Disorders of Upper and Lower Motor Neurons

21

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Abbreviations

ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS Functional Rating Scale; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; ENG, electroneuronography; FTD, frontotemporal dementia; LMN, lower motor neurons; HD, Hirayama Disease; IV, invasive ventilation; MG, myasthenia gravis; MMN, multifocal motor neuropathy; MN, motor neuron; MND, motor neuron disease; MS, multiple sclerosis; MSA, multiple system atrophy; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; SAP, sensory action potential; SBMA, spinal bulbar muscular atrophy; SMA, spinal muscular atrophy; SMN1, survival motor neuron 1 gene; UMN, upper motor neuron.

Motor neuron disorders are a group of diseases characterized by the degeneration of cortical motor neurons, lower motor neurons, or both, which may be secondary to various conditions, or have unknown etiology. The course can be acute or chronic progressive.

The most common clinical forms are amyotrophic lateral sclerosis (ALS), spinal bulbar muscular atrophy (SBMA or Kennedy disease), and spinal muscular atrophy (SMA).

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21.1 Amyotrophic Lateral Sclerosis (ALS)

Key Facts

- **Terminology and definitions** – Motor neurons disorders (ALS, SBMA, SMA) are a group of diseases characterized by the degeneration of cortical motor neurons, lower motor neurons, or both.
- **Clinical features** – ALS incidence in Western countries is 2–3/100,000/year; prevalence is 6–9/100,000. Clinical hallmarks: relentless, progressive degeneration of MNs with weakness, muscle wasting, and fasciculations, plus spasticity and hyperreflexia. Up to 50% of patients display frontal syndromes.
- **Diagnosis** – The diagnosis of ALS remains clinical.
  - **Blood/CSF** – Nonspecific.
  - **Genetics** – More than 20 genes are implicated in ALS; 60% of the risk is genetically determined.
  - **Imaging** – Neuroimaging as well as laboratory and pathological exams are performed to rule out other diseases.
  - **Neurophysiology** – Electromyography supports the diagnosis, showing active and chronic denervation in bulbar, upper limb, thoracic and lower limb muscles.
- **Top differential diagnoses** – Cervical radiculopathies, CIDP, MMN, MG, MS, MSA.
- **Prognosis**
  - **Principles of treatment** – No specific therapies. Riluzole prolongs survival, but only by a few months.
  - **Disability** – ALS is invariably fatal. Median survival time of patients is 2–3 years in the general population; 4–5 years if followed up in referral centers.

21.1.1 Definition

Amyotrophic lateral sclerosis (ALS) (synonyms: motor neuron disease in UK or Lou Gehrig's disease in USA) is a neurodegenerative disorder of adult life, characterized by the involvement of upper (UMN) and lower motor neurons (LMN) at spinal and bulbar levels that results in a relentlessly progressive paralysis of voluntary muscles.

After the recent discoveries of involvement of extra-motor areas associated to cognitive symptoms and of new causative genes, ALS cannot be considered a disease confined solely to the motor system anymore, but rather a syndrome due to a combination of genetic and environmental factors, characterized by a marked phenotypic and pathogenetic heterogeneity.

21.1.2 Demographics

The incidence of ALS in Western countries is between 2 to 3 cases/100,000/year in the general population. ALS prevalence is between 6 to 9/100,000 individuals [1]. The incidence of ALS has been rather constant in the last two decades. Most ALS cases are sporadic, while 5–10% of patients report a family history of the disease.

The only defined risk factors are old age and male gender (M/F 1.2 to 1.5:1).

The mean age at onset is between 60 and 68. In both genders, incidence rates increase up to a peak in the eight decade of life and decline rapidly afterwards.

The overall lifetime risk of developing ALS is about 1:400 in male and 1:500 in female.

21.1.3 Clinical Features

The clinical hallmark of ALS is the combination of UMN and LMN features which manifest with weakness, muscle wasting, and fasciculations, variably combined with spasticity, hyperreflexia, pseudobulbar affect, and other corticospinal tract signs. At the extreme of this spectrum, there are forms with a pure LMN involvement, called progressive muscular atrophy (PMA) and of pure UMN involvement, called primary lateral sclerosis (PLS). Both these forms usually have a more benign course.

21.1.3.1 Clinical Phenotypes

ALS is characterized by a marked heterogeneity in both its presentation and rate of clinical progression. Within clinical presentations, it is possible to recognize eight distinct phenotypes: classic, bulbar, flail arm, flail leg, pyramidal and respiratory, plus PMA and PLS [2].

Classic phenotype Characterized by the presence of symptoms in upper or lower limbs, without predominant pyramidal signs.

Bulbar phenotype Shows bulbar onset without spinal involvement for the first 6 months from onset. Pyramidal signs often are not present at onset but occur later.

Flail arm phenotype Characterized by progressive predominantly proximal weakness and wasting in the upper limbs. Functional involvement has to be confined to upper limbs for at least 12 months from onset.

Flail leg phenotype (also called "pseudopolyneuritic" or Patrikios syndrome) Characterized by a progressive distal onset of weakness and wasting in the lower limbs.

Pyramidal phenotype (or predominant-UMN ALS) in which clinical manifestations are dominated by pyramidal signs (mainly severe spastic para/tetraparesis), sometimes associated to pseudobulbar signs. At the same time, clear-cut signs of LMN impairment must be present.

Respiratory phenotype Characterized by a prevalent respiratory impairment at onset, with only mild spinal or bulbar signs in the first 6 months after onset.

21.1.3.2 Symptoms

About 2/3 of patients present with limb symptoms (spinal onset), while 1/3 has symptoms of bulbar dysfunction (bulbar onset). Respiratory onset accounts for 2–3% of cases. Disease onset and progression are asymmetrical. Extraocular and sphincter muscles are usually spared.

The main symptoms are weakness and fatigue. Bulbar involvement is present in most ALS patients with dysphagia and dysarthria.

Disease progression is extremely variable in every single ALS patient; each individual has his/her own progression rate, which tends to have a linear decline during the course of the disease. Death is usually due to a progressive respiratory failure often precipitated by pneumonia.

A dysexecutive syndrome or behavioral changes are found in up to 50% of patients, meeting the criteria for frontotemporal dementia (FTD) in 15% of cases [3] (see Chap. 16). There is clinical and neuropathological evidence to support the notion of ALS and FTD are extremes of a spectrum unified by TDP-43-positive, ubiquitin-positive inclusions; for this reason, they are called TDP-43 proteinopathies.

21.1.4 Diagnosis

The diagnosis of ALS remains clinical, focused on the presence of progressive UMN and LMN signs and their distribution in four regions: bulbar, upper limb, thoracic and lower limb, together with progression of symptoms.

Electromyography/electroneurography, showing active and chronic denervation in muscles of the four regions, supports the diagnosis.

Neuroimaging, laboratory and pathological exams are performed to rule out other diseases. Sometimes, slight hyperintensity along corticospinal tracts and slight hypointensity in central cortex may be noted (Fig. 21.1).

No specific biomarker of the disease is available, with the exception of mutations of ALS-related genes. Delay from onset of the disease to confirmation of the diagnosis can vary from 10 to 18 months. Such delay creates considerable distress in patients and the risk to undergo unnecessary surgery.

21.1.4.1 Main Differential Diagnosis

Cervical and thoracolumbar radiculopathies, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy

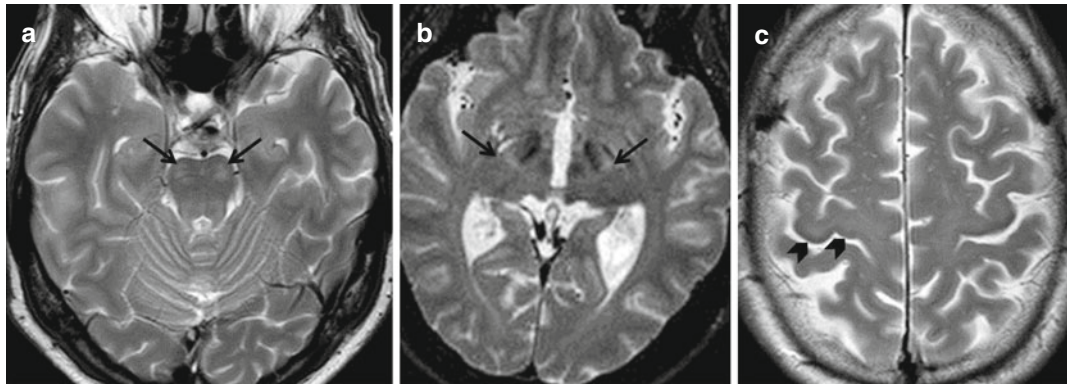

Fig. 21.1 ALS. In (**a**) and (**b**) T2-weighted images demonstrate slight hyperintensity along cortico-spinal tracts (*arrows*). In (**c**), note a slight hypointensity in both Rolando's cortex (*arrowheads*)

(MMN), myasthenia gravis (MG), multiple sclerosis (MS), multiple system atrophy (MSA).

21.1.4.2 Diagnostic Criteria

The revised El Escorial and the Awaji–Shima criteria were developed to increase the level of confidence of a diagnosis of ALS in order to facilitate inclusion criteria in clinical trials, classifying patients in different degrees of diagnostic certainty (definite, probable, probable with laboratory confirmation, possible). They both reflect the spread of the disease rather than diagnostic certainty, and therefore are not very useful in clinical practice. In fact they have been criticized because they are too restrictive, causing the exclusion of ~20–30% of ALS patients from clinical trials. Besides, they do not have a clear correlation with ALS outcome.

Genetics

Twin studies showed that about 60% of the risk of ALS is genetically determined, and the remaining 40% is environmentally determined. More than 20 genes are implicated in ALS pathogenesis. The four major ALS-related genes are *C9ORF72, SOD1, TARDBP,* and *FUS*. They account for 2/3 of familial and ~10% of apparently sporadic ALS cases [4].

In 2011, another major advance in the understanding of ALS was the identification of a large GGGGCC hexanucleotide repeat expansion in the first intron *C9ORF72* gene. This dominantly inherited condition causes both ALS and FTD. It is present in a high percentage of familial ALS and FTD, but it is also present in about 7% of apparently sporadic ALS cases. As for *TARDBP* and *FUS*, *C9ORF72* points to defective RNA processing as a central mechanism in neuronal degeneration.

Other minor ALS-related genes have roles in RNA metabolism, while some rarer forms of ALS are caused by mutations in genes involved in protein degradation pathways.

Pathology

The pathological characteristics of ALS are the presence of astrogliosis and degeneration of motor neuron cell bodies in the motor cortex, brain stem, and spinal cord. The remaining neurons contain cytoplasmic ubiquitin inclusions. In almost all cases, such inclusions stain for the protein TDP-43. Exceptions are *SOD1* and FUS-related ALS cases in whom the inclusions contain respectively SOD1 and FUS proteins abnormally aggregated. The *C9ORF72* genetic defect is associated with deposition of TDP-43 and p62, a protein involved in autophagy, in some cortical regions, and in the hippocampus. Moreover, there are ubiquitinated inclusions containing aggregates of abnormally translated dipeptide repeats derived from the hexanucleotide repeat expansion found in the cerebellum and hippocampus.

Current pathogenic hypotheses ascribe neurodegeneration to a combination of disrupted RNA metabolism and abnormal protein aggregation,

partly due to clearance failure of the proteasome system and autophagy. These mechanisms are accompanied by an immune reaction with microglial activation. Other candidate pathogenic mechanisms include glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, and failure of axonal transport [4].

21.1.5 Therapy

There are currently no specific therapies, with the exception of riluzole, which prolong survival, but only by a few months.

The mainstay of ALS management remains symptomatic treatment through a multidisciplinary approach. In the advanced phases, the use of percutaneous endoscopic gastrostomy (PEG) and of non-invasive (NIV) or invasive ventilation (IV) has demonstrated to be effective in treating malnutrition and respiratory failure.

21.1.6 Prognosis

In population-based studies, the median survival of ALS patients is 2–3 years from symptom onset, while ALS referral centers report survival times to 4–5 years [1]. There is a considerable variability in survival; in fact, about 10 % of cases survive for more than 10 years [5]. Most studies report no gender effect on ALS outcome.

Factors that predict rapid progression include an older age of onset, bulbar site of onset, short duration from first symptom to diagnosis, presence of cognitive impairment, and genotype.

21.1.6.1 Age

Age is a strong prognostic factor, and survival is inversely related to age at onset both in males and in females; older patients have a significant short survival compared to younger patients, without a gender effect [1].

21.1.6.2 Diagnostic Delay

A shorter delay from symptom onset to diagnosis (6–9 months) carries a worse prognosis. This can be explained by a more aggressive disease, with earlier neurological evaluation and diagnosis [6].

21.1.6.3 Clinical phenotypes

One study demonstrated that clinical phenotypes have significantly different prognostic characteristics [2].

PLS has a benign outcome with a median survival of more than 12 years. Also pyramidal phenotype has a relative benign prognosis, with the longest survival among ALS phenotypes, and similar to PMA. Flail arm phenotype has a median survival time of 4 years. Classic and flail leg phenotype carry an intermediate survival time. At the end of the spectrum, bulbar and respiratory phenotypes have the worst prognosis, less than 2 years. In this study, ALS phenotype was independently related to survival.

21.1.6.4 Cognitive functions

It is now clearly evident that 10 to 15% of ALS patients develop an overt FTD and that another 30–35% have a mild to moderate impairment of frontotemporal function with dysexecutive syndromes or behavioral changes. Some recent population-based studies found that patients with ALS-FTD have a shorter survival than those with normal executive and behavioral function (median survival, 28 months vs. 39 months) [7]. This difference could be explained in part to a poor compliance of these patients for procedures (PEG, NIV) in the advanced phases of the disease. A mild cognitive impairment, on the contrary, seems to have little or no effect on ALS outcome.

21.1.6.5 Nutritional status

It is widely accepted that malnourishment carries a poor prognosis in ALS. Body Mass Index is a marker of nutritional status; it has been repeatedly found to be an independent prognostic factor for death [8].

21.1.6.6 Respiratory status

Respiratory function is generally considered a critical aspect in ALS, as most patients die for respiratory failure.

Prognostic indices include: (1) percent predicted forced vital capacity; (2) upright and supine forced vital capacity; (3) percent predicted vital capacity; (4) slope of decline of vital capacity; (5) sniff nasal pressure; (6) maximal inspiratory pres-

sure and maximal expiratory pressure. All these indices were significantly correlated to survival [9].

21.1.6.7 Functional scores

The ALS Functional Rating Scale-Revised (ALSFRS-R) is the most widely used functional scale for ALS. It has been shown to be significantly related to outcome, particularly its respiratory subscore [10]. The progression rate of the ALSFRS-R, calculated as the ratio between points of score lost from disease onset to diagnosis/months of disease duration, resulted also to be significantly related to prognosis.

21.1.6.8 Multidisciplinary approach

The interdisciplinary care approach performed in tertiary ALS centers can modify patients' outcome. Increasingly, ALS patients are referred to tertiary ALS centers, whose practice is based on the interdisciplinary care paradigm. ALS patients followed by a multidisciplinary clinic have a better prognosis than those attending general neurology clinics, with a median survival from onset ~10 months longer [11]. Moreover, the hospitalization rate is markedly reduced, and the hospital stay is shorter for patients attending tertiary ALS centers. These effects were independent from all other known prognostic factors (e.g., PEG and NIV) and could be explained with a better provision of supportive care of all problems related to the disease .

21.1.6.9 Procedures

PEG is widely used for avoiding starvation and dehydration and improving quality of life. Nevertheless, whether enteral nutrition has a positive effect on survival is still a matter of debate.

NIV is the treatment of choice in the management of respiratory disturbances in ALS. One controlled trial performed in ALS demonstrated a significantly longer survival in spinal-onset patients and only a better quality of life in bulbar-onset patients [12]. A population-based study confirmed that NIV has positive effects on survival, in particular among patients followed by tertiary ALS centers compared to patients followed by general neurological clinics (316 vs 229 days) [13]. This positive effect was present also in patients with mild to moderate bulbar signs, while patients' age at the time of NIV determined a significant difference in survival (≤49, 451 days; 50–69, 268 days; ≥70, 164 days).

21.1.6.10 Genetics

Recent genotype–phenotype studies have demonstrated that gene mutations can influence age at onset and outcome [14].

Cases carrying *C9ORF72* repeat expansion have a median survival from onset of ~3 years. Patients carrying *TARDBP* mutations have a median survival of ~5 years, while *FUS* mutations are often characterized by a rapid progression and death occurring in less than 2 years.

SOD1 mutations are extremely heterogeneous in outcome. There are mutations such as the Ala4Val, which has a rapidly progressive course, whereas the Asp90Ala recessive variant is associated with a very slow course.

There are genes not causing ALS but modulating its clinical expression. They are sought with the genome wide association screening approach. The common variant rs12608932, located within an intron of UNC13A gene on chromosome 19, was found to be significantly associated with the risk of developing ALS but homozygosity for the minor allele of rs12608932 also shortens survival by approximately 12 months [15]. Another example is NI-PA1, also associated to a shorter survival.

21.1.6.11 Biomarkers

One of the most critical aspects in ALS is the lack of biological markers of disease progression to be used in clinical trials to evaluate therapeutic response.

21.1.6.12 Fluids

The search of protein biomarkers has focused mostly on blood and cerebrospinal fluid, but also on muscle and other tissues. Inflammatory cytokines and chemokines (MCP-1 and IL-8), phosphorylated neurofilament heavy chain (pNfH), CD14, S100β have been proposed but with contrasting results in terms of correlation with disease progression.

A recent population-based study in a series of ALS patients investigated several hematological markers evaluated at diagnosis [16]. Authors found

that only serum albumin, creatinine, and lymphocytes were significantly associated with ALS outcome with a dose–response effect (better survival with increasing levels) in both genders, even after correction for known prognostic factors. Serum creatinine was correlated with fat-free mass and reflects the state of muscle mass. Serum albumin was correlated with indices of inflammatory state and not with nutritional parameters, and represents a marker of chronic inflammatory state rather than of nutritional status. Sensitivity and specificity values in predicting 1-year mortality indicated that serum albumin and creatinine have properties similar to the well-established prognostic factors of ALS such as ALSFRS-R score and age. None of the other hematological factors examined – in particular lipid status and uric acid, previously reported to influence survival – were predictive of ALS outcome.

21.1.6.13 Neurophysiology

EMG signs include the presence of fibrillation potentials and positive sharp waves and enlarged motor units. However, these abnormalities do not predict disease progression.

Motor Unit Number Estimation (MUNE) is a group of techniques to estimate the number of intact motor units. It has been proposed for longitudinal assessments of motor unit death and changes in single motor unit size. However, this technique needs extensive training of healthcare staff and has a rather high test–retest variability; at present, there is no consensus about its use to follow disease progression in clinical trials.

21.1.6.14 Neuroimaging

Advanced neuroimaging techniques, being noninvasive, have considerable potential for translation into diagnostic and prognostic biomarkers [17]. If validated, these biomarkers could be easily applied into routine clinical evaluation to monitor the progression in ALS. One limit of most neuroimaging studies is that they involve small numbers of patients.

Diffusion tensor imaging and voxel-based morphometry of the cortex have revealed thinning of the primary motor cortex and degeneration in many regions including frontal lobe, corpus callosum, basal ganglia, corticospinal tract, and brainstem.

A study of magnetic resonance spectroscopic imaging (MRSI) of brain showed that ALS patients with an N-acetylaspartate/choline ratio in the motor cortex lower than 2 had a reduced survival of 19.4 months versus 31.9 of patients with a ratio over 2. If replicated in large cohorts, this observation could represent a sensitive marker of ALS outcome.

21.1.6.15 Environment

Up to date, no environmental risk factors have proven to modify prognosis in ALS [18].

21.2 Hirayama Disease

Key Facts

- **Terminology and definitions** – HD (monomelic amyotrophy) is a juvenile cervical myelopathy with a usually monolateral and auto-limited muscular atrophy of the upper extremity.
- **Clinical features** – HD is a rare disease with insidious and most often unilateral weakness and wasting of hand and forearm muscles (often C7, C8, T1 myotomes).
- **Diagnosis**
  - **Blood/CSF** – Nonspecific.
  - **Imaging** – Routine MRI is often normal. Flexion of the neck causes forward displacement of the cervical dural canal with asymmetric cervical cord flattening.
- **Neurophysiology** – Electromyography shows denervation in C7, C8, and T1 myotomes of affected limbs.
- **Top differential diagnoses** – Cervical radiculopathies, CIDP, MMN, MG, MS, MSA.
- **Principles of treatment** – Cervical collar to reduce neck flexion. Duroplasty.

  Prognosis – HD typically has a progressive course for 2–3 up to 6 years, followed by steadiness of symptoms.

21.2.1 Definition

Hirayama disease (HD) (synonym: "juvenile muscular atrophy of the unilateral upper extremity, "also known as" monomelic amyotrophy") is a rare cervical myelopathy (formerly classified as motor neuron disease by some authors) with onset in the second to third decades of life and definite male preponderance. Most cases are described in Asia, particularly Japan and India.

The pathogenesis of HD is attributed to the anterior shifting of the cervical dura mater with consequent compression of the spinal cord against the vertebral bodies when the neck is in flexion.

21.2.2 Clinical Features

Clinically, HD is characterized by the insidious onset of unilateral or bilateral asymmetric weakness and wasting of hand and forearm, without sensory or pyramidal abnormalities. In some cases, autonomic dysfunction in the involved upper extremities is reported.

21.2.3 Diagnosis

Electromyography - Shows acute and/or chronic denervation in C7, C8, and T1 myotomes in clinically affected limbs.

Cervical MRI - Is the gold standard exam for the diagnosis; it should include imaging in neutral position and imaging in neck hyperflexion. MRI reveals loss of attachment of the dura to the lamina, asymmetric lower cervical spinal cord atrophy, and forward displacement of the dura with neck flexion (Fig. 21.2).

21.2.4 Therapy

The use of a cervical collar to reduce neck flexion often prevents progressive muscular weakness. In selected cases, surgery with duraplasty and anterior cervical decompression has been proposed.

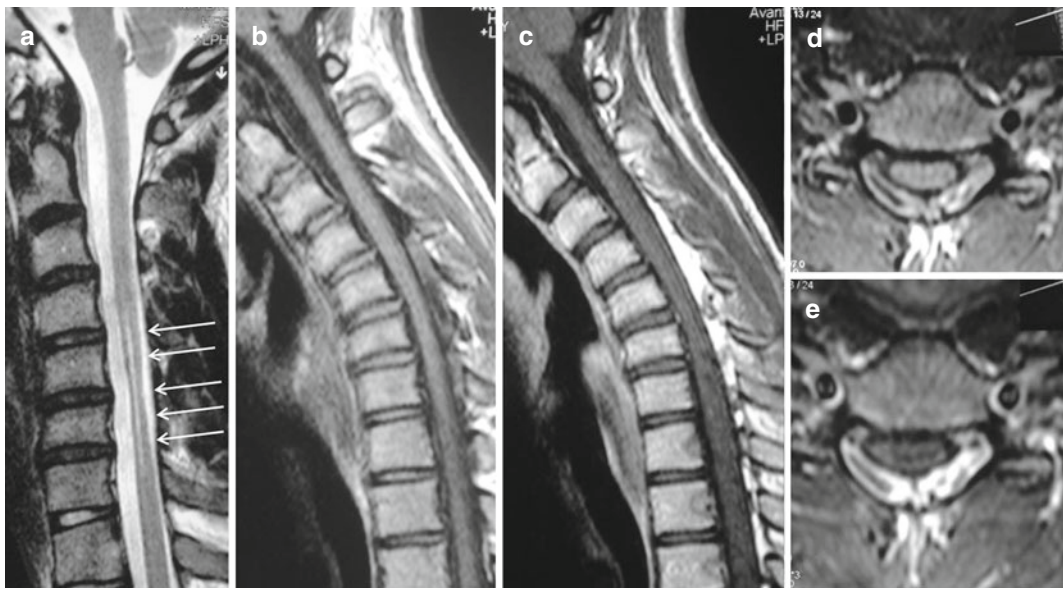

Fig. 21.2 Hirayama disease. MRI sagittal T2-weighted image, (**a**), performed 4 years after the onset of the disease, demonstrates spinal focal atrophy at C5–C6 level and hyperintense signal between C4–C7 (*arrows*). MRI sagittal and axial T1-weighted images pre- (**b**, **d**) and post-contrast medium administration (**c**, **e**) during neck flexion showing anterior displacement of the posterior dural wall and the presence of enlarged posterior epidural space with flow void images, enhancing after contrast medium administration (*arrowheads*)

21.2.5 Prognosis

Prognosis of HD is benign, and it differs from ALS because it is self-limiting. The disease has a progressive course for 2–3 up to 6 years, followed by steadiness of symptoms [19]. Nevertheless, a timely diagnosis is important to undertake early therapeutic interventions that could halt the disease.

21.3 Spinal Bulbar Muscular Atrophy

Key Facts

- **Terminology and definitions** – SBMA (Kennedy's disease) is a rare adult-onset, X-linked recessive motor neuron disease disorder, due to expansion of a CAG repeat.
- **Clinical features** – Onset usually occurs in the fifth decade with weakness and wasting in limbs and bulbar muscles. There is a variable degree of sensory nerve and endocrine involvement.
- **Diagnosis**
  - **Blood** – May show endocrine system involvement (gynecomastia, reduced fertility, diabetes)
  - **Genetics** – Males with SBMA have 38–62 CAG repeats on X chromosome, whereas individuals without the disorder have 9–36 CAG repeats.
  - **Imaging** – Neuroimaging rules out other diseases.
  - **Neurophysiology** – Fasciculations and cramps are a prominent feature. SAP can be reduced or absent.
- **Top differential diagnoses** – Cervical radiculopathies, CIDP, ALS
- **Principles of treatment** – Clenbuterol may be effective in improving motor function.
- **Prognosis** – Patients' long-term survival is only slightly reduced. CAG repeat size is significantly inversely correlated with onset and progression of the disease.

21.3.1 Definition

Spinal bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare adult-onset, X-linked recessive motor neuron disease disorder, caused by the expansion of a CAG repeat, giving rise to a polyglutamine tract, in the gene encoding the androgen receptor on the X chromosome. Patients with SBMA have 38–62 CAG repeats, whereas individuals without the disorder have 9–36 CAG repeats.

21.3.2 Clinical Features

Clinical onset usually occurs in the fifth decade with postural tremor and fatigability, followed by weakness and wasting in limbs and bulbar muscles. Fasciculations and cramps are a prominent feature. Patients have also variable degrees of involvement of peripheral nerve sensory system, with reduced/absent SAP at ENG, and of endocrine systems, including gynecomastia, reduced fertility, and diabetes. Most patients also have high serum concentrations of creatine kinase.

21.3.3 Diagnosis

SBMA is a rare disease, though it is possible that some patients are misdiagnosed with other neuromuscular diseases.

SBMA can mimic ALS. The main difference is that it is confined to LMN, without UMN involvement. Moreover, a genetic test can now easily confirm the diagnosis.

21.3.4 Therapy

Management of SBMA includes physiotherapy, provision of assistive devices (cane, walker, wheelchair), and evaluation of swallowing and respiratory functions. PEG is rarely performed in SBMA patients. Some patients use nocturnal NIV.

Recently, a pilot study provided Class IV evidence that clenbuterol is effective in improving motor function in SBMA.

21.3.5 Prognosis

SBMA progression is usually very slow, and patients' long-term survival is only slightly reduced compared to general population. Patients maintain a relatively good functional status years after the diagnosis. Only a minority of the patients lose their ability to perform activities of daily living independently until very late in the disease. Sometimes, severe pneumonia can occur in the advanced stages. CAG repeat size is significantly inversely correlated with onset, progression, and use of assistive devices [20].

21.4 Spinal Muscular Atrophy (SMA)

Key Facts

- **Terminology and definitions** – SMA is an autosomal recessive motor neurons disease due to a homozygous deletion of the SMN1 gene on chromosome 5q13.
- **Clinical features** – Progressive and generalized atrophy of bulbar and limbs muscles. Four clinical subtypes (Type I to Type IV) are recognized according to age at onset and type of progression.
- **Diagnosis** – The diagnosis of SMA remains clinical.
  - **Laboratory**
    - **Muscle biopsy** – Shows a pattern of "grouped fascicular atrophy."
    - **Genetics** – SMN1 test is 95% sensitive and 100% specific.
  - **Imaging** – Nonspecific.
  - **Neurophysiology** – Electromyography supports the diagnosis, showing active and chronic denervation in bulbar, upper limb, thoracic and lower limb muscles.
- **Top Differential Diagnoses** – Cervical radiculopathies, CIDP, MMN, MG, MS, MSA.
- **Prognosis**
  - **Principles of treatment** – No specific therapies available.
  - **Disability** – Death within 2 years (type I), within the second decade (type II); able to walk in adult life, and sometimes with favorable prognosis quoad vitam (Type III and Type IV).

21.4.1 Definition

Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disease, caused by a homozygous deletion of the survival motor neuron 1 gene (SMN1) on chromosome 5q13, leading to reduced SMN protein levels and a selective degeneration of spinal cord motor neurons. The SMN protein is ubiquitous, but particularly elevated in motor neurons; its activity seems to be related to the maintenance of a normal axonal transport and of the integrity of neuromuscular junction.

21.4.2 Clinical Features

Clinical features show hypotonia, generalized weakness, and atrophy of skeletal muscles. Weakness is usually symmetric and more severe in proximal muscles. Kyphoscoliosis often requires surgical or orthotic procedures. Bulbar involvement is prominent, particularly in the more severe forms, leading to malnourishment, weak cough, and aspiration pneumonia.

A classification in four clinical subtypes (Type I to Type IV) is based on age at onset and type of progression.

21.4.3 Diagnosis

EMG – Shows diffuse active denervation and motor unit action potentials of high amplitudes and long duration.

Muscle biopsy – Exhibits a distinctive pattern of "grouped fascicular atrophy" with a mosaic of groups of atrophic fibers alternated to fascicles entirely composed of hypertrophic fibers.

–*Genetic* Patients with suspected SMA should be tested for SMN1. The test is 95% sensitive and 100% specific.

21.4.4 Therapy

No medical treatment is available at present.

Promising novel therapeutic approaches are currently underway. They include compounds noted to increase SMN mRNA, gene therapy, and use of stem cells.

21.4.5 Prognosis

The phenotypic heterogeneity of SMA is striking, given the fact that patients have a defect in the same gene. There is a relation between age at onset and disease severity; an earlier onset bears a worse prognosis.

Type I disease is the most common and most severe form; the onset of the disease is before 6 months of age and death within 2 years, usually by aspiration pneumonia.

Type II disease is characterized by onset between 7 and 18 months of age. Death occurs during the second decade due to respiratory failure. In the last two decades, the multidisciplinary approach, with a careful management of respiratory, nutritive, and orthopedic problems, the use of NIV, mechanical in-exufflation, and PEG have increased significantly the outcome. Recent studies show a mean survival probability from 1 to 4 years, with outliers surviving up to 24 years [21].

Type III and Type IV have an older age at onset with slower progression. Most patients are able to walk in adult life, and some have a favorable prognosis quoad vitam.

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