	Cytosine Adenine Guanine
<b>CASPR2</b>	Contactin-Associated Protein 2
<b>CIPD</b>	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
<b>CK</b>	Creatine Kinase
<b>C9ORF72</b>	Chromosome 9 Open Reading Frame 72
<b>DGM</b>	Deutsche Gesellschaft für Muskelkranke
<b>EMG</b>	Electromyography
<b>ENG</b>	Electroneurography
<b>fALS</b>	Familial amyotrophic lateral sclerosis
<b>FAS</b>	Flail Arm Syndrome
<b>FLS</b>	Flail Leg Syndrome
<b>FUS</b>	Fused in Sarcoma
<b>GBS</b>	Guillain-Barré syndrome
<b>GM1/2-AB</b>	Ganglioside GM1/2 Antibodies
<b>HSP</b>	Hereditary Spastic Paraparesis
<b>IOD1</b>	Dorsal Interosseous Muscle I
<b>IVIG</b>	Intravenous Immunoglobulins
<b>LGI1</b>	Leucine-rich, Glioma Inactivated 1
<b>MAG-AB</b>	Myelin-associated Glycoprotein Antibodies
<b>MMN</b>	Multifocal Motor Neuropathy
<b>MND</b>	Motor Neuron Disease
<b>MRI</b>	Magnetic Resonance Imaging
<b>NVC</b>	Nerve Conduction Velocity
<b>PEG</b>	Percutaneous Endoscopic Gastrostomy
<b>PLS</b>	Primary Lateral Sclerosis
<b>PMA</b>	Progressive Muscular Atrophy
<b>POEMs</b>	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and skin changes
<b>sALS</b>	Sporadic Amyotrophic Lateral Sclerosis
<b>SBMA</b>	Spinal and Bulbar Muscular Atrophy (Kennedy disease)
<b>sIBM</b>	Sporadic Inclusion Body Myositis
<b>SMA</b>	Spinal Muscular Atrophy
<b>SMN gene</b>	Survival Motor Neuron Gene
<b>SOD1</b>	Superoxide Dismutase 1
<b>SPG gene</b>	Spastin Gene
<b>STIR</b>	Short-Tau Inversion Recovery
<b>TDP-43</b>	Transactive Response DNA Binding Protein 43 kDa
<b>TSE</b>	Turbo Spin-Echo
<b>VGKC</b>	Voltage Gated Potassium Channel

## Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disease of the motor nervous system, which leads to progressive paresis of the entire voluntary musculature, including the swallowing, speech, and respiratory muscles, and after an average period of disease of 2–5 years, results in death, mostly due to progressive respiratory

insufficiency. Disease incidence is approx. 1.2–4.0 per 100,000 among Caucasians; thus ALS is the most common motor neuron disease (MND) [1]. Prevalence varies between 2.7–7.4 per 100,000 [2]. The risk of developing ALS increases with age; the peak age ranges between 50 to 80 years. Men are somewhat more frequently affected than women (1.5:1) [3]. Sporadic forms of ALS (sALS) comprise approx. 90% of all cases; only about 10% are considered familial ALS cases (fALS), generally with underlying autosomal-dominant inheritance factors [4]. To date, more than 25 genes have been identified that are related to the development of ALS. The most common are SOD1, TDP-43, C9ORF72 and FUS mutations.

The diagnosis is primarily based on clinical symptoms. Classical ALS exhibits damage of the upper and lower motor neuron on several levels, i. e. bulbar, cervical, thoracic and lumbosacral. Indicators for an involvement of the upper motor neuron which originates in the motor cortex include increased reflexes, positive pyramidal tract signs and spasticity. Damage to the lower motor neuron ( $\alpha$ -motor neuron in the spinal cord or brain stem) leads to flaccid paralysis, fasciculation and muscular atrophy. Primary lateral sclerosis (PLS) exclusively involves clinical and electrophysiological affection of the upper motor neuron over at least 4 years, and has a slower progression with a better prognosis [5]. Similarly, progressive muscular atrophy (PMA) is a pathology continuing at least 4 years affecting only the lower motor neuron [6]. It is difficult to distinguish these special forms from classical ALS, since signs of the lower and respectively the upper motor neuron may develop even after several years of symptom onset, thus making a transition to ALS possible. Generally, ALS shows a focal onset and progressively spreads and affects other regions of the body. Patients may develop a primary bulbar paralysis with dysarthria, dysphagia, fibrillation and atrophy of the tongue, for example. In most of the cases though, the limbs are affected first. Flail arm (FAS) and flail leg syndrome (FLS) which typically exhibit atrophy and paresis of the shoulder and arm musculature (FAS) or leg musculature (FLS) represent special forms of ALS, whereby the disease progresses relatively slowly in the other regions and compared to classical ALS, shows a distinctly better prognosis.

Even though motor symptoms clearly dominate the pathology, ALS is now regarded as a multi-system disease which in late stages can particularly affect cognition, the extrapyramidal system, as well as the sensitive and autonomic nervous system. Molecular neuropathology has demonstrated the propagation of pTDP-43, a hyperphosphorylated ubiquitinated and attenuated protein in the brain and spinal cord of ALS patients, thus allowing a breakdown of ALS into four stages [7]. Analogous to the neuropathological expansion of the disease, initial imaging studies using diffusion tensor imaging have exhibited involvement of the corticospinal, corticorubral and corticopontine tracts, the corticostriatal signaling pathway and proximal section of the perforant path [8]. Based on these findings, it should be expected that in coming years new biomarkers will be developed which will support an improved delineation of the above-described pathologies with respect to early stages of ALS.

Electromyography (EMG) and electroneurography (ENG) represent significant supplementary diagnostics which can partially show damage to the lower motor neuron prior to clinical signs, thus supporting early detection. We recommend using the revised El-Es-

corial criteria of 2015 for diagnosis [9]. These criteria include progressive impairment in the region of the upper and lower motor neuron in at least one limb/body region or clinical and/or electrophysiological damage to the lower motor neuron in at least two body regions (bulbar, cervical, thoracic, lumbosacral). Typical changes in the EMG can be fibrillation potentials, positive sharp waves as well as chronic neurogenic changes. Motor neurography indicates axonal damage in the affected nerves; sensitive neurography is unremarkable. Motor conduction blocks are considered signs of multifocal motor neuropathy (MMN) (see below).

Supplementary cranial and spinal MR imaging should be performed as ALS should be a diagnosis of exclusion. Increased creatine kinase (CK) as an expression of secondary muscle damage is regularly found as a chemical biomarker. Furthermore, recent research has shown that the amount of neurofilament light chains in the cerebrospinal fluid of ALS patients is significantly increased when compared to controls or ALS mimics [10].

To date, there is no causal treatment of ALS. Only riluzole, a glutamate antagonist, has been shown to prolong average survival by 3–5 months [11]. Physio- and ergotherapy, as well as speech therapy and the use of various aids are being used as symptomatic treatment. Adaptation of non-invasive home ventilation is recommended if the respiratory system is adversely affected. Frequently, as the disease progresses, a PEG tube is necessary for feeding due to progressive dysphagia. In addition, there are a number of medical approaches for treating aggravating symptoms such as mucus, salivary flow, spasticity, muscle cramps, depression and pain that may occur during the course of the disease.

A correct diagnosis can be difficult, particularly during the initial stages of the disease in which only the upper or lower motor neurons are affected. This is exacerbated by the fact that some diseases are quite similar to the onset of ALS, the so-called “ALS mimics”. In view of the fact that these conditions have a better prognosis, and that there may be causal therapy options, early differentiation in the clinical routine is important: on the one hand, to allow early therapy, and on the other, to avoid confronting the patient with an inaccurate fatal prognosis.

The following will describe the ALS mimics which are most relevant for everyday clinical practice as well as present the most important differentiation criteria with regard to ALS. An experience-based opinion can be found at the end of this review article.

## Immune-mediated Neuropathies

### Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) represents an important differential diagnosis to ALS. MMN is a chronically progressive, immune-mediated disease with distinct distal asymmetric paresis, particularly affecting the upper limbs, but with only slight muscle atrophy. Initial symptoms frequently include paresis of the hand muscles or dorsal flexors of the foot; proximal muscle groups are usually spared. Sensitivity deficits or involvement of the upper motor neuron are absent, but cramping, fasciculations and myocymia can occur [12]. MMN was first described in 1986. Similarly to CIDP men are more frequently affected than women (2.6:1), with a prevalence of about 0.6/100,000. The average age of onset is 40

years of age [13, 14]. Unlike ALS, electroneurography reveals motor conduction blocks. Furthermore, high-titer ganglioside GM1-antibodies can be found in the serum in some cases and CSF protein may be slightly elevated. Likewise, neurosonography can also contribute to differentiation [15, 16]. Nerve biopsy, however, is not indicated for MMN since the usually biopsied sural nerve is not affected by MMN. The high relevance of the distinction from ALS lies in the possibility of treatment and good prognosis of MMN. Therapy of choice is the administration of intravenous immunoglobulins, the treatment regime should be customized for each patient. Patients with MMN have a normal life expectancy [12, 17]. The diagnosis of MMN should be questioned if there is no positive response to the administration of IVIGs in the form of recovery of the motor deficits. Unlike with CIDP, administering glucocorticoids has no effect; clinical symptoms can even worsen.

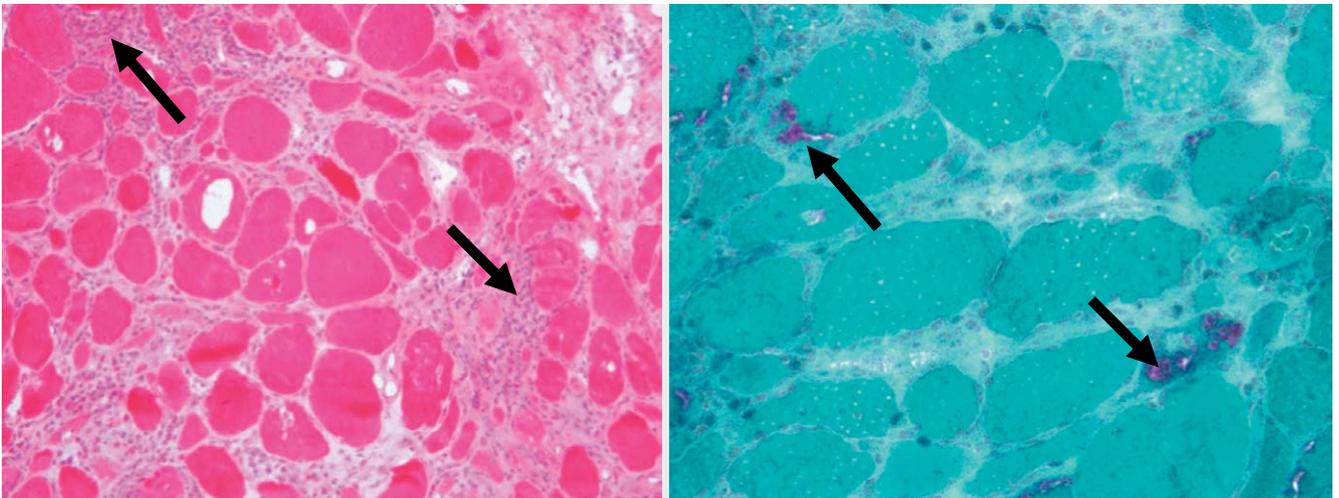
In rare cases, there are also purely motor forms of CIDP which can be confused with ALS (see following section).

### Chronic inflammatory demyelinating polyradiculoneuropathy

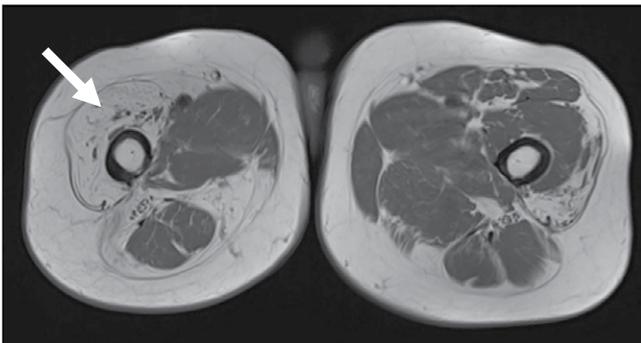
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a neuropathy based on advanced demyelination of spinal roots and peripheral nerves. Depending on the source cited, its prevalence is about 1–2 per 100,000 [18]; men are more commonly affected than women (approx. 2.3:1) [19]. The typical age of onset is in the 5th to 6th decade of life, although the literature describes cases of children suffering from CIDP [20]. The term CIDP was coined by Dyck et al. (1975) who examined patients with polyradiculoneuropathy which had previously been considered chronic Guillain-Barré syndrome (GBS) [21]. CIDP comprises the most common of all acquired demyelinating neuropathies, including anti-MAG (myelin-associated glycoprotein) neuropathy, MMN and neuropathy related to the POEMs syndrome (multi-system disease with the occurrence of polyneuropathy, organomegaly, monoclonal gammopathy and skin changes). Since there are currently no specific biomarkers for the presence of CIDP, it is basically a diagnosis of exclusion [22].

The diagnosis is made mainly through clinical observation; electrophysiology and CSF diagnostics provide important supplementary information. The “classical” phenotype is distinguished by peripheral paresis, hyporeflexia or areflexia as well as the loss of large-caliber sensory fibers [23, 24]. The progression of the disease can proceed both episodically as well as chronically, with the distinction compared to GBS becoming apparent over the course of time. CIDP can be considered only if the illness continues for more than 8 weeks. Compared to ALS, paresis is more frequently symmetrical, although at the onset of the disease an asymmetrical pattern is often evident. Furthermore, due to the loss of sensory fibers, deep and superficial sensitivity is impaired, generally in the form of paresthesia. Brain nerve involvement is rarely observed.

Analogously to GBS, albuminocytologic dissociation is found in the CSF, i. e., there is an increased protein concentration without or only slightly elevated cell counts [25]. This characteristic distinguishes it from ALS which exhibits normal CSF. Electrophysiological criteria for the diagnosis of CIDP include a reduction in nerve conduction velocity, elongation of distal latencies, absent or prolonged latencies of the F-waves and partial conduction blocks [26, 27].



► **Fig. 1** Muscle biopsy of sIBM with myositic lymphocyte infiltrates (left image, arrows) in hematoxylin-eosin (HE) staining, vacuolization of muscle fibers, increased fiber caliber spectrum, endomyseal fibrosis and rimmed vacuoles (right image, arrows) in Gomori trichrome staining.



► **Fig. 2** T1w TSE FS (turbo spin echo, fat-saturated sequence) transversal MRI of a thigh with typical asymmetric involvement of quadriceps muscle in the case of sIBM (arrow: highly atrophied and fatty degenerated portion of the quadriceps femoris muscle compared to the opposite side).

Therapeutically, glucocorticoids, intravenous immunoglobulins and plasmapheresis are the medications of choice for induction therapy and are probably equally effective, although comparative studies with the highest evidence are currently lacking. In addition, we have had good experiences with immunoadsorption in our clinic. The initially successful therapy should be used as a remission maintenance therapy. Therapeutic resistant cases should be treated with immunosuppressants such as azathioprine, rituximab or cyclophosphamide. However, approximately 2/3 of all patients respond well to the initially selected form of therapy [28].

## Sporadic Inclusion Body Myositis

In 1978, Carpenter et al. developed the concept of sporadic inclusion body myositis (sIBM) as a separate disease entity which can be differentiated from other inflammatory myopathies such as polymyositis, dermatomyositis and necrotic myositis [29]. The characteristic filamentary inclusion bodies detectable under electron microscopy in the nucleus and cytoplasm of muscle cells had already

been described in 1971 by Yunis and Samaha [30]. With a prevalence of approx. 3.3/100,000, sIBM is a chronically progressive muscle disease affecting mainly patients over the age of 50. Males are significantly more frequently affected (3:2) [31].

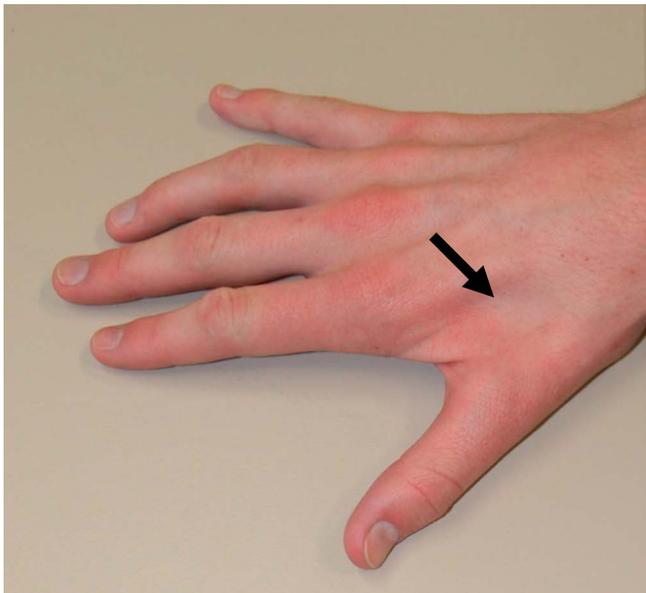
The underlying disease mechanisms consist of inflammatory and degenerative components, although it remains unclear whether the inflammation is the cause or consequence of the degeneration. Macrophages and cytotoxic CD8+ cells seen in the muscle biopsy are signs of inflammation. Indications of degeneration are characterized by typical rimmed vacuoles (► **Fig. 1**), and infrequently as ragged red fibers. Electron microscopy can also detect intravacuolar and intranuclear inclusions [32]. A muscle biopsy should be obtained from an affected muscle previously identified using MR imaging. In short-tau inversion recovery (STIR) sequences and fat-saturated T1w sequences, focal enhancements can be detected [33] as edema or fatty atrophy (► **Fig. 2**).

Clinically, sIBM is characterized by a gradual onset which frequently results in a late diagnosis. The quadriceps muscles and distal extremities are particularly affected, resulting in pronounced atrophy of the relevant muscle groups. At disease onset, the finger flexors are typically asymmetrically affected (► **Fig. 3**), likewise as the knee extensors and dorsal flexors of the foot. Involvement of the quadriceps muscles results in difficulties in standing up from a sitting position or when climbing stairs. Unlike ALS in which the finger extensors are earlier and more severely affected than the finger flexors [34], there is no typical atrophy of the first dorsal interosseous muscle (IOD1, ► **Fig. 4**). In the further course of the disease, the neck and bulbar muscles are frequently affected. Occasionally, dysphagia can appear as an initial symptom. In contrast to ALS, atrophy of the tongue is rare. Visible fasciculation is likewise atypical. Muscle reflexes are reduced in most cases; in some cases they are absent. Involvement of the upper motor neuron does not appear in sporadic inclusion body myositis. CK-levels are usually normal in sIBM, an elevation higher than 10 times of normal levels does generally not occur [32].

Spontaneous activity in the form of fibrillation and positive sharp waves in the affected muscles is often found in the EMG. Ad-



► **Fig. 3** Classical finger flexor palsy (depicting intended fist) in the case of sIBM.



► **Fig. 4** Classical "split hand" in the case of ALS with severe IOD1 atrophy (arrow).

ditionally, both low-amplitude short and high-amplitude long action potentials of the motor units can arise [35]. However, these findings should not be considered as specific. Increased action potentials in conjunction with increased spontaneous activity could also result in a misdiagnosis of ALS [35, 36]. A muscle biopsy should always be performed as the gold standard for patients with very slow disease progression and an uncertain diagnosis.

Unlike dermatomyositis and polymyositis, sIBM is largely therapy-resistant to immunomodulatory and immunosuppressive approaches. In severe cases, intravenous administration of immunoglobulins over a period of five days can be attempted. If the patient does not respond to IVIGs, a therapeutic attempt with prednisolone is justified. Additionally, supportive measures such as physiotherapy and respiratory exercises are recommended [37].

## Spinal and Bulbar Muscular Atrophy (Kennedy Disease)

Spinal and bulbar muscular atrophy (SBMA, Kennedy disease) was first described in 1968 by the neurologist W.R. Kennedy [38]. It is a rare X-chromosomal recessive inherited disease with a prevalence of about 1/300,000. The general age of manifestation is between the ages of 20 to 40, although later initial occurrences have been described [39]. The cause for SBMA is a trinucleotide repeat (CAG) in exon 1 of the AR gene, which is located on the long arm of the X chromosome (Xq11–12). The gene encodes for the androgen receptor. An average of 9 to 36 repeats is present in the healthy population, whereas trinucleotide repeat expansions of >40 CAG repeats are formed in Kennedy syndrome [40]. This repeat encodes the amino acid glutamine, thus creating toxic polyglutamine chains, which – presumably via a "gain of function" mechanism – cause degeneration of the lower motor neuron. The repeat length is related to the severity of the disease [41]. Due to the X-linked inheritance, the disease affects only men. It does not occur among heterozygously affected women; instead they act as conductors. The literature describes subclinical phenotypes [42].

SBMA manifests through some characteristic clinical features that make it distinguishable from other motor neuron diseases: gynecomastia, testicular atrophy and reduced fertility as an expression of peripheral androgen resistance [43]. In addition, some patients present with other endocrine disorders such as hypercholesterolemia and type II diabetes mellitus, the causes of which are previously largely unknown [44]. Other characteristics include fasciculation of the limbs, facial and tongue muscles, asymmetrically expanding paresis, postural tremor as well as bulbar symptoms with dysarthria and dysphagia [45]. Typically, innervation-triggered myocymia of the facial muscles are found in addition to classical fasciculation at rest. Although similarly to ALS, patients with SBMA demonstrate significant atrophy of the tongue, due to absent involvement of the upper motor neuron, the tongue remains relatively movable and can be easily extended; likewise, dysarthria is generally weak (► **Fig. 5**). In addition, hypo- or areflexia are signs of involvement of the lower motor neuron. Upper motor neuron signs do not appear in SBMA [46]. More often than in the case of ALS, SBMA involves the sensory fibers and therefore results in paresthesia [47].

In contrast to patients with ALS, SBMA patients have an almost normal life expectancy [48]. The diagnosis should be confirmed by analysis of the androgen receptor gene. A result with >38 CAG repeats confirms the diagnosis of Kennedy-type spinal and bulbar muscular atrophy [40]. There is no effective causal therapy.

## Monomelic Amyotrophy (Hirayama Disease)

Hirayama monomelic amyotrophy was first described in 1959 [49]. The authors described twelve cases of what is now considered an independent entity that had previously been classified as part of a degenerative motor neuron disease. In subsequent years this assessment was supported by the publication of additional case stud-



► **Fig. 5** Tongue atrophy in SBMA (left) compared to tongue atrophy in ALS (right).

ies [50]. Clinically, patients exhibit acute weakness, and in the course of the disease, experience unilateral atrophy in the region of the distal upper extremity. Symptoms are usually progressive and spontaneously remit within a few years (on average 2–4 years). Compression of the cervical myelon due to neck flexion is mentioned as a cause of the disease, among other things. The average age of onset is between 15 and 20 years of age [51]. Male patients are largely affected, with a gender distribution of approx. 2.8:1 [52]. Hirayama himself offered pathophysiological ideas on the subject [49]. He suspected that the cause may be an imbalance between the growth of the bony vertebral canal and the dural sac during the juvenile growth phase. The disease occurs mainly among patients of Asian ancestry, whereas in Germany and Europe only a few cases have been described [53]. The course of the disease entails slow progressive paresis and atrophy of the distal upper extremity affecting the thenar and hypothenar muscles, interossei muscles as well as the wrist extensors and flexors, but sparing the brachioradialis muscle. In contrast to ALS, Hirayama disease is typically characterized by an atrophy pattern with predominant atrophy of the hypothenar compared to the thenar musculature, the so-called “reverse-split-hand syndrome” [54]. The right extremity is more frequently affected, irrespective of the patient’s handedness [52, 55]. While usually only one limb is initially affected, the disease often leads to a progression to the opposite side, although the symptoms usually remain asymmetrical [51]. The lower extremities can also be affected, but to a lesser extent, however [56]. Paresis appears to increase during cold exposure, possibly due to blockage of the conductivity of the muscle fiber membrane after denervation with subsequent re-innervation processes [57]. In addition to this so-called “cold paresis”, about 33% of all patients experience fatigue as a common symptom [58]. Only a few patients experience sensitive symptoms such as hypesthesia in the region of the hand [51]. Muscle fasciculation at rest does not occur, however, fasciculation in the area of the lower arm or tremor-like movements of the fingers can appear, induced by extension of the affected muscles [59]. In the EMG, denervation signs are found in the affected muscles as well as in the muscle biopsies. On the other hand, neurography is generally unremarkable. Reduced muscle mass action potentials with prolonged latency after repetitive stimulation can be demonstrated in the context of the described cold paresis.

Clinical differential diagnosis for ALS mainly concerns progression forms with predominant involvement of the lower motor neuron and the clinical ALS subform of FAS. In addition to the ethnicity and the sex of the patient, assistance in the context of differential diagnosis is provided mainly by the age at disease onset and disease progression. Frequently after an acute onset, paresis develops slowly over years, certainly slower than in classical ALS, and unlike ALS, demonstrates spontaneous remission. Bulbar symptoms are not evident, and signs of the upper motor neuron have been described only in individual cases [56]. Cold paresis is not observed among ALS patients.

Therapeutically, some authors recommend a conservative approach by prescribing a neck brace which should be worn continuously for three to four years in order to avoid antelexion of the neck, but this approach is controversial [59]. Neurosurgical cervical decompression should be seen even more critical. Causal therapy with sufficient supporting evidence is not known.

## Benign Fasciculation and Cramp Fasciculation Syndrome

Benign fasciculation syndrome (BFS) is an innocuous disorder involving neither paresis nor atrophy. The fasciculations frequently intensify after physical stress.

Since the diagnosis is not a disease in the narrowest sense, differentiation to early stages of a motor neuron disease is essential. This results in the dilemma that a positive distinction is possible only in the course of the disease, a fact that often leads to significant psychological stress on the patient who is concerned about ALS. The consequence are multiple physician consultations and increased concentration on the fasciculations and other physical symptoms which can develop into complex psychosomatic complaints which are difficult to resolve.

Although benign fasciculations are themselves harmless, a definite and early diagnosis is significant, with a thorough neurological examination being highly important.

Decisive is the total absence of atrophy, paresis or clinical signs of pathology of the upper motor neuron. On the other hand, location and frequency of fasciculation are not particularly indicative.

ALS is more likely, the more sites that are involved in the process and the more frequently fasciculation occurs. However, benign fasciculation can be multilocal and frequent, and can be associated with muscle cramping (Cramp Fasciculation syndrome). In this case further differential diagnoses must be considered, especially channelopathies such as neuromyotonia (Isaacs syndrome) that are associated with the presence of voltage-gated potassium channel antibodies (VGKC), and in some cases can appear as a paraneoplastic syndrome [60]. If additional symptoms occur, such as limbic encephalitis accompanied by short-term memory loss, disorientation or concentration disturbances as well as vegetative abnormalities, Morvan syndrome should be taken into account. If one of these syndromes is clinically suspected, VGKC diagnostics should be performed including screening for CASPR2 and IGL1 antibodies as well screening for tumors.

Beyond the clinical findings, electromyography can provide additional help in differentiating between benign fasciculation syndrome and motor neuron disease. The evidence for the following criteria is generally slender, and the distinguishing features are less reliable than clinical characteristics. The diagnosis or exclusion of benign fasciculations should not be performed primarily electromyographically, just like the diagnosis or exclusion of a motor neuron disease. Electromyography is best used to support the clinically suspected diagnosis. Mainly, in the case of benign fasciculations, the absence of pathological spontaneous activity in the form of fibrillation potentials and positive sharp waves, as well as chronic neurogenic changes should be expected. In addition, there are efforts in the literature to distinguish benign from malignant fasciculation potentials based on their morphology [61]. In our opinion, definite differentiation using electromyography is not possible.

A new and promising starting point could lie in the determination of neurofilament light chains in patients' CSF. A positive predictive value of 87% was found for the distinction between motor neuron diseases and "mimics" (including benign fasciculation) in a study of 455 patients with a cut-off value of 2200 pg/mL with a diagnostic sensitivity of 77% and specificity of 85% [10]. However, this biomarker has not found a place in routine neurological diagnostics yet.

Based on our experience, drug treatment of fasciculation is required only in the rarest cases. As a rule, psychological stress does not arise from the fasciculations themselves, but rather by the fear of suffering from ALS. A detailed explanation of the harmlessness of the disease according to adequate exclusion diagnostics presented above is therefore the most important means to reassure the patient. If psychological aggravation of the symptoms is anticipated, supportive and psychotherapeutic measures can be helpful.

If fasciculations are so severe that drug therapy is indicated, membrane-stabilizing drugs are especially suitable for their treatment. The evidence for all substances is weak, and previous experience suggests that there is a drug group effect. From our point of view, therefore, anticonvulsants with a comparatively good side-effect profile such as gabapentin, pregabalin, lamotrigine or mexiletine (available through the international pharmacy) are preferable. If there is a lack of response, then it is possible to change to other more active substances.

## Metabolic Illnesses

A few, generally very rare metabolic illnesses can be clinically presenting as motor neuron diseases. Regarding the selection of the following diseases, it should be kept in mind that verified causal therapies are not currently available. However, a proper diagnosis is relevant in the context of genetic counseling and the best possible symptomatic therapy.

Adrenoleukodystrophy (adrenomyeloneuropathy) is a recessive genetic disease linked to the X chromosome, resulting in demyelination due to the inability to oxidize long chain fatty acids. Clinically spastic tetraplegia and pseudobulbar paralysis are regularly evident, but other non-motor symptoms are also common such as dementia, ataxia and vision and hearing deficits. This rare differential diagnosis should be considered especially with respect to young men, who, in addition to symptoms of a motor neuron disease, also exhibit one or more of the above-mentioned additional symptoms. Supplementary to MR imaging which frequently discloses demyelinating foci in the brain and spinal cord, identification of long-chain fatty acids (C22–C26) in the blood plasma is diagnostically indicative. Patients frequently exhibit an Addison's disease constellation (hyperkalemia and hyponatremia).

Metachromatic leukodystrophy is an autosomal recessive hereditary disease characterized by an arylsulfatase A deficiency. Similar to adrenoleukodystrophy, demyelinating foci occur in the central and peripheral nervous system; as with a motor neuron disease, clinical signs of damage of both the upper and lower motor neuron are apparent. Likewise, in the case of metachromatic leukodystrophy, there are frequently non-motor symptoms, which besides a young age of onset, can point the way to a diagnosis. It should be noted, however, that metachromatic leukodystrophy, in addition to infantile onset, also has an adult form with a disease peak around the age of 40. Diagnosis is confirmed by absent or greatly reduced arylsulfatase A activity in leukocytes and fibroblasts.

Finally, Tay-Sachs syndrome should be mentioned. It belongs to the group of GM2 gangliosidoses and is based on an autosomal recessive hereditary defect of the enzyme hexosaminidase A. This syndrome results in paresis and growth retardation usually during the first months of life, but there is also an adult form with a later manifestation. Non-motor symptoms that clinically suggest GM2 gangliosidosis are an increased fright response, decreased attention, epileptic seizures and visual impairment. In the adult form, other symptoms such as dystonia, cerebellar symptoms and psychoses may particularly be present. Diagnosis of the disease is based on the detection of missing or greatly reduced beta-hexosaminidase A activity in the serum accompanied by normal or increased activity of beta-hexosaminidase B [62].

Due to the rarity of the disease, high related costs and low therapeutic consequences, standard determination of long-chain fatty acids, arylsulfatase A and hexosaminidase A is not advisable. Instead, an appropriate diagnosis should be sought only if there is a concrete and image-based suspicion of the previously mentioned criteria.

## Adult-onset Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) comprises a group of diseases involving progressive loss of motor neuron cells in the anterior horn of the spinal cord. The incidence of SMA is 1 per 11,000 live births

[63]. The cause of the disease is a mutation in the survival motor neuron 1 (SMN1) gene on chromosome 5q13. Humans have two forms of the SMN gene, the SMN1 gene which exclusively encodes for the fully functional full-length SMN protein, as well as the SMN2 gene, which due to fewer base differences, provides a transcription of functionless protein and – to a lesser extent – functional full-length protein. The clinical severity of SMA thus correlates with the surviving quantity of functional SMN2 protein. Autosomal recessive inheritance can be detected in more than 95% of cases, whereas autosomal dominant inheritance is observed in adult forms (type 4) [64]. SMA is classified into four stages, depending upon clinical presentation. SMA types 0–3a appear in the first months of life or early childhood, and are thus distinguished from ALS due to age distribution. SMA type 3b (also called Kugelberg-Welander disease) appears above the age of 3 years; the children are able to walk independently, but in the course of the disease there is progressive paresis and atrophy of the proximal muscle groups of the lower extremities, resulting in problems with standing up, climbing stairs, and ultimately resulting in the need for a wheelchair. SMA type 4 patients are less affected; weakness and atrophy of the lower extremities are usually manifest after the age of 30. Life expectancy of both forms is largely normal, since the respiratory musculature is not affected and there are no bulbar manifestations. Fasciculation in juvenile and adult forms of SMA is an additional sign of an affected lower motor neuron. In contrast to ALS, significant proximal paresis is evident, there are no signs of affection of the upper motor neuron. Genetic testing with detection of the deletion of the SMN1 gene confirms the diagnosis of SMA [64]. Neurography discloses the loss of compound muscle action potentials as an expression of atrophy and evidence of pathological spontaneous activity with fibrillation potentials in the electromyogram (especially in adult forms of the disease). Nerve conduction velocity is usually in the normal range. In the muscle biopsy, SMA types 3b and 4 mostly show secondary myopathic changes in addition to neurogenic atrophy which are not prognostically significant [65].

In general, therapy takes the form of supportive physiotherapy and use of physical aids. In November 2016, the drug nusinersen reached the primary endpoint in clinical phase 3 trials [66]. The medication (Spinraza®), an antisense oligonucleotide applied intrathecally to increase the levels of functional SMN2 protein, has in the meantime been approved in Germany for all types of 5q-associated spinal muscular atrophy (5q-SMA). It was demonstrated that children treated with nusinersen exhibited improved motor function after 3 months of treatment [67].

## Hereditary Spastic Paraparesis

Hereditary spastic paraparesis (HSP), a group of hereditary neurodegenerative diseases, was first described in 1880 by Adolf von Strümpell; in 1898 Maurice Lorrain described additional case reports (Strümpell-Lorrain syndrome). Reliable data on prevalence do not exist. There are two disease peaks, one before the age of six, and one between the second and fourth decades of life. Both sexes are equally affected [68]. According to clinical criteria established by Anita Harding, HSP is classified in both uncomplicated and complicated forms. In both forms of the disease, the main clinical symptom is

symmetrical spastic muscle tonus increase of the legs, thus causing a typical gait disturbance (scissor gait with pronounced affection of the adductors). Other signs of the upper motor neuron include heightened reflexes and positive pyramidal tract signs. In addition, there may be disturbances of depth sensitivity and autonomous abnormalities such as bladder disorders, pollakisuria and urge incontinence as well as a rare rectal disorder. As the disease progresses, spastic muscle tonus elevation of the arms is also possible. Symptoms steadily progress in the course of time. In its complex form, other neurological complications occur, such as optic atrophy, retinopathy, dementia and mental retardation, ataxia and extrapyramidal motor disturbances as well as deafness or epilepsy and changes in the skin [69]. Restless legs syndrome appears also to be a comorbidity [70]. Genetic classification is according to autosomal dominant, autosomal recessive and X-linked chromosomal recessive forms. More than 70% of all HSP cases are of the autosomal dominant type. X-linked recessive inheritance is limited to individual cases. Mutations in the SPG4 gene (Spastin gene) have been shown for the autosomal dominant form. Autosomal recessive mutations are found in the SPG5, SPG7, SPG11 and SPG14 genes [68].

The clinical distinction with respect to ALS is the classical symmetrical spasticity of the legs as well as the presence of disturbance of both deep sensitivity and the above-described autonomic functions. As a rule, atrophy occurs only after long duration of the disease and is found distally. The greatest extent of paresis is located in the dorsal flexors of the foot, the hamstring muscles and the iliopsoas muscles. Frequently, the patient cannot walk despite minor paresis due to pronounced spasticity. Analysis of the above-described genes can confirm HSP [69].

There is no causal therapy for HSP; symptomatic treatment includes spasmolytics such as baclofen, tizanidine and intramuscular injection of botulinum toxin. In addition, there should be intensive physiotherapeutic and ergotherapeutic treatment.

Life expectancy is not reduced in uncomplicated forms of HSP. A wheelchair is usually required only very late in the course of the disease. Within the family, however, due to the effect of anticipation, the disease usually starts earlier in younger generations and exhibits a more severe course.

## Cervical Myelopathy

Strictly speaking, cervical myelopathy is not a separate disease, but rather describes damage to the cervical spine due to various pathologies. One of the most common causes is cervical compression, which can be caused by spinal masses, intervertebral disk events or bony changes of the cervical spine (cervical spondylotic/spondylogenous myelopathy, osteosclerosis, stenosis of the bony vertebral canal). T2-weighted MR imaging reveals hyperintense signal elevation which is a typical “myelopathy signal” as an expression of the structural damage of the cervical spinal cord. Clinically, cervical myelopathy is an ALS mimic since the affection of the cervical spinal cord can lead to damage of the upper motor neuron (heightened reflexes, positive pyramidal signs, spastic tonus elevation) in the lower extremities. Furthermore, if additional spinal root damage is present, such as in cervical spondylotic myelopathy, signs of the lower motor neuron with paresis and atrophy in the area of the

▶ **Table 1** Distinguishing features of ALS compared to ALS mimics.

	ALS	MMN	CIDP	sIBM	SBMA	Hirayama disease	Benign fasciculations	SMA Type 3b/4	HSP	Cervical myelopathy
<b>Peak age</b>	50–80	30–50	50–70	50–70	20–40	15–20	Any age	> 3 and > 30	0–6 and 10–40	> 50
<b>Ratio m:f</b>	1.5:1	2.6:1	2.3:1	3:1	Males only	2.8:1	-	1:1	1:1	-
<b>Heritability</b>	10%, autosomal dominant	-	-	-	X-recessive	-	-	Autosomal recessive	80%, autosomal dominant 20% autosomal recessive	-
<b>Upper (U)/ Lower (L) motor neuron</b>	U+L	L	L	L	L	L	L	L	U	U+L
<b>Clinical characteristics</b>	Asymmetrical Rapidly progressive “Split hand” Fasciculations	Asymmetrical Predominantly distal Motor paresis only Only limited atrophy Distribution pattern corresponds to peripheral nerve	Additional sensory symptoms	Quadriceps + finger flexors involved	Gynecomastia Testicular atrophy Infertility Endocrinal disorders Tongue atrophy Facial myocymia	Cold paresis Upper extremity Acute onset, spontaneous remission	Fasciculations without paresis or atrophy Occasionally muscle cramps	Predominant proximal (UE > LE)	Leg spasticity partly urinary incontinence + sensory deficits	(poly-) radicular pattern, radicular pain
<b>Life expectancy/progression</b>	Lethal within 2–5 years	Normal/maintenance therapy with IVIGs	Normal / chronic-progressive	Normal / frequently loss of mobility, dysphagia	Almost normal / mobility generally preserved	Normal / spontaneous remission	Normal	Almost normal/ Loss of mobility (type 3b)	Normal / prog. paraparesis, loss of mobility	Almost normal/ Progression variable, depends on etiology
<b>EMG/ENG</b>	Spontaneous activity Chronic-neurogenic changes	Demyelination Proximal conduction blocks	Demyelination	Spontaneous activity Enlarged / diminished MSAP	Spontaneous activity Chronic-neurogenic changes	Deneration in affected muscles / generally normal	No spontaneous activity, no chronic-neurogenic changes	Spontaneous activity Chronic-neurogenic changes	Generally normal	(poly-) radicular pattern
<b>CSF</b>	Normal Neurofilaments +	Raised protein	Cytoalbuminary dissociation	Normal	Normal	Normal	Normal	Normal	Normal	Normal
<b>CK</b>	+	+	(+)	+ - + +	++	(+)	=	+	=	=
<b>Supplementary diagnostics</b>	MRI, (Neurofilaments)	GM1-AB	MAG-/GM1-AB	Muscle MRI Muscle biopsy	Genetics	MRI cervical spine	(Neurofilaments)	Genetics	Genetics	MRI cervical spine

▶ **Table 1** Continued.

Therapy	ALS	MMN	CIDP	sIBM	SBMA	Hirayama disease	Benign fasciculations	SMA Type 3b/4	HSP	Cervical myelopathy
	Riluzole	IVIgs	Cortisone IVIgs Plasmapheresis Immunoadsorption Immunosuppressants	IVIgs Cortisone	-	-	Psychotherapy Anticonvulsants if required	Nusinersen	-	Conservative Operation if progression is rapid

Shown are diagnostic differences regarding peak age, gender distribution, inheritance, affection of the upper or lower motor neuron, clinical characteristics, progression of the disease, typical findings in EMG / ENG, CSF, creatine kinase level, recommended additional diagnosis and therapy options

CK increase = normal, (+) in some cases/slightly raised, + 2–5 fold increase, ++ severely raised >5X

*Explanation of terms and abbreviations* ALS: amyotrophic lateral sclerosis; MMN: multifocal motor neuropathy; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; sIBM: sporadic inclusion body myositis; SBMA: spinal and bulbar muscular atrophy; SMA: spinal muscular atrophy; HSP: hereditary spastic paraparesis; EMG/ENG: electromyography/electroneurography; CK: creatine kinase; GMT-AB: GMT ganglioside antibodies; MAG-AB: myelin-associated glycoprotein antibodies; IVIGs: intravenous immunoglobulins

arms and hands may also occur. In contrast to ALS, however, they follow a (poly-) radicular pattern. Likewise, depending on the cause, radicular pain may also occur in some patients; up to 50 % of all patients complain of vesicorectal disorders. Therapeutically, indication for surgical care should take into account the clinical symptoms and disease dynamics as well as existing comorbidities. Frequently a multifactorial gait disorder and motor problems are found in older patients, which often cannot be adequately improved by surgical intervention. In addition, degenerative spinal column abnormalities and spinal canal stenoses occur regularly in elderly patients and often do not adequately explain clinical symptoms, thus a careful comparison of symptoms is essential. Conservative therapy should be accompanied by regular clinical and imaging follow-up. An absolute and urgent indication for surgery is an acute onset and/or rapidly progressive symptoms of paraplegia and the occurrence of autonomic functional disorders based on cervical myelopathy [71].

## Conclusions

Various diseases can mimic the symptoms of ALS. In our review, we have presented the relevant differential diagnoses for ALS. We recommend using the revised El Escorial criteria of 2015 for diagnosis [9]. These criteria include progressive impairment in the region of the upper and lower motor neuron in at least one limb/body region or clinical and/or electrophysiological damage to the lower motor neuron in two body regions (bulbar, cervical, thoracic, lumbosacral). Typical changes in the EMG can be fibrillation potentials, positive sharp waves as well as chronic neurogenic changes. CSF is generally normal; the extent of neurofilaments affecting diagnosis of ALS remains to be seen.

The clinical picture with the presence of signs of the upper and/or lower motor neuron already limits the number of differential diagnoses. Age of disease onset, family history, disease progression as well as distribution and propagation patterns of the pareses provide further information. Particular attention should be given to whether and to what extent non-motor symptoms such as sensory disturbances or endocrine disorders are present.

If after considering the patient's history, clinical symptoms and electrophysiology, the diagnosis remains doubtful despite differentiating criteria, additional diagnostic approaches can be used such as genetic testing, antibody diagnostics, muscle/nerve biopsy, tumor screening, etc. ▶ **Table 1** presents the most important features, with which mimics can be distinguished from ALS.

Despite reliance on all of the above-described measures, differential diagnosis in individual cases can be problematic, especially in the initial stages of the discussed diseases. In such cases, neurological follow-up controls are recommended, since a correct diagnosis can often be made in the later course of the disease due to the increasingly distinct clinical characteristics.

## Conflict of Interest

The authors declare no conflicts of interest.

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