Amyotrophic Lateral Sclerosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that primarily affects motor neurons. The characteristic form of this devastating disorder features the simultaneous presence of both upper and lower motor neuron signs with progression from one region of the neuraxis to the next and eventual death, typically from respiratory compromise. This condition first appeared in the literature in 1850 when François Aran reported a family of 11 patients of the ALS subtype, progressive muscular atrophy (PMA) [1]. Amand Duchenne first described progressive bulbar palsy (PBP) a decade later [2]. In 1869, Jean Martin Charcot, professor of neurology at the Salpêtrière, comprehensively described both the clinical and pathological features of classic ALS, and, a few years later, Heinrich Erb first described primary lateral sclerosis (PLS), a condition felt to be a subtype of ALS rather than a distinct separate entity [3, 4]. The term *motor neuron disease* was coined by Brain in 1933 to unify PMA, PBP, PLS, and ALS under one name [5]. Lou Gehrig, an American baseball player named "Iron Horse," was diagnosed with ALS in 1939, although the eponym "Lou Gehrig's disease," perhaps in response to efforts to increase public awareness of the condition, did not come into popular use for another 35 years [6]. In the 1950s, epidemiological studies identified the presence of a condition characterized by a combination of ALS, parkinsonism, and dementia in several distinct regions of the Western Pacific including the Marianas Islands, the Kii Peninsula of Japan, and the Irian Jaya region of New Guinea [7–9]. A great breakthrough in the understanding of ALS came when, in 1993, Rosen et al. showed that 15–20 % of familial ALS patients manifest a mutation in the Cu/Zn superoxide dismutase (SOD1) gene located on chromosome 21 [10]. Since then, multiple different SOD1 mutations have been discovered [11] along with mutations in other "ALS" genes including FUS, optineurin, dynamin, and C9ORF72.

There has always been some confusion regarding the terminology of ALS. In Europe it is better known as Charcot's disease or *motor neuron disease*, whereas, in the USA, the terms amyotrophic lateral sclerosis, ALS, and Lou Gehrig's disease are in more common use. Perhaps the most important distinction to be made is whether to call the disease ALS or motor neuron disease; the former is considered to be more specific. The World Federation of Neurology Research Group on Neuromuscular Diseases has grouped sporadic ALS, PMA, and PBP together as disorders of motor neurons of undetermined etiology [12].

Epidemiology

The incidence and prevalence rates for non–Western Pacific ALS are similar across the globe. The annual incidence of ALS is roughly 2 per 100,000 population with a prevalence rate of about 6 per 100,000. Differences in methods of case identification, database maintenance, death certification, and treatments may account for the variations seen from region to region [13, 14]. Several different risk factors such as race, age, sex, and occupation have been analyzed separately with a view to better understanding the disease. The incidence and prevalence rates appear to be higher in Caucasians than in non-Caucasians in western countries although this may be a reflection of underreporting rather than a true racial predisposition [15]. Age is the single most important risk factor for ALS with an age-related increase in mortality up until the

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eighth decade and peak mortality rate between the approximate ages of 65 and 75 years [13, 16]. Men develop ALS more often than women, the male-to-female sex ratio being 1.4:1–2.5:1. On the other hand, most studies show that bulbar-onset ALS displays a female predominance [17–20]. Epidemiological studies identified an increased mortality risk from ALS among electrical utility workers, the risk being greater with more prolonged exposure to electromagnetic fields [21, 22]. An increasing body of evidence indicates an association between higher levels of physical fitness and ALS, which appears to be independent of physical trauma or actual muscle strength [23–25]. Somewhat paradoxically, however, smoking also appears to be an independent risk factor [26]. Rarely, one encounters reports of "ALS clusters" (including conjugal ALS) which provide tantalizing evidence that local environmental or toxic factors play a significant part in the pathogenesis of the disease, but there is insufficient evidence to associate ALS with pesticides, heavy metals, or solvents despite interesting studies suggesting that they may play a pathogenic role [27, 28]. However, certain toxins have gained particular attention, namely, β-N-oxalylamino-alanine (BOAA) and cycasin. BOAA is the cause of *lathyrism* in India, a condition characterized by UMN signs, occurring in individuals who have consumed chickling pea flour. A similar condition, *konzo*, seen in East Africa, may be related to ingestion of insufficiently prepared cassava roots which yield an aminothiazolidine carboxylic acid which is similar to BOAA. Cycasin is a cycad nut-derived toxin found in high concentration in certain foodstuffs of the Chamorro Indians of Guam, but the exact role of cycasin in the pathogenesis of *ALS–parkinsonism–dementia complex* remains uncertain.

Clinicoanatomic Correlation

Both the classic and familial forms of ALS feature a combination of upper motor neuron (UMN) and lower motor neuron (LMN) signs (Table 20.1) affecting limb, trunk, and bulbar musculature. The UMN syndrome is the result of an interruption of the corticospinal and corticobulbar tracts occurring over a protracted time. These tracts originate in the primary motor cortex, premotor areas, temporal cortex, and sensory cortex; converge in the internal capsule; pass through the ventral midbrain; and separate into bundles in the basis pontis (Fig. 20.1). At this level, the corticobulbar tract separates off and bilaterally projects to the motor neurons of cranial nerves V, VII, IX, X, and XII. In the medulla, some of the corticospinal bundles coalesce ventrally to form the pyramids with 75–90 % of these fibers decussating at the level of the lower medulla to form the lateral corticospinal tracts [29]. The latter project to ipsilateral motor neurons, innervating the extremities, and associated interneurons in

Table 20.1 Signs in ALS

Upper motor neuron	Lower motor neuron	Others
Weakness	Weakness	Dementia [b]
Spasticity	Atrophy	
Poor dexterity	Fasciculations[a]	Atypical/rare:
Pathologic reflexes	Cramps	Sensory loss
Hyperreflexia	Hyporeflexia	Sphincter dysfunction
Pseudobulbar signs		Extraocular dysmotility
Retained reflex in atrophic limb		

[a]Debate as to origin of fasciculations (see text)
[b]Dementia is no longer considered rare or atypical (see text)

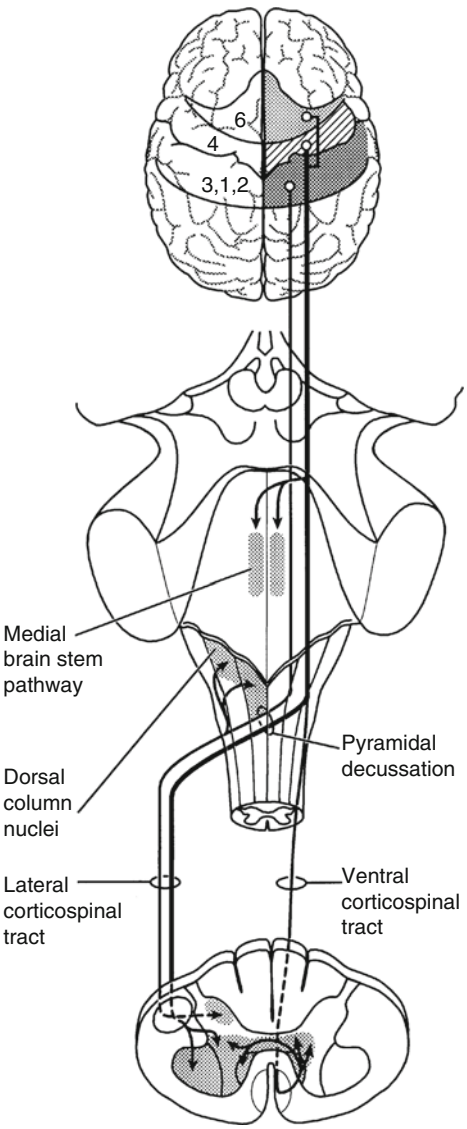

Fig. 20.1 Anatomic pathways involved in amyotrophic lateral sclerosis. The corticospinal tracts originate from multiple areas of the cortex (Brodmann's areas *1*, *2*, *3*, *4*, and *6*), pass through the brainstem, and emerge as both crossed and uncrossed corticospinal tracts that synapse upon alpha motor neurons and interneurons in the anterior horns of the spinal cord. The corticobulbar tracts (not illustrated) also originate from a broad region of cerebral cortex including connections to the limbic system

the lateral anterior horn. The remaining corticospinal fibers descend as the uncrossed anterior corticospinal tracts to project onto ventromedial motor neurons and interneurons which innervate axial and postural muscles. Recent electrophysiological evidence suggests that there is preferential involvement of the fast-conducting direct corticospinal tracts in ALS while sparing the slower, polysynaptic pathways [30]. Axons within these tracts provide excitatory input to alpha motor neurons, gamma motor neurons, and Ia inhibitory interneurons. Brainstem nuclei are intimately connected to the motor neurons in the anterior horn via the vestibulospinal, tectospinal, and reticulospinal tracts. In addition, an independent limbic motor system with medial, lateral, and periaqueductal gray components influences somatic motor neurons together with emotional, autonomic, endocrine, and visceral functions [31].

The lower motor neurons in the spinal cord are centered in the anterior horns forming longitudinally arranged columns extending from one to four spinal segments. Motor neurons that innervate the distal muscles of the extremities are more dorsally located in the anterior horn, whereas those innervating proximal muscles are more ventrally positioned. The individual cells are composed of large alpha motor neurons, medium-sized beta motor neurons, gamma neurons (fusimotor neurons), and interneurons. The alpha motor neurons are among the largest neurons in the nervous system and possess long axons together with broad dendritic receptive fields.

Clinical Presentation

Typical Features

The classic form of ALS is characterized by the coexistence of both UMN and LMN signs (see Table 20.1). Weakness, the most common presenting complaint, typically begins in the limbs, is asymmetric, and progresses over time to adjacent myotomes in the same limb and thence to the opposite side. It has recently been reported that onset in the upper limb is usually in the dominant limb, but the same cannot be said of the lower limb, where "footedness" appears not to play a role [32].

The UMN syndrome comprises those abnormalities attributable to involvement of the corticospinal and corticobulbar tracts which include loss of dexterity, weakness, spasms, spasticity, hyperreflexia, and pseudobulbar palsy. Poor dexterity is often described as clumsiness or slowness of certain activities, such as buttoning clothing or tying shoelaces. Complaints of muscle slowness, fatigability, or stiffness are common. Spasticity, the defining feature of the UMN syndrome, is thought to arise from increased excitability of the lower motor neurons caused by denervation hypersensitivity of the anterior horn cell interneuron population in the setting of damage to the integrity of the corticospinal tract [33].

With loss of inhibitory pathways in the spinal cord, muscle stretch reflexes become exaggerated so that even the slightest of hammer taps may elicit a response. A deep tendon reflex may spread to muscles that should not be involved in the tested reflex arc (i.e., "pathologic spread"). Easily elicitable reflexes in the setting of a flaccid, atrophic limb should also be considered an UMN sign. A study comparing the corneomandibular reflex in ALS to that in stroke (with resulting pseudobulbar palsy) showed that this reflex is a sensitive indicator of ALS [34].

Primitive reflexes may become disinhibited as a result of loss of UMN control. The most important is the Babinski sign whose presence correlates well with corticospinal tract involvement but which may be masked by muscle atrophy (in such a situation one should look for contraction of the tensor fascia lata when one stimulates the sole of the foot) [35]. Hoffmann's and Tromner's signs may be present, although these primitive reflexes may be seen in some normal individuals and, thus, should be interpreted as definitely pathologic only if there are associated UMN signs.

Compared to the UMN type, weakness in the LMN syndrome is more pronounced and often associated with significantly greater degree of muscle atrophy. Additionally, the reflexes are hypoactive or even lost. Weakness is typically focal in onset, is painless, and subsequently spreads to contiguous muscles. The most common site of onset is the distal extremity, the intrinsic muscles of the hand being more frequently affected than elsewhere. One should assess for clinical evidence of the "*split hand*," a phenomenon whereby the muscles of the lateral aspect of the hand are more severely involved than those of the medial aspect (see the electrodiagnostic examination below). When onset presents as foot drop, wrist drop, or claw hand alone, the presentation is said to be "pseudoneuritic" (although some prefer to restrict this term to lower limb onset, also known as "flail leg"). Involvement of cervical paraspinal musculature can present as head drop, whereas involvement of thoracic and lumbar paraspinal muscles can lead to bent spine and marked camptocormia [36]. As motor units continue to be lost, muscle atrophy occurs, which, in ALS, is most commonly seen in the form of intrinsic hand muscle wasting or sharpening of the tibial border. With severe degrees of atrophy, loss of muscle stretch reflexes, palpable flaccidity, and trophic joint changes occur. The latter may be associated with painful contractures and pericapsulitis.

Fasciculations are an important sign in ALS, presenting as involuntary, painless, rapid twitches in muscles of the limbs and the trunk. They represent spontaneous contractions of muscle fibers belonging to a particular motor unit. It is postulated that fasciculations arise from hyperexcitable

distal motor axons, although there is some evidence in support of a supraspinal origin. While a relatively uncommon presenting symptom, they are eventually seen in almost all ALS patients, and accordingly, their absence should prompt one to carefully rethink the diagnosis. Cramps or "charley horses" are often described by patients with ALS and occur in a far more widespread distribution than that seen in the normal population. These sudden, involuntary, painful, sustained muscle contractions can arise at rest and may awaken the patient from sleep. Yet again, they are rarely the presenting complaint but are frequently seen as the disease progresses.

The bulbar palsy syndrome in ALS typically involves damage to both upper and lower motor neurons. The patients present with dysarthria, dysphagia, sialorrhea, aspiration, and pseudobulbar signs. As in limb involvement, there are both UMN and LMN syndromes referable to the bulbar region. The UMN syndrome may present with spastic dysarthria characterized by a slowness of oral and tongue movement and a strained vocal quality. Dysphagia, initially more for liquids than solids, may also occur. There may be a hyperactive gag reflex and a brisk cough reflex. One may also elicit a brisk snout reflex and jaw jerk, which may even become clonic. UMN involvement affecting the muscles of mastication may lead to a slowness and stiffness of chewing (patients complain of taking a long time to eat) or jaw pain after prolonged chewing. The pseudobulbar affect is a feature peculiar to the UMN bulbar syndrome that presents as inappropriate, spontaneous, forced crying, laughing, or yawning. It is thought to arise from disruption of the bilateral corticobulbar pathways bearing fibers of the limbic motor control system [37].

Compared to the UMN bulbar syndrome, LMN bulbar impairment leads to greater degrees of weakness affecting the face (particularly the perioral region), palate, and tongue. In the earlier stages, the patient may have a horizontal smile, be unable to pucker the lips or whistle, and may have difficulty holding air in the cheek. With more advanced bulbar weakness, there is additional difficulty elevating the palate, the gag and jaw jerks disappear, and the tongue becomes increasingly, and often somewhat asymmetrically, atrophic and flaccid (Fig. 20.2). Fasciculations may also be seen on the surface of the tongue. It is important to differentiate these pathologic movements from the twitches that may be seen in normal, anxious individuals and view the tongue while at rest on the floor of the mouth as protrusion may exaggerate normal surface undulations.

Excessive drooling (sialorrhea) is a frequent complaint caused by impaired automatic swallowing and clearance of oral secretions. When neck extensor weakness coexists, this disturbing problem is worsened. Both silent and symptomatic aspiration, a major concern in ALS, may present as frequent bouts of mealtime choking and coughing, nocturnal awakenings, or even fatal laryngospasm.

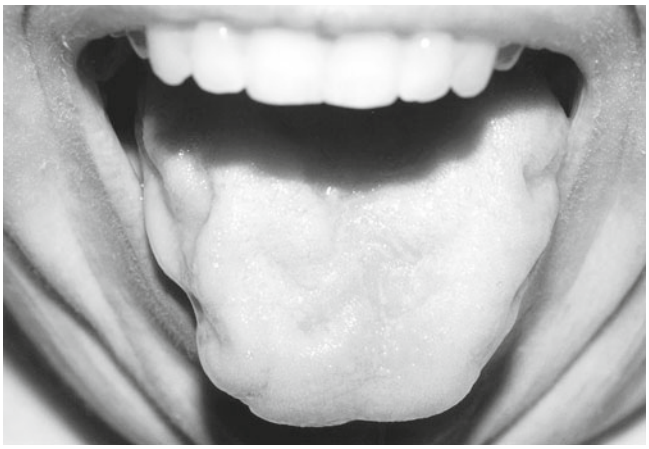

Fig. 20.2 Tongue atrophy in amyotrophic lateral sclerosis. Note the scalloping of the lateral tongue surface

Diaphragmatic and intercostal muscle involvement is frequent in ALS, albeit rarely at disease onset [38–40]. Patients may complain of sleep disturbance, orthopnea, dyspnea on exertion, dyspnea at rest, or morning headaches. Thus, one should look for use of accessory muscles of respiration, paradoxical abdominal movements, and signs of CO2 retention such as cyanosis, chemosis, papilledema, and bounding pulses. The voice may become softer and weaken at the end of long sentences, and frequent sighs may be observed. Many abnormalities of sleep architecture are described in ALS, including increased sleep latency, persistence of EMG activity during REM sleep, frequent awakenings, and a reduction in total sleep time. It has been postulated that both bulbar and diaphragmatic weaknesses may result in increased hypopneas and apneas, even at an early stage, that may lead to excessive daytime sleepiness and increase the amount of perceived muscle fatigue. In fact, fatigue similar to that seen in neuromuscular transmission disorders is a common complaint in ALS and is associated with disease severity [41]. The pathogenesis of this fatigue is unclear with evidence implicating sources from the level of cerebral cortex to beyond the neuromuscular junction [42], but it is important to consider the possibility that fatigue may be a side effect of riluzole, the most commonly used therapeutic drug in ALS. Many of the common symptoms and signs of ALS, such as sighing, fatigue, frequent crying, sleep disturbance, and weight loss, are also seen in and may actually represent depression [41]. Weight loss may be severe in ALS. It does not appear to be simply related to reduced caloric intake, and there is evidence that some patients suffer from a form of "ALS cachexia" [43, 44].

Atypical Features

It has become clear that a spectrum of cognitive impairment, once considered uncommon in ALS, often accompanies

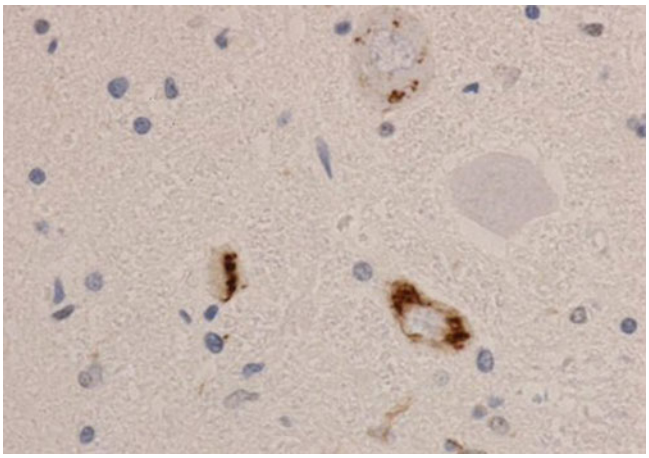

Fig. 20.3 Pathological TAR DNA-binding protein, TDP-43 (*brown*), in the hippocampus of a patient with sporadic ALS (Courtesy of Professor M Farrell, Beaumont Hospital, Dublin, Ireland) (For a more detailed discussion, see Neumann et al. [54])

motor neuron degeneration [45–50]. The range of cognitive syndromes reflects frontotemporal dysfunction, including a cognitive-behavioral syndrome, a dysexecutive syndrome, and a frank frontotemporal dementia. Both sporadic and familial variants of ALS can be affected. Neuroimaging, neuropsychological, and pathological studies demonstrate abnormalities beyond the primary motor cortex with evidence that language deficits, especially anomia, may be relatively frequent in ALS patients but are often masked by dysarthria. A recent prospective population-based study of cognitive function identified that comorbid dementia occurs in approximately 14 % of patients with a new diagnosis of ALS. Cognitive impairment, predominantly but not exclusively in the form of executive dysfunction, was present in more than 40 % of ALS patients without overt evidence of dementia [51]. Thus, although cognitive impairment in ALS is not a universal feature, it may previously have been underreported and its manifestations may be more heterogeneous than previously recognized. In addition to motor-onset ALS presentations, a subgroup of patients (maybe up to 30 %) may initially present with FTD, later developing ALS symptoms [52]. The clinical overlap in most cases of FTD with ALS is reflected by significant pathologic overlap between clinically pure FTD and those with classic ALS—i.e., underlying frontotemporal lobar degeneration (FTLD) with linear spongiosus, atrophy, neuronal loss, and pathological TDP-43(transactive response DNA-binding protein) ubiquitinated inclusions in astrocytes and neurons [53] (Figs. 20.3 and 20.4). Thus, recent pathologic findings suggest that FTD–ALS is part of a clinicopathologic spectrum of TDP-43 proteinopathy. The inheritance of ALS and FTD as a single trait has been recently described, confirming an intronic expansion of the GGGGCC hexanucleotide repeat within the C9ORF72 gene as the cause of a large proportion of familial ALS–FTD, in addition to apparently sporadic disease [55, 56]. C9ORF72 cases show features of a relatively rapidly progressive, but otherwise typical, variant of ALS associated with familial and sporadic presentations. All show classical ALS pathology with TDP-43 inclusions along with extra-motor pathology in the frontal cortex and the hippocampal CA4 subfield [57–59]. Better understanding of the pathological subtypes and clinical phenotypes of these ALS–FTD overlap syndromes is essential to inform development of effective targeted therapies, particularly as these conditions are often the most rapidly progressive neurodegenerative diseases.

The extraocular muscles and those muscles subserving bladder and bowel functions are relatively spared in ALS although advanced patients maintained on ventilators may eventually develop overt dysfunction in these areas. If one performs quantitative testing of saccades, one may detect a reduction of saccade velocities and smooth pursuit movements [60, 61]. A recent study replicated findings that visual acuity, gaze impersistence, voluntary upgaze restriction, eyelid opening apraxia, and saccadic horizontal smooth pursuits are more frequent in patients with ALS than in similar-aged controls. These ocular motility abnormalities are potential clinical markers of neurodegeneration beyond upper and lower motor neuron disease in ALS, suggesting dysfunction of supranuclear control. Several autopsy studies demonstrated neuronal loss in many subcortical regions subserving eye movement control. Further study is required regarding their application to disease categorization and outcomes assessment [62].

Within the sacral cord, the motor neurons of Onufrowicz that control the muscles of the pelvic floor, anal sphincter, bladder, and urethra are essentially spared in ALS. However, while frank urge incontinence and bowel dysfunction are rarities, mild urgency of micturition and urinary retention may occur [63].

The sensory system is also characteristically spared which perhaps contributes to the rarity of decubitus ulcers in this population of immobilized patients (local autonomic reflexes being intact). Despite an overall absence of objective signs, some patients do report vague sensory complaints in the distal extremities; detailed quantitative sensory testing and somatosensory evoked potential studies identified objective sensory disturbances in a small proportion of patients, suggestive of a disruption of the ascending afferent system [64]. There appears to be specific changes in the skin composition in ALS patients. Studies have revealed increased levels of type III procollagen in the skin and serum of ALS patients as compared to controls with excessive deposition of β-amyloid protein and increased dermal ciliary neurotrophic factor and insulin-like growth factor I (IGF-I) suggesting that a metabolic alteration growth factors may take place in the skin of patients with ALS. Perhaps this helps explain the low incidence of pressure sores in immobilized patients with ALS [65]. Extrapyramidal involvement may occur in about 5 % of

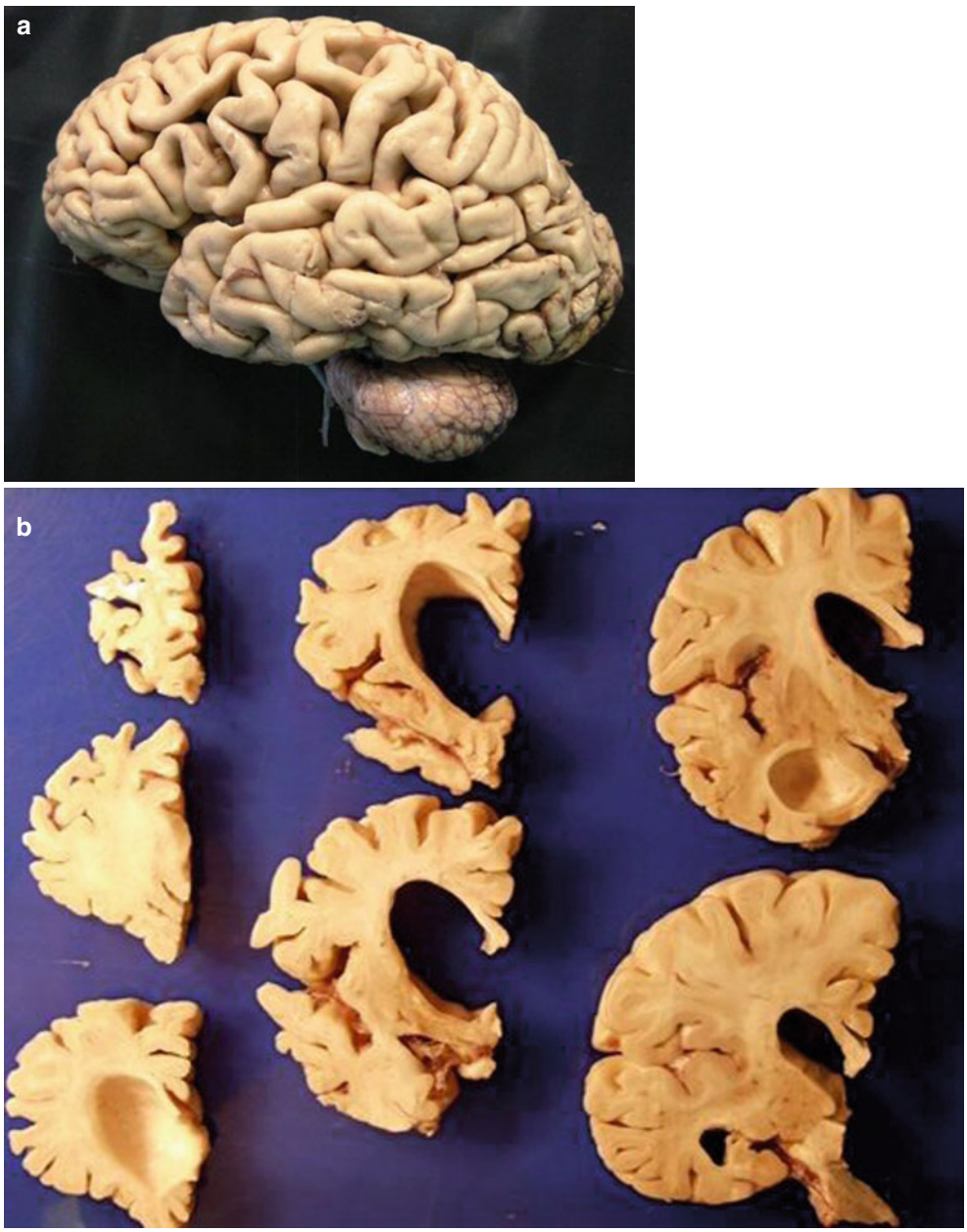

Fig. 20.4 (**a**) Pathology in ALS-FTD: Gross frontal and anterior temporal atrophy (Courtesy of Professor M Farrell, Beaumont Hospital, Dublin, Ireland) (For further detail, please see "Pathology" section in main text). (**b**) Marked frontal and temporal lobe atrophy in ALS-FTD (Courtesy of Professor M Farrell, Beaumont Hospital, Dublin, Ireland) (For further detail, please see "Pathology" section in main text)

ALS patients and may present as an impairment of postural reflexes or retropulsion during attempted ambulation [66].

When one considers these facts, it appears reasonable to conclude that ALS is a widespread, multisystem disorder rather than a pure "motor neuron disease," although it does appear that the motor neuron pool is particularly vulnerable to damage from the injurious processes involved.

ALS Subtypes

Bulbar palsy can be the initial symptom in ALS (Table 20.2). It is most commonly seen in postmenopausal women and may

Table 20.2 Presentations of ALS

Spinal (classic, sporadic)
Primary lateral sclerosis
Progressive muscular atrophy
Progressive bulbar palsy
Familial
Monomelic
Flail-leg syndrome (pseudoneuritic)
Flail-arm syndrome
Mills' (hemiplegic) variant
ALS–FTD (ALS–frontotemporal dementia)
ALS–parkinsonism–dementia complex

portend a worse prognosis. Various studies report that bulbar-onset ALS accounts for 19–28 % of all presentations. Clinically, affected individuals present with dysarthria and dysphagia. The pattern of speech impairment may be more strained, as seen in the UMN predominant presentation, or more slurred as seen in the LMN pattern. Combinations of tongue weakness, wasting, fasciculations, slowness, and lower facial weakness are seen. Often there is coexistent UMN jaw jerk exaggeration and a hyperactive gag (although the LMN type may have no gag at presentation). Emotional lability is frequent and can be embarrassing for the patient. There is often a history of recurrent cough during meals, and there may also be weight loss and aspiration events. This disturbing condition advances locally first and spreads first to the lower cervical/upper thoracic region and thence to lumbosacral myotomes by which time the patient has increasing difficulties with speech and swallowing. Very rarely, the disease does not advance beyond the bulbar region at all; this is true *progressive bulbar palsy (PBP),* an exceedingly rare disease.

Between 2 and 3.7 % of all ALS patients present as a pure UMN syndrome called *primary lateral sclerosis (PLS)* that never goes on to involve the lower motor neurons. Age of onset is typically between 50 and 55 years and the rate of progression may be very slow. A common presentation is that of spastic paraparesis progressing rostrally over many years to eventually cause pseudobulbar palsy. The most recent natural history study suggests that clinically pure PLS can be defined by isolated UMN signs 4 years after symptom onset and is a syndrome of slow progression with high levels of function and longer survival compared with ALS [67]. Diagnosis of PLS cannot be made with certainty before the fourth year of symptoms because many patients develop LMN signs within that time frame (this rendering a diagnosis of upper motor neuron–onset ALS) [68, 69]. Although detailed neuropsychological test batteries may reveal subtle cognitive changes in PLS, overt dementia is uncommon [70, 71].

Progressive muscular atrophy (PMA), the rarest "ALS" presentation (2.4 %), presents as a pure LMN syndrome and tends to harbor a more favorable outcome. Clinically, it is characterized by signs of lower motor neuron dysfunction. By definition, the condition must be pure LMN before designation as PMA, but, as with PLS, one must continue to reevaluate patients for later development of UMN signs [72]. Comparison of survival of patients with PMA or ALS and analysis of clinical features that influence survival in PMA suggest that, although patients with PMA tend to live longer than those with ALS, shorter survival in PMA is associated with the same risk factors that predict poor survival in ALS. Additionally, PMA, also a TDP-43 proteinopathy, is progressive, and UMN involvement can eventually occur. For these reasons, PMA should be considered a form of ALS [73].

Mention should be made of three distinctive presentations of ALS: Mills' (hemiplegic) variant, flail-arm syndrome and flail-leg syndrome. *Mills' variant* is a well-recognized, hemiplegic presentation featuring a combination of UMN and LMN signs isolated to one side [74]. The *flail-arm syndrome*, also known as brachial amyotrophic diplegia, occurs in about 10 % of patients and presents as relatively symmetric proximal and distal bibrachial wasting with additional evidence of corticospinal tract involvement (positive Babinski sign). *Flail-leg syndrome* represents a pseudopolyneuritic variant of ALS and occurs in approximately 6 % of all patients. Survival in both syndromes is significantly better than in classical ALS [75].

Familial ALS

Familial ALS (fALS) describes the 5–10 % of all cases in whom ALS is known to be an inherited trait. The true frequency of fALS is probably higher, and reduced penetrance may account for apparently sporadic disease. There are autosomal dominant, autosomal recessive, and X-linked dominant forms, some juvenile, and others adult, onset. Familial ALS-known genes and phenotypes are outlined in Table 20.3.

Familial ALS should be suspected when family members of successive generations are definitely affected by the disease. However, family history may be incomplete, and phenotypic variability abounds so that few clinical features separate sporadic from familial forms. Overall, fALS has a younger age at presentation, lacks male predominance, and has shorter disease duration and a predilection for lower extremity onset. Most ALS research in the past has focused on the neurotoxicity of mutant SOD1, and this has directed therapeutic research. More recently, TDP-43 has been identified as the major pathological protein in sporadic ALS, ALS–FTD, and *SOD1*-negative familial ALS [10, 83–85].

Up to 20 % of fALS patients are associated with a mutation in the Cu/Zn superoxide dismutase 1 (SOD1) gene on chromosome 21, and since its discovery, many different mutations have been described in all five exons [10, 86]. Cumulative evidence suggests that a toxic gain of function rather than a loss of function is conferred by the mutations. The most common is an alanine for valine substitution at codon 4 (shortened to A4V) that seems to correlate with shorter patient survival (mean 1.5 years). Usually SOD-1 fALS is autosomal dominant, but aspartate for alanine substitution in exon 4 (D90A,) seen most commonly in Scandinavians is recessive. The alsin mutation on chromosome 2q33 (known as ALS2) and affecting predominantly Tunisians, Saudi Arabians, and Kuwaitis has a mean age of onset of 12 years and progresses very slowly. Both PLS and ALS presentations occur. The disorder is proposed to occur

Table 20.3 Familial ALS: genes and features

ALS	Gene mutation	Chromosome and gene product function	Inheritance	Details
ALS 1	SOD1	21q21; oxidative stress	AD (rarely AR)	Late onset >30 years, 15–20 % all familial ALS (1–2 % all ALS) [10]
ALS 2	ALSIN	2q33; trafficking and signaling	AR	Rare, juvenile ALS; loss of function of gene product
ALS 3	Not identified	18q21	AD	
ALS 4	(SETX) Senataxin	9q34, RNA processing	AD	Juvenile onset, slowly progressive, distal amyotrophy, and UMN signs, not bulbar
ALS 5	Spatacsin	15q15-q22	AR	Juvenile onset
ALS 6	FUS–TLS	16q21; RNA processing	AD	5 % non-SOD1 familial ALS, 1 % sporadic ALS [76]. FUS is immunoreactive with TDP43 and ubiquitin [56]. Associated with FTD and hallucinations
ALS 7	Not identified	20ptel-p13	AD	Rare, late onset
ALS 8	VAPB (vesicle-associated membrane protein)	20q13.3; trafficking and signaling	AD	Heterogenous phenotype [77]
ALS 9	Angiogenin	14q11.2; RNA processing	AD	Adult onset
ALS 10	TDP-43 (transactive response DNA-binding protein)	1p36.2; RNA processing	AD	ALS with limb/bulbar onset. Although not specific to ALS, the frequency of TDP-43 inclusions in familial (2–5 %) and sporadic ALS suggest pathogenic role [78, 79]
ALS 11	FIG-4	6q21; trafficking and signaling	AR	ALS/PLS onset. Familial and sporadic ALS [80] FIG-4 mutation also causes CMT4J
X-linked AD	Ubiquilin 2	Xp11; protein turnover	X-linked AD	Combined UMN/LMN
ALS12	OPTN; optineurin	10p13; trafficking and signaling	AR, AD	[81]
Dynactin	Dynactin (p150 glued subunit) (Puls et al. 2005)	2p13; trafficking	AD	Distinctive phenotype: early bilateral vocal cord paralysis, then intrinsic hand muscles, legs, face. Other mutations: ALS or FTD
FTD–ALS overlap				
ALS–FTD 1	Not identified	9q21-q22	AD	
ALS–FTD 2	Not identified	9p21.3	AD	
ALS–FTD 3*	CHMP2B	3, trafficking and signaling	AD	ALS, ALS–FTD, PMA [82]
*Autosomal-dominant ALS–FTD		9q21-22	AD	
C9ORF72 hexanucleotide repeat expansion	GGGGCC hexanucleotide repeat within the *C9ORF72* gene	9		Familial and sporadic ALS. Associated with TDP-43 proteinopathy. Classic ALS and extra-motor pathology [57]
FTD with some ALS features—progranulin	Progranulin (PGN)	17		Neuronal and glial TDP43-positive, tau-negative ubiquitinated inclusions
DDPAC (disinhibition–dementia–parkinsonism–amyotrophy complex)	TAU	17	AD	Tau-immunoreactive inclusion bodies in affected regions of CNS

through loss of function of the gene product (which is important in cell trafficking) [87]. Autosomal dominant ALS 10, associated with a TDP-43 (transactive response DNA-binding protein) mutation, is characterized by ALS with limb/bulbar onset and is not reliably distinguishable from sporadic ALS aside from family history [78, 79]. Most recently, the gene underlying inheritance of ALS and FTD as a single trait within the same family has been described, with confirmation that a hexanucleotide expansion on chromosome 9 underlies a large proportion of familial ALS and FTD, in addition to apparently sporadic disease [57]. Other implicated genes include FUS–TLS (chromosome 16q21) [76], ubiquilin [56], senataxin [88], FIG-4 (chromosome 6q21) [80], and optineurin/OPTN [81]. As outlined in a later section of this chapter, these various genes have overlapping functions, some associated with RNA processing, some concerned with endosomal trafficking/cell signaling, and others involved in oxidative stress responses. Intracellular inclusion bodies are found in many of these genetic disorders including SOD1, TDP-43, FUS/TLS, and optineurin [89].

Western Pacific ALS

A combination of ALS and Parkinsonism on the island of Guam was first described by Mulder et al. in 1954. This was followed by Hirano's first complete pathological description of the syndrome of Guamanian ALS–Parkinsonism–Dementia Complex [90]. Subsequently, the incidence of ALS was noted to be particularly higher in West New Guinea and the Kii Peninsula of Japan, being between 50 and 150 times, than elsewhere [7–9, 90]. Clinically, about 5 % of patients develop a predominantly ALS type of disorder, whereas 38 % manifest principally with a combination of parkinsonism and dementia. The pathology is similar to that of Alzheimer disease, with prominent loss of CNS neurons and the presence of abundant tau-immunoreactive neurofibrillary tangles. However, the characteristic pathology of Guamanian ALS and PDC also includes TDP43-positive inclusions in neurons and glial cells. α-Synuclein pathology also is detectable in the amygdala of affected brain tissue [91]. Various environmental substances, including cycad seeds, aluminum, and silicon, have been studied with regard to its pathogenesis, but their roles, including that of cycad seeds in neurotoxicity, is still subject to debate [92–94]. The cycad seed has many uses: in West Papua and Guam as a topical medicine for skin lesions and in Japan as an oral medicine [95, 96]. Cox and Sacks (2002) proposed a process of biomagnification of cycad toxins in Guam through the Chamorro practice of eating flying foxes, which themselves feed on cycad seeds. ALS–parkinsonism–dementia complex is beginning to disappear from the endemic regions, and it has been proposed that this may be due to altered exposure to an unidentified trigger as well as changes in social/cultural practices in endemic regions. The cycad-derived BMAA (beta-methylamino-L-alanine) neurotoxin hypothesis has wider implications for research in SALS worldwide. It has been recently shown that protein-bound BMAA is present in the brains of North American patients dying with ALS and Alzheimer disease, and it has been hypothesized that such patients may be genetically susceptible to BMAA-induced neurodegeneration [97, 98].

Etiology and Pathogenesis

The cause of ALS remains unknown, but there are several intertwining strands of evidence that together suggest multiple molecular mechanisms that may ultimately combine to effect loss of motor neurons and their support systems. Much of this evidence stems from research in the field of fALS. As the first ALS-associated gene, superoxide dismutase 1 (SOD-1) is an antioxidant protein. One of the most studied areas in this regard is *oxidative stress* wherein overproduction of, or failure to clear, potentially harmful oxygen free radicals in aging motor neurons may precipitate eventual cell failure (probably in concert with other pathogenic processes). Markers of free-radical damage are elevated in tissue samples of patients with ALS, and signs of oxidative stress have been identified in the organelles of cells from fALS cases (notably SOD 1-associated diseases) and in animal models of fALS [99, 100]. *Excitotoxicity* is another mechanism whereby overstimulation/activation of glutamate receptor subtypes (most notably amino-3-hydroxy-5-methylisoxasole-4-propionic acid, AMPA receptors) leads to disordered calcium homeostasis and triggers intracellular protein breakdown and generation of harmful levels of oxygen free radicals. Evidence to support this theory includes elevated glutamate levels in cerebrospinal fluid levels of ALS cases and reduced activity/expression of the major excitatory amino acid transporter EAAT2 not only in ALS cells but also in animal model studies [101–103]. Most recently, a new ALS-associated gene has been identified: the gene product (D-amino oxidase, DAO) is a protein involved in oxidative deamination of amino acids involved in glutamate receptor activation [104].

A burgeoning theory in ALS pathogenesis is that of *altered cellular energy* [43]. Motor neurons have particularly high energy requirements as they pertain to cell soma size, axonal transport, and activation of large terminal arborizations. As mentioned earlier in this chapter, there appears to be an association between higher metabolic rate/physical fitness and ALS. Furthermore, upper limb onset is more often in the dominant limb. Mitochondria play a major role in the energy production in cells, and there is evidence to implicate dysfunction of these organelles in the pathogenesis of the disease. Oxidative damage impairs respiratory chain function in the mitochondria of patients with ALS, and mutant SOD1 protein can adhere to the mitochondrial membrane and disrupt chaperone-assisted organelle folding [103, 105, 106]. There may be abnormal transport, and therefore reduced numbers, of mitochondria in the terminal axons, thus depriving them of vital energy at a site of high energy requirement [107]. An ALS presentation with ragged-red fibers has been reported in five families and is associated with mtDNA mutations in some patients [108–110].

Other organelle systems under scrutiny in the molecular pathogenesis of ALS are endosomes and neurofilaments. Endosomes are a cargo delivery system from the cell surface to the interior. Recently discovered mutations in genes such as Alsin (ALS2), VAPB (vesicle-associated membrane protein-associated protein B) [77], VCP (valsolin-containing protein) [111] FIG4 (polyphosphoinositide phosphatase) [80], optineurin [81], and CHMP2B (charged multivesicular protein 2B) [82] support a theory of altered endosome mobility within cells in ALS. Motor soma and axons are rich in neurofilaments, microtubules, kinesins, and dyneins, all of which are critical in bidirectional axonal transport. However,

this system can be impaired in ALS not only via oxidative stress but also through (rare) mutations in genes for neurofilament heavy chains, peripherin, and tau. This process may precipitate a form of axonal strangulation that disrupts transport of cargo and indeed energy to where it is required both proximally and, especially, distally.

An *inflammatory process* likely plays an important role in the cell injury process in ALS. Studies of mutant SOD1 models have yielded evidence of early activation of microglial cells, astrocytes, and an overall pro-inflammatory T-cell response [112]. Furthermore, it is known that certain viral infections and paraneoplastic inflammatory disorders can selectively damage motor neurons and cause an ALS-like presentation (polioviruses, HIV, West Nile virus, anti-Hu antibody syndrome). This body of evidence suggests some promising therapeutic targets despite the fact that anti-inflammatory therapeutic trials have disappointed to date.

The pathological hallmark of ALS is the presence of the ubiquitinated intracellular inclusion body in motor neurons and glial cells; TDP-43 (43 kDa transactive responsive sequence DNA-binding protein) is normally a largely nuclear protein and is important in transcription, splicing, and micro RNA processing. TDP-43 is the major protein in sporadic ALS but it is mislocalized so that it mostly lies in the cytoplasm in the form of a *protein aggregates*. This type of protein mislocalization has been observed in many other neurodegenerative disorders such as Huntington's disease and the dominantly inherited spinocerebellar ataxias. It is also seen in some forms of familial ALS including those related to TDP-43, SOD-1, FUS, and ubiquilin (see "Familial ALS"). The accumulation of misfolded cytoplasmic proteins into aggregates may, at least initially, be a normal cytoprotective process in the cell mediated via the endoplasmic reticulum unfolded protein stress response. How these protein aggregates cause ALS is still unclear, but it is likely through an imbalance in lost nuclear function in concert with disruption in cytoplasmic function.

Many of the recent studies in ALS report genetic disorders that involve RNA regulatory genes such as TDP-43, FUS, ANG [113], and SETX which in turn support an evolving theory of *aberrant RNA metabolism* in the pathogenesis of this disease (see Table 20.3 with genetic mutations and their gene functions). Various processes may be involved from regulation of transcription to alternative splicing and mRNA transport.

Pathology

Gross pathologic specimens may exhibit atrophy of the motor cortex together with grayness and atrophy of the ventral spinal roots. There may be a gray appearance to the lateral columns of the spinal cord suggesting sclerotic changes caused by gliosis. In addition, there may be gross muscle atrophy. Microscopically, there is evidence of both upper and lower motor neuron loss. As such, there is some degree of loss of large motor neurons of the anterior horns of the spinal cord and/or brainstem motor nuclei (V, VII, IX, X, and XII) and loss of large pyramidal cells in the motor cortex and/or large myelinated axons of the corticospinal tracts. Degeneration of the corticospinal tracts occurs at the same level, and both normal and abnormal neurons are intermixed, reflecting different stages of neuronal degeneration. Lipofuscin accumulation and loss of Nissl substance is seen in degenerating neurons.

At the cellular level, ALS is characterized by the abnormal accumulation of insoluble ubiquitinated proteins in the cytoplasm of degenerating motor neurons [91, 114, 115]. These ubiquitin-immunoreactive inclusions, most common in lower motor neurons, are a highly sensitive and specific marker for ALS. In the past 5 years, the TAR DNA-binding protein, TDP-43, has been identified as a major component of the neuronal inclusions in sporadic ALS (see Fig. 20.3), as well as in the most common pathological subtype of frontotemporal dementia (frontotemporal lobar dementia with ubiquitinated inclusions [FTLD-U]) [54].

In combination with recent studies showing both clinical and pathological overlap between ALS and frontotemporal dementia, these findings support the view that sporadic ALS and some FTD represent a spectrum of neurodegenerative disease linked mechanistically to pathological TDP-43 (see Fig. 20.4 a, b).

A recently described hexanucleotide intronic expansion of the GGGGCC hexanucleotide repeat within the *C9ORF72* gene on chromosome 9 underlies a large proportion of familial ALS and FTD in addition to apparently sporadic disease [55]. These *C9ORF72* cases demonstrate features of a relatively rapidly progressive, but otherwise typical, variant of amyotrophic lateral sclerosis associated with familial and sporadic presentations. All show classical amyotrophic lateral sclerosis pathology, but extra-motor pathology in the frontal cortex and the hippocampal CA4 subfield neurons distinguishes *C9ORF72* cases. Inclusions in CA4 neurons, absent in non-*C9ORF72* cases, indicate that this pathology predicts mutation status [57, 116]. Although the mechanism is not clear, phenotype is determined by initial location and spread of degeneration [59].

Diagnosis

The Clinical Examination

The diagnosis of ALS is largely made on the basis of the clinical examination, with ancillary testing used to confirm the clinical suspicion and to refute alternative diagnoses.

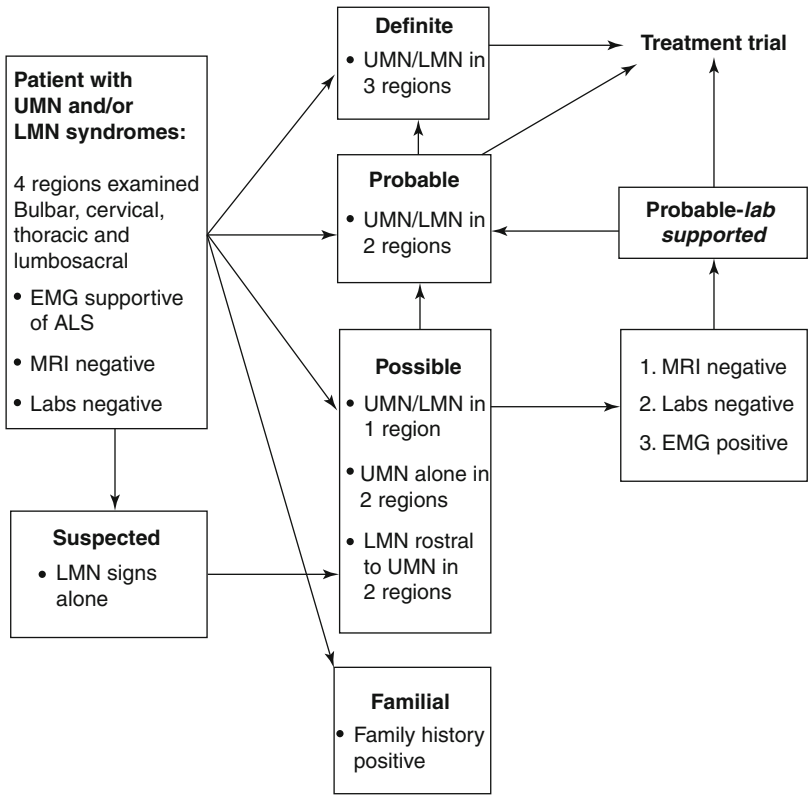

Fig. 20.5 Simplified diagnostic algorithm for the diagnosis of amyotrophic lateral sclerosis. Currently, neuroimaging and blood testing are used as tests to exclude other diagnoses. The electrodiagnostic examination is an ancillary test to aid in making the diagnosis. Regular reexamination is critical (For a detailed review, see Ref. [117] (World Federation of Neurology, Revised Criteria))

A meeting of the World Federation of Neurology at El Escorial, Spain, provided a set of clinical, electrodiagnostic, and pathological criteria for the diagnosis of ALS. The clinical criteria divide candidates into those with *definite, probable, possible,* and *suspected* ALS, based upon the particular pattern of LMN and UMN signs seen in bulbar, cervical, thoracic, and lumbosacral regions (Fig. 20.5). A further review of the criteria, carried out at Airlie House, includes the criterion of spread of disease from region to region and spread within a region [118]. In addition, these criteria demand an absence of electrodiagnostic, pathologic, or radiologic evidence in support of other diseases that may mimic ALS. These criteria have proved important in research and clinical fields, allowing accurate research trial selection and assistance in the day-to-day management of patients.

Definite ALS implies that both UMN and LMN signs are seen together in at least three separate central nervous system regions. *Probable* ALS refers to the presence of UMN and LMN signs in only two regions wherein the UMN signs lie rostral to the LMN signs. If only one region is affected or UMN signs are seen alone in one region with additional electromyographic (EMG) evidence of LMN dysfunction in two regions, the clinician may use neuroimaging and clinical laboratory testing to exclude alternative diagnoses and classify the patient as *probable-laboratory-supported* ALS. Clinically suspected ALS refers to a pure LMN presentation and is regarded as insufficient to allow patient inclusion in a research study.

The revision of the original criteria was implemented to allow earlier access of patients into clinical trials and highlights the importance of EMG and ancillary testing in the diagnostic work up of the candidate patient. There are occasions when UMN and LMN signs are found in only one region and ancillary tests fail to support a diagnosis of ALS. Such patients fall into the *clinically possible* category but follow-up evaluation must be performed to assess for disease progression at which time the patient may be upgraded to a probable or definite category.

Electrodiagnostic Studies

The electrodiagnostic (EDX) examination is an indispensable part of ALS evaluation, essentially serving as an extension of the clinical examination and most useful in identifying LMN dysfunction. Not only may EDX reveal characteristic changes in those regions clinically manifesting signs but also serves to disclose asymptomatic areas of involvement. Since the 1960s, the "Lambert criteria" have aided the electrodiagnostician in making the diagnosis of ALS [119]. These criteria include (1) normal sensory nerve action potentials (SNAPs), (2) motor conduction velocities no less than 70 % of the lower limit of normal values for age, and (3) fibrillation and fasciculation potentials in bulbar and/or limb muscles with reduced number of motor unit action potentials (MUAPs) and increased duration and amplitude.

However, only more advanced patients may meet such criteria, potentially excluding some patients from therapeutic trials. Thus, new criteria were devised at a meeting in El Escorial, Spain, in 1990, which, upon critical review, were later modified [118].

Motor and sensory conduction studies are part and parcel of the EDX examination in ALS and are principally used to exclude alternative diagnoses. Characteristically, the SNAPs are normal. However, coexistent entrapment neuropathies, peripheral polyneuropathies, and the normal effects of aging may reduce SNAP amplitudes. With significant axon loss, low compound muscle action potential (CMAP) amplitudes with modest degrees of slowing may be found. When widespread, this "generalized low motor-normal sensory" pattern is characteristic of more advanced ALS and often portends a worse prognosis [119, 120]. However, it is not specific for the diagnosis and may be seen in spinal muscular atrophies, diffuse myelopathies, certain neuromuscular transmission disorders, polyradiculopathies, and myopathies. Of interest is the finding of the "split hand," i.e., low-amplitude median and ulnar CMAPs recorded from the thenar eminence and first dorsal interosseous muscles, respectively, with a normal or near normal ulnar CMAP amplitude recording from the hypothenar eminence. A possible explanation for this pattern is relative increased cortical representation of the thenar eminence musculature, but it is also possible that the neurons innervating these muscles are more liable to oxidative stress [121]. Median distal motor latencies may also be prolonged out of proportion to the degree of axon loss, which probably reflects the relatively slow conduction along the terminal axons of collateral sprouts. As with conventional motor conduction studies, F-wave latencies remain within normal limits until significant degrees of axon loss have occurred, and, with progressive motor axon loss, they may disappear altogether.

On needle EMG of affected muscles, features of both active and chronic denervation must be observed. Active denervation consists of fibrillation potentials and positive sharp waves, whereas chronic denervation consists of MUAPs that are increased in duration, occasionally increased in amplitude, and often polyphasic. In addition, these MUAPs usually fire at a rapid rate (>10 Hz) unless there is significant upper motor neuron disease, wherein slower rates of firing may occur. Moment-to-moment MUAP amplitude variation, representing motor unit instability, may often be appreciated. Fasciculation potentials are a characteristic feature, seen in almost all patients; they typically occur in a widespread distribution and often have an abnormal configuration (depending on the motor unit generating them). If fasciculation potentials are not readily detected during the EDX examination, considerable doubt must be cast upon the diagnosis. The Awaji algorithm has been devised to increase the importance of fasciculation potentials in the diagnosis of suspected ALS and is particularly helpful in the early diagnosis of bulbar-onset disease. The algorithm uses fasciculations as evidence of active denervation as long as the muscle that is being studied shows additional chronic neurogenic change [122–124]. Neither fibrillation nor fasciculation potentials are easily appreciated in the tongue, as it is difficult to achieve adequate relaxation, and the MUAPs normally appear rather similar to fibrillation potentials in terms of both their size and configuration. Ultrasound of the tongue may prove to be a useful test to diagnose fasciculations not only in the tongue but also in other muscles [125]. Repetitive discharges, also known as doublets, are a particularly frequent finding in ALS where the interval between the first and second waveform is short but variable suggesting that both are derived from the same cell soma. It is postulated that they represent hyperexcitability of the cell membrane.

As in the clinical examination, the EDX features must be observed in a certain topographical distribution. In fact, none of the previously described EDX findings are specific for ALS. Rather, it is the widespread pattern of involvement that is characteristic, affecting multiple segments of the neuraxis with progression over time. Changes should be found in at least two of the four regions (bulbar, cervical, thoracic, and lumbosacral regions). In cervical and lumbosacral regions, at least two muscles derived from different roots and peripheral nerves must be involved. Abnormalities in the opposite limb should only be included if they involve a separate spinal cord segment. When the bulbar region is assessed, changes must be observed in at least one muscle (including tongue, jaw muscles, and facial muscles). Similarly, if one examines the thoracoabdominal segments, one should demonstrate EDX changes in abdominal muscles or in a paraspinal muscle at or below the T6 level. Evaluation of higher thoracic segments may be misleading as denervation changes derived from cervical segments may manifest as far caudally as the T6 level. The EDX examination should ideally be performed on three or more regions and should assess all the major segments in the limbs examined. In conjunction with the inclusive criteria as described previously, there are a number of EDX findings considered incompatible with the diagnosis of ALS, including marked conduction slowing, conduction block and abnormal sensory responses otherwise unexplained by advanced age or coexisting neuropathy.

A number of special EDX techniques may be employed in the evaluation of patients with suspected ALS; these techniques have been helpful as outcome measures in the assessment of efficacy in therapeutic trials. Manual and computer-based motor unit number estimation (MUNE) techniques have been used to monitor disease progression (see Chap. 9) and can help distinguish subtypes of ALS [126]. Swash and de Carvalho devised the Neurophysiological Index derived from the CMAP, distal motor latency, and

F-wave frequency to determine rapid from slowly advancing disease [127]. Repetitive stimulation studies, although not routinely performed, may show a decrementing response (albeit usually less dramatic than that seen in myasthenia gravis) that is likely due to impaired neuromuscular transmission at the immature nerve terminals of collateral sprouts. Similarly, increased fiber density, abnormal jitter, and blocking may be detected during single-fiber EMG [128]. Macro-EMG refers to the use of a specialized recording electrode that samples all muscle fibers within a single motor unit and estimates the degree of motor unit loss and the extent of collateral reinnervation. Other methods for evaluating chronic partial denervation include turns/amplitude analysis, EMG decomposition, and quantitative motor unit potential analysis (see Chap. 9). Transcranial magnetic stimulation (TMS) studies can provide useful information in assessing the central motor pathways in ALS. Many, but not all, patients with sporadic ALS have low motor evoked potential amplitudes on TMS, with prolongation of both the response threshold latencies and central motor conduction times. A gradual reduction in the motor evoked potential amplitudes over time is a particularly useful way to determine upper motor neuron system involvement in apparently pure lower motor neuron disease and also is a valuable technique to monitor disease progression [129].

Neuroimaging

The most important role for neuroimaging remains exclusion of structural, inflammatory, or infiltrative disorders that may mimic ALS. All patients should undergo brain and spinal cord imaging. However, in addition, more sophisticated techniques may allow discernment of abnormal signal in the motor tracts in ALS. In patients with more severe disease, signal change reflecting wallerian degeneration may be visualized on proton density-weighted MRI (Fig. 20.6). FLAIR and T2-weighted fast-spin echo sequences are less specific in detection of such corticospinal tract signal changes. Nonspecific atrophy of the frontal and parietal cortex may also be seen. Surface-based cortical morphology analyses performed on structural 3T MRI data reveal cortical thinning of the primary motor cortex, which may be a diagnostic marker for upper motor neuron degeneration in ALS; relative thinning in temporal regions has been associated with a rapidly progressive disease course [130]. The search for ALS biomarkers has led to the investigation of other imaging techniques such as magnetization transfer ratio (MTR) imaging, magnetic resonance voxel-based morphometry, magnetic resonance spectroscopy, and diffusion tensor MRI (DTI). The latter demonstrates that corpus callosum involvement is a consistent feature of ALS, with extension of reduced fractional anisotropy in primary motor cortices, supplementary motor regions, and in temporal lobe regions. Whole brain-based and DTI tractography analysis can define a distinct white-matter pathoanatomy of different MND geno-/phenotypes [131]. Furthermore, DTI of white-matter tracts has also demonstrated structural differences between ALS and PLS [132], and differences in intracerebral corticospinal tract changes of patients with familial and apparently sporadic ALS have facilitated study of genotype/phenotype interactions [133]. FDG-PET studies reveal frontal and temporal hypometabolism (parietal hypometabolism often also present), with relatively preserved perirolandic metabolism [134].

Although functional imaging with blood oxygenation level–dependent (BOLD) functional MRI and magnetoencephalography may reveal abnormal activity in motor and non-motor areas in ALS, further studies are needed to determine their role in UMN assessment [135, 136]. Additional research is also necessary to clarify the role of transcranial magnetic stimulation (TMS), alone or in combination with DTI, in the evaluation of the UMN system.

Laboratory Testing

There is no serologic test to diagnose sporadic ALS. Indeed, normal results are supportive of the diagnosis. Testing of serum, urine, and CSF is primarily performed to exclude alternative diagnoses, the array of tests being tailored to each particular presentation (see section on "Differential Diagnosis"). Nevertheless, there are certain blood tests performed at initial evaluation. These include complete blood count, chemistry panel (including calcium, phosphate, and magnesium), creatine kinase (CK), VDRL, HIV, erythrocyte sedimentation rate, serum protein immunofixation or immunoelectrophoresis and anti-GM1 antibody assay, angiotensin-converting enzyme (ACE) and glycosylated hemoglobin (HbA1c), thyroid function studies including thyroid-stimulating hormone, serum parathormone (if calcium is raised), and vitamin B12 levels. Anti-neuronal antibody testing, to exclude a paraneoplastic syndrome, should be considered, as paraneoplastic encephalomyelitis may present as myelopathy with motor neuron symptoms alone, resembling ALS (although sensory and autonomic features may occur later). Associated anti-neuronal antibodies, including anti-amphiphysin, anti-Hu, anti-Ma, and anti-CRMP5, may be detected [137, 138]. By definition, these tests should be normal except for possible modest elevation of CK which commensurate with the degree of muscle atrophy in early disease in active males.

Patients older than 50 years and smokers of any age should have a chest radiograph and fecal occult blood testing. If any chest lesion is identifiable, or if the presentation is subacute with atypical features such as sensory loss, a

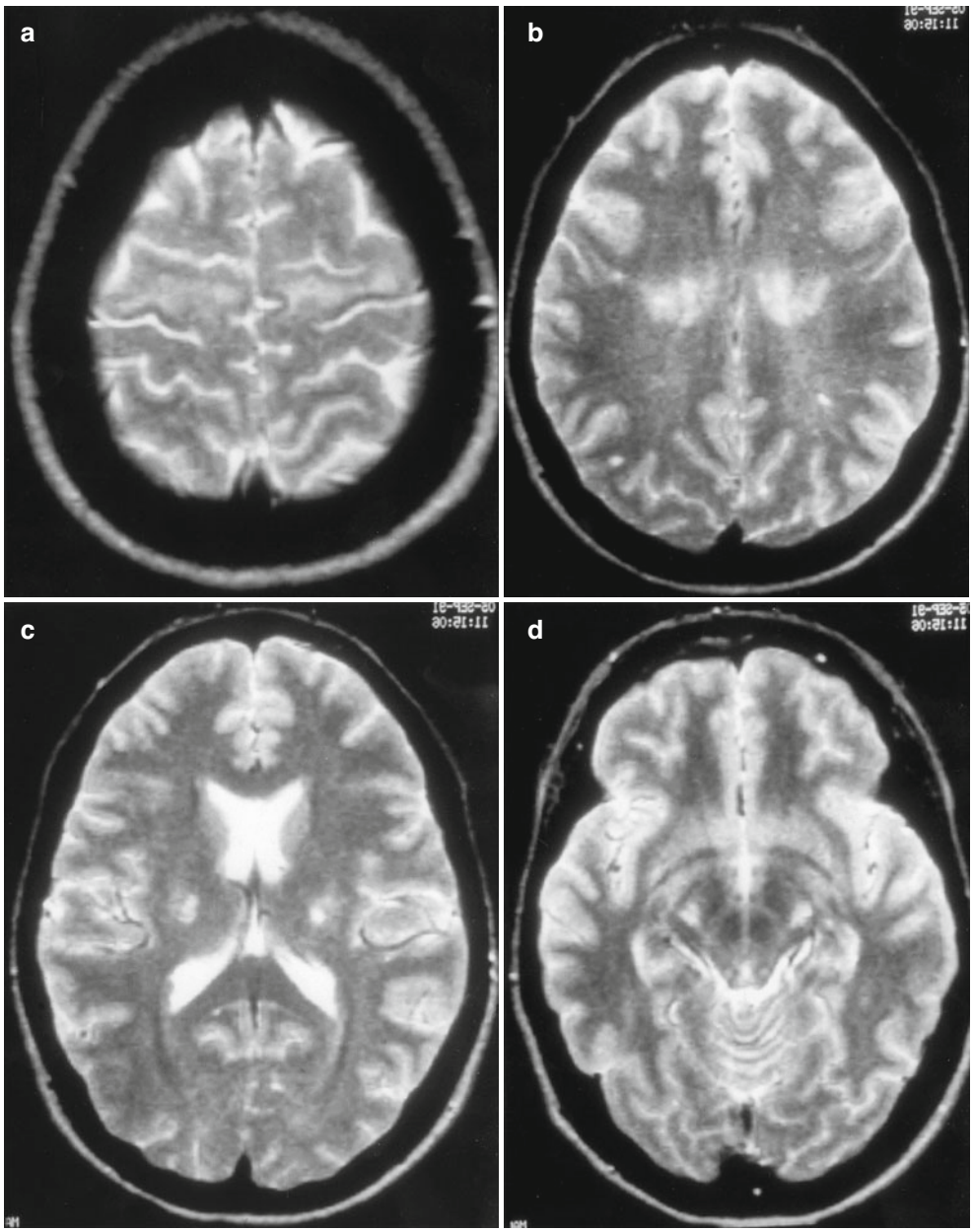

Fig. 20.6 (**a**–**d**). T2-weighted cerebral magnetic resonance images at four levels in a female patient with rapidly progressive amyotrophic lateral sclerosis. Note the increased signal intensity in the corticospinal tract as it extends from the motor cortex to the brainstem

paraneoplastic anti-neuronal antibody screen, particularly anti-Hu antibody levels, should be performed. Some patients may have clinical features suggesting a neuromuscular junction disorder and should have testing for antibodies against the acetylcholine receptor or voltage-gated calcium channel. If there is biochemical evidence of adrenal insufficiency, it is prudent to obtain a very long-chain fatty acid (VLCFA) assay to investigate for possible adrenomyeloneuropathy. Young-onset ALS with atypical clinical features such as early dementia, cramps, and tremor should prompt the physician to obtain a leukocyte hexosaminidase-A assay. Young age at onset, with perioral fasciculations and gynecomastia, should prompt genetic assessment for the trinucleotide repeat expansion on the androgen receptor gene associated with Kennedy's disease (spinobulbar muscular atrophy). If there is a positive family history of ALS or frontotemporal dementia in otherwise typical ALS, it is important to counsel the patient in preparation for appropriate mutation analysis. Reserve cerebrospinal fluid examination for cases with features suggestive of an infectious or infiltrative process such as lymphoma or basal meningitis or suspected CIDP. No specific features on muscle biopsy distinguish ALS from other neurogenic disorder. (It may reveal changes of chronic denervation and muscle fiber regeneration and, in long-standing patients, replacement of muscle fibers by fibro fatty tissue.) Thus, reserve biopsy for cases that are more suggestive of a myopathy.

Differential Diagnosis

Many diseases, both neurologic and systemic, may mimic ALS, making the differential diagnosis rather extensive. Depending upon the particular study, the misdiagnosis rate varies between 27 and 42 %, with more misdiagnoses occurring in patients over 60 years [139]. One may approach the differential diagnosis in terms of the anatomy, symptoms, or clinical presentation. For this discussion, we discuss the differential in terms of nervous system anatomy (Table 20.4).

Brain

Certain early manifestations of *Parkinson's disease* bear resemblance to ALS such as increased tone, hypophonia, sialorrhea, and dysarthria. However, tremor and response to levodopa help to distinguish the two conditions. Furthermore, the EMG fails to show widespread changes of denervation. Similarly, *multiple system atrophy (MSA)* may present with long tract signs and amyotrophy. However, ataxia, dysautonomia, sphincter disturbance, and oculomotor disturbances are common in MSA and rare in ALS. Also, there is evidence of external anal sphincter chronic denervation in MSA on needle EMG. *Spinocerebellar ataxia type 3 (Machado Joseph disease)* may exhibit spasticity and distal extremity wasting, usually with prominent extrapyramidal and oculomotor signs. Rarely, mild phenotypes of *Huntington's disease*, particularly when lacking a family history, may resemble ALS with increased tone and dysarthria. However, the progression of both disorders is dissimilar, and there are characteristic basal ganglionic MRI findings seen in Huntington's disease. *Stroke* with multiple subcortical ischemic lesions may produce marked pseudobulbar affect, weakness, and corticospinal tract signs, but MRI, especially T2-weighted and FLAIR images, should readily demonstrate these changes.

Polyglucosan body disease is a rare, late-onset, slowly progressive disorder characterized by combined UMN and LMN signs, cognitive decline, distal sensory loss, and disturbances of bladder and bowel function. MRI of the brain may reveal diffuse white-matter signal increase on T2-weighted images, but diagnosis is based on characteristic pathological changes in tissue from peripheral nerve, cerebral cortex, spinal cord, or skin. Axons and neural sheath cells contain non-membrane-bound cytoplasmic periodic acid–Schiff-positive polyglucosan bodies. Ultrastructural examination shows inclusions consisting of 6–8-nm branched filaments, most abundant in myelinated nerve fibers. In Ashkenazi Jewish patients (and one reported non–Ashkenazi Jewish patient), the disorder was caused by mutations of the glycogen-branching enzyme (GBE) gene, with subsequent deficiency of the protein product. However, adult polyglucosan body disease occurs in many different populations, and considerable molecular heterogeneity has been observed, with otherwise typical cases lacking GBE mutations despite deficiency of enzyme activity [140, 141]. Incidentally, two types of polyglucosan body may be seen in typical ALS—Lafora bodies and corpora amylacea—although neither could be considered characteristic pathological features.

Brainstem and Spinal Cord

Cervical spondylosis is probably the most important consideration in the differential diagnosis of ALS, and may closely mimic ALS, potentially presenting with asymmetric weakness of all extremities and UMN signs due to spinal cord compression and LMN signs due to foraminal stenosis. Lesions at the foramen magnum and various medullary lesions, such as infarct, syrinx, demyelination, and neoplasm, may simulate the bulbar presentation of ALS, rendering neuroimaging essential in the evaluation. Although *syringomyelia* may present with weakness and wasting, a characteristic pattern of dissociated sensory loss typically occurs and the disease progresses at a much slower pace in a generally younger population than ALS. A combination of UMN and LMN signs may be seen in *multiple sclerosis* in the setting of plaque formation at root exit zones. Characteristic MRI and CSF findings help to differentiate multiple sclerosis from ALS. Another consideration, in patients presenting in their third or fourth decade, is *adrenomyeloneuropathy*, a peroxisomal disorder caused by a defect in beta-oxidation of very long-chain fatty acids. Patients present with spastic paraparesis, areflexia, sphincter disturbance, and sensory loss. The diagnosis is established by demonstrating increased plasma levels of very long-chain fatty acids [142]. The prominence of sensory findings usually distinguishes ALS from subacute combined degeneration due to *vitamin B12 deficiency*. However, since patients may occasionally lack sensory features, it is prudent to routinely measure a vitamin B12 level to exclude this eminently treatable condition.

"Four-A" syndrome (Allgrove syndrome), a very rare autosomal recessive disorder that derives its name from the combination of achalasia, alacrima, adrenocorticotrophic insufficiency, and amyotrophy, can manifest from the first decade of life with dysphagia and adrenocortical insufficiency. A broad range of neurological problems can arise later in life including cognitive deterioration, optic atrophy, seizures, autonomic disturbance (dry mouth, postural hypotension, and syncope), and bulbospinal amyotrophy (amyotrophy of limbs and tongue, with tongue fasciculations and pyramidal signs) [143]. The AAAS gene is located on chromosome 12q13 and encodes *aladin* in the neuroendocrine system with

Table 20.4 Differential diagnosis of ALS

Anatomical location	Disorder	Test
Brain	Parkinson's disease	Levodopa
	Huntington's disease	MRI, CAG repeat
	Cerebrovascular disease	MRI brain
	Prion disease, HIV	EEG, CSF, biopsy
	Multiple systems atrophy	Autonomic testing
	Spinocerebellar atrophy	Genetic testing
Brainstem and spinal cord	Brainstem glioma, plaque, infarct	MRI
	Foramen magnum mass	
	Syringobulbia	
	Kennedy's disease	CAG repeat
	Spondylosis, syringomyelia, MS, SCDC, HTLV-1/2, HIV/2	MRI, EMG, CSF
	Adrenomyeloneuropathy	Serology, B12 levels
	Hereditary spastic paraparesis	VLCFAs Gene tests
Anterior horn cell	Spinal muscular atrophy	
	Kennedy's disease	CAG repeat, EMG
	Monomelic amyotrophy	
	Hexosaminidase A deficiency	Hexosaminidase A assay
	Post-polio syndrome	
	West Nile virus	WNV IgM serum and CSF
	Paraneoplastic	
		Anti-Hu, Anti-Ma, anti-amphiphysin
Root, plexus, and nerve	Radiculopathy	EMG, MRI
	Diabetic polyradiculoneuropathy	EMG, glucose
	Polyradiculopathy (CIDP, GBS, porphyria, HIV, CMV, lyme, syphilitic, postradiation)	EMG, labs, serology
	Neuralgic amyotrophy	
	POEMS, MMNCB, mononeuropathies	EMG
		EMG, SPI, anti-GM1
Neuromuscular Junction	Lambert–Eaton syndrome	Repetitive stimulation
	Myasthenia gravis	EMG, SFEMG, AchR AB assay
Muscle	Inclusion body myositis	Biopsy
	Oculopharyngeal dystrophy	GCG repeat, biopsy
	Myotonic dystrophy	CTG repeat,
	Isolated neck extensor myopathy	EMG
	Metabolic and congenital myopathies	EMG, Biopsy
Systemic	Hyperthyroidism	TSH, T4
	Hyperparathyroidism	$Ca^{++,}$ PTH assay
	Benign fasciculations	EMG
	Cramp–fasciculation syndrome	EMG
	Paraneoplastic syndrome	Anti-neuronal Abs, imaging, CSF

HIV human immunodeficiency virus, *MS* multiple sclerosis, *SCDC* subacute combined degeneration of the cord, *CK* creatine kinase, *HTLV-1* human T-lymphotropic virus, *VLCFAs* very long-chain fatty acids, *CIDP* chronic inflammatory demyelinating polyneuropathy, *GBS* Guillain–Barré syndrome, *CMV* cytomegalovirus, *SPI* serum protein immunofixation, *AchR AB* acetylcholine receptor antibody, *PTH* parathormone, *anti-neuronal Abs* anti-neuronal antibodies, *CSF* cerebrospinal fluid

roles in regulation of the cell cycle, cell signaling, and the cytoskeleton.

Both *hereditary spastic paraparesis* (HSP) and *tropical spastic paraparesis* should be considered in the differential diagnosis of slowly evolving spastic paraparesis. However, the former is differentiated by a family history together with very slow progression, sphincter disturbance, and an absence of LMN, bulbar, or respiratory involvement [144]. Tropical spastic paraparesis, a chronic myelopathy associated with human T-lymphotropic virus type 1 (HTLV1), presents in the third or fourth decade with UMN signs involving the bladder and lower extremities. Human T-cell leukemia virus

type 1 (HTLV-1) is a replication-competent human retrovirus associated with two distinct types of disease only in a minority of infected individuals: the malignancy known as adult T-cell leukemia (ATL) and a chronic inflammatory central nervous system disease HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-2 may also cause a similar myelopathy [145]. Antibodies against HTLV1 may be detected in serum and CSF, and MRI often shows evidence of demyelination. Another virus that should be considered is human immunodeficiency virus (HIV) which may present with a vacuolar myelopathy in the setting of a low CD4 count. However, both sensory and sphincter complaints are much more prominent in HIV myelopathy than in ALS.

Anterior Horn Cell

Although most *spinal muscular atrophies* (SMAs) are disorders of childhood and youth, some crossover with the ALS population exists in the form of juvenile-onset ALS and adult-onset SMA. Overall, the SMAs usually manifest with slowly progressive, symmetrical, proximal muscle weakness and atrophy without additional UMN signs (see Chap. 21). *Kennedy's disease*, or X-linked bulbospinal neuronopathy/spinal and bulbar muscular atrophy (SBMA), is a rare X-linked trinucleotide polyglutamine disorder, caused by an abnormally large expansion of tandem CAG (cytosine–adenine–guanine) repeats in exon 1 of the androgen receptor (AR) gene on chromosome Xq11-12 (see Chap. 22). It is characterized by degeneration and loss of lower motor neurons in brainstem and spinal cord and typically presents in males in the third or fourth decade with weakness and wasting of bulbar, facial, and limb girdle muscles; tremor; perioral fasciculations; mild cognitive impairment; sensory disturbance; and signs of endocrine dysfunction such as diabetes mellitus, gynecomastia, and testicular atrophy [146]. In normal individuals, the CAG repeat ranges in size between 9 and 36, and expansion over 38 and up to 62 is pathogenic [147]. Additional useful features that help to separate Kennedy's disease from ALS include a moderately high CK and low SNAPs. To confirm the diagnosis, a genetic test that detects the CAG repeat expansion of the androgen receptor gene is available.

ALS rarely occurs in an individual with a history of poliovirus infection.

A separate anterior horn cell disorder, the *post-poliomyelitis syndrome* (PPS), is a late consequence of prior infection with poliovirus (see Chap. 19). It typically presents, after a prolonged stable course following the original paralytic illness, as worsening of weakness in previously affected muscles and ill-defined pain in the low back, neck, and many joints together with significant fatigue, dizziness, and somnolence. While many of these complaints are shared with ALS, there is a paucity of UMN signs and the rate of progression in PPS is very slow. Criteria for the diagnosis of PPS include a history of paralytic poliomyelitis, partial or complete recovery of neurological function followed by a period of stability (usually decades), persistent new muscle weakness or abnormal muscle fatigability, and exclusion of other causes. The condition is thought to occur as a result of distal degeneration and premature neuronal dysfunction of preexisting, enlarged polio-affected motor neurons. Potential contributing factors include aging (with motor neuron loss), overuse, and disuse. Although no specific treatment exists, a multidisciplinary management program can be useful in modifying symptoms [148]. West Nile arthropod-borne flavivirus infection can cause epidemics of meningitis and encephalitis. A small proportion of patients (<1 % overall but 10–50 % with neuroinvasive disease) develop a polio-like, and sometimes painful, disorder characterized by acute asymmetrical flaccid paralysis, due to viral infection of anterior horn motor neurons in the spinal cord that can precipitate respiratory failure and even death [149].

Acidic-hexosaminidase deficiency, or Hex A deficiency, a GM2 gangliosidosis that causes a recessively inherited progressive neurologic disorder, may present from childhood to the fifth decade and may resemble ALS. It is most often, but not exclusively, seen in the Ashkenazi Jewish population [150]. The enzyme has two subunits, alpha and beta, and hydrolyzes lysosomal GM2 gangliosides in neuronal membranes. Complete absence of the alpha polypeptide results in Tay–Sachs disease, which manifests in infancy with encephalopathy, myoclonic seizures, macular cherry-red spots, and death. Compound heterozygotes with less severe mutations in one of the alpha subunits resulting in a deficiency of the enzyme develop later-onset disease characterized by elements of LMN weakness, dysarthria, cerebellar ataxia, cramps, spasticity, cognitive deterioration, and tremor. EDX studies may reveal prominent complex repetitive discharges on needle EMG and abnormal SNAPs. Overall, this rare disorder should be considered in atypical cases of ALS, in particular in a young person. It can be confirmed by serum analysis of Hex A activity in leukocytes and Hex A gene mutation analysis [151].

It may be difficult to differentiate monomelic-onset ALS from benign *monomelic amyotrophy* (MMA), a condition originally reported in Japan and India, which typically presents as focal atrophy of one limb, or part thereof, predominantly affecting young men in their second and third decades. Segmental anterior horn cell involvement causes wasting and weakness of predominantly one upper or lower limb, without evidence of sensory dysfunction. Reflexes may be either reduced or normal, and fasciculations are prominent. Progression may occur for a few years with eventual stabilization [152]. Needle EMG may reveal relatively sparse

fibrillation potentials in affected muscles along with neurogenic changes in both affected and clinically uninvolved limbs. MRI may reveal focal cervical cord segmental atrophy and ventral root atrophy if performed late in the disease.

Paraneoplastic disease particularly that associated with lymphoma may present subacutely with LMN manifestations arising typically in the lower extremities, although there are rare patients that present with a combination of both UMN and LMN signs, thus bearing close resemblance to ALS. One should consider this diagnosis if a paraprotein is detected in the blood. Apart from lymphoma, a similar motor neuron disease may be the presenting manifestation of Waldenstrom's macroglobulinemia and myeloma. Paraneoplastic encephalomyelitis may present as a transverse myelopathy with motor neuron symptoms alone, resembling ALS (although sensory and autonomic features and ataxia may occur later). Associated anti-neuronal antibodies, including anti-amphiphysin, anti-Hu, anti-Ma, and anti-CRMP5, may be detected. The anti-amphiphysin presentation is usually PLS-like, but with rapid deterioration (thus unlike true PLS) and the anti-Ma, associated disorder varies but can be like PMA [137, 153]. The association of ALS with solid malignancy is somewhat unclear; one study reported a frequency of tumor in ALS patients more than twice that of controls, but patients with both ALS and cancer do not differ clinically from patients with ALS without cancer. Furthermore, with rare exceptions, ALS does not respond to tumor treatment [154–156].

Radiculopathies, Polyradiculoneuropathies, and Polyradiculopathies

Compressive radiculopathy must be considered in the differential diagnosis of any patient presenting with focal LMN signs in a limb. Foot drop may either be the first symptom of ALS or an L5 radiculopathy, and hand interosseous wasting may occur in both ALS and C8 radiculopathy. While pain and sensory loss may serve as clues to the presence of a nerve root lesion, some patients with radiculopathy present with weakness alone. EDX studies reveal changes restricted to a particular root distribution, and MRI or CT myelography reveals nerve root compromise in the clinically manifesting root distribution. *Neoplastic* (such as lymphoma, or leukemia related), *radiation-induced,* and *infectious* (viral and spirochetal) *polyradiculopathies* may superficially mimic ALS. Additional historical clues and characteristic signs such as skin or retinal changes may point to alternative diagnoses, with appropriate serology and CSF analysis required to identify the specific cause. *Diabetic polyradiculoneuropathy* is a rare condition that may present as progressive asymmetric weakness in the proximal lower extremities thus simulating PMA (see Chap. 31). In its most severe form, diabetic cachexia, multiple roots extending from the cervical to sacral areas are involved, but pain and sensory loss are typically prominent findings and EDX often reveal associated polyneuropathy.

Neuropathies and Plexopathies

Multifocal motor neuropathy with conduction block (MMNCB) is a rare disorder (see Chap. 22), characterized by onset of focal motor weakness, usually in a distal upper extremity. Those sites typically involved in entrapment neuropathies are spared and both fasciculations and cramps are common. Progression is very slow, over months or even years. An important clue to the diagnosis is the absence of muscle atrophy despite very significant weakness, until late in the disease course. The pattern of motor weakness is typically restricted to multiple separate peripheral motor nerves with a striking absence of sensory involvement. As the name implies, MMNCB is defined by demyelinating conduction block in affected motor nerves [157]. A variable percentage of patients have a high titer of serum antibodies against GM1 ganglioside, a neuronal membrane glycolipid present in high concentrations at nodes of Ranvier. However, these antibodies are not specific for MMNCB and their absence does not rule out the diagnosis.

Up to 10 % of ALS patients have a monoclonal gammopathy in the absence of any disease association, such as neoplasm or motor neuropathy with conduction block, although only about half of these patients have high titers. Of particular interest, however, is the motor neuropathy seen with *POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)* (see Chap. 30). This disorder can lead to a wasted appearance as seen in ALS, but may have tremor, papilledema, but no UMN features. One should perform a skeletal survey to seek out an osteosclerotic myeloma lesion, and CSF analysis may reveal elevated protein levels (often in excess of 100 mg/dl). The EDX studies are invaluable in revealing a sensory and motor polyneuropathy pattern characterized by generalized slowing of motor conduction velocities. Because of their demyelinating features on EDX, POEMS and MMNCB may closely resemble *chronic inflammatory demyelinating polyneuropathy (CIDP),* albeit with less sensory phenomena. CIDP may be difficult to distinguish clinically from ALS, although it classically features hypo-/areflexia and sensory changes and also is associated with elevated CSF protein concentrations. Yet again, performing EDX studies is essential to identify the characteristic changes of CIDP. In general, differentiating *Guillain–Barré syndrome (GBS)* from ALS poses less of a problem; there are unusual patients that lack sensory features and progress asymmetrically in a manner similar to PMA. Also, there are acute axonal variants of GBS that affect predominantly motor fibers (acute motor axonal neuropathy). However, the fast rate of progression of GBS

and reflex loss serve as diagnostic clues, and ancillary testing with EDX studies and CSF clarifies the issue.

Neuralgic amyotrophy or Parsonage–Turner syndrome, also known as brachial neuritis, may resemble limited forms of ALS such as monomelic-onset disease. This disorder, however, is classically preceded by significant deep, aching pain in the affected limb and shoulder that lasts several days and then fades away only to be replaced by motor weakness. The nerves involved are all largely motor in nature, often including one or more of the following: the long thoracic, suprascapular, axillary, anterior interosseous, and phrenic nerves. The EDX examination may reveal bilateral upper limb neurogenic changes on needle EMG, even in the presence of unilateral symptoms, but they are not as widespread as seen in ALS. In fact, involvement of motor nerve fibers can be curiously patchy, such as severe changes in infraspinatus but sparing of supraspinatus, although both muscles are innervated by the same nerve. This disorder usually improves spontaneously, but recovery can take months and there is recent evidence that early treatment with immune therapy may help speed recovery [158, 159].

Disorders of the Neuromuscular Junction

Myasthenia gravis (MG), an autoimmune disease characterized by antibodies directed against the acetylcholine receptor, may present with weakness of bulbar and neck extensor muscles without extraocular manifestations, thus mimicking bulbar-onset ALS (see Chap. 48). Patients may also present with significant respiratory compromise. Clues to the diagnosis of MG include the absence of UMN signs and fasciculations. One can confirm the diagnosis of MG by checking acetylcholine receptor antibodies and performing repetitive nerve stimulation looking for a decremental response and/or single-fiber EMG studies looking for abnormal jitter. However, in more severe patients of ALS, a decremental response may occur, albeit to a lesser extent than typical of MG. Similarly, single-fiber EMG studies may reveal increases in jitter and in fiber density in ALS just as in MG. To further blur the picture, edrophonium testing may be positive in both conditions. On the other hand, it is very rare to detect fibrillation potentials in MG, and fasciculations are not a feature of MG unless patients are overtreated with cholinergic agents. *Lambert–Eaton myasthenic syndrome* (LEMS) is an autoimmune disorder, caused by antibodies directed against voltage-gated calcium channels on the presynaptic nerve terminal (see Chap. 49). It typically presents with limb girdle weakness without atrophy or fasciculations and often with associated signs of autonomic dysfunction such as dry mouth and impotence. One of the characteristic features of LEMS is the transient increase in muscle strength and deep tendon reflexes after a brief contraction. On EDX examination, there may be generally low-amplitude CMAPs as may be seen in advanced ALS. However, EDX studies distinguish LEMS from ALS by the demonstration of post-tetanic facilitation and by the absence of fibrillation and fasciculation potentials [160].

Myopathies

Inclusion body myositis (IBM) may mimic ALS, sharing distal muscle involvement, painless asymmetric weakness, and difficulty swallowing. However, fasciculations are conspicuously absent and there are no UMN signs [161]. The CK levels are often similar in both conditions (slightly elevated or normal), but needle EMG features predominantly myopathic rather than neurogenic changes in IBM. Muscle biopsy is required to confirm the presence of rimmed vacuoles and intranuclear inclusions, the characteristic abnormalities of IBM. In addition to IBM, there are *sporadic and inherited distal myopathies* that appear between the ages of 40 and 60 years and present as weakness and wasting of distal upper and lower extremities; they may be diagnosed by EMG and muscle biopsy. Distal muscle weakness is also characteristic of *myotonic dystrophy,* but there are several clinical features such as a distinctive facial appearance, myotonia, and systemic abnormalities including cataracts, frontal balding, and diabetes mellitus, which help to lead to the correct diagnosis. Needle EMG reveals prominent myotonic discharges. Testing for the presence of an abnormally large expansion of the CTG trinucleotide on the serine–threonine protein kinase gene located on chromosome 19 confirms the diagnosis. *Oculopharyngeal muscular dystrophy*, an uncommon myopathy caused by a trinucleotide repeat expansion, may mimic progressive bulbar palsy (see Chap. 60). Indeed, as the disease advances, weakness spreads to the shoulder girdle, but the condition usually involves the eyelids and extraocular muscles, thus setting it apart from ALS and its variants. A muscle biopsy may be required to confirm the diagnosis, especially in those rare patients that present with dysphagia and subtle extraocular manifestations. Another interesting disorder, *isolated neck extensor myopathy*, presents in older individuals with dropped-head syndrome and is associated with signs of active denervation in cervical paraspinal muscles. This may be initially mistaken for ALS, but the weakness does not spread to other regions.

Systemic Disease

Hyperthyroidism may present with corticospinal tract signs, fasciculations, weight loss, and weakness, thus simulating ALS. However, there usually are additional signs such as heat intolerance, anxiety, tremor, tachycardia, insomnia, and goiter that lead to the correct diagnosis. It is prudent to include a thyroid-stimulating hormone assay in the screening

evaluation of ALS. *Hyperparathyroidism* may present with clinical weakness and even a myopathy and as such may mimic the PMA form of ALS. There may be a high level of ionized calcium, and the diagnosis is confirmed by elevated serum parathormone.

Benign fasciculations typically occur in people under the age of 30 years, and often have a relapsing–remitting course over months or years without any other abnormalities. They occur in a wide variety of disorders and are frequent in the normal population. Fatigue, stress, alcohol, caffeine, and vigorous exercise exacerbate them. Similarly, one must be able to recognize *cramp–fasciculation syndrome*, a benign condition that may be sporadic or inherited, manifests as cramps and fasciculations in the calves, and responds to carbamazepine. There are certain features on needle EMG that reportedly serve to differentiate benign from ALS-associated fasciculations. The latter tend to have a more complex waveform and may be induced by joint displacement, and benign fasciculations, as suggested by the name, are not associated with clinical and EDX features of a widespread disorder of anterior horn cells.

As already outlined, motor neuron disease may rarely occur as a paraneoplastic phenomenon. Patients present with features typical of pure ALS or manifest as PMA or PLS. Other motor neuron manifestations may represent only one part of a larger paraneoplastic syndrome, such as anti-Hu antibody–associated encephalomyelitis, presenting initially as a transverse myelopathy with motor neuron symptoms alone, resembling ALS. Atypical features (sensory and autonomic features and ataxia) may occur later on, and associated anti-neuronal antibodies, including anti-amphiphysin, anti-Hu, and anti-CRMP5, may be detected. Most paraneoplastic motor disorders are typically unresponsive to treatment of the underlying malignancy.

HIV infection may also mimic ALS clinically. A retrospective review of 1,700 cases of HIV-1-infected patients with neurological symptoms identified six cases presenting as a reversible ALS-like syndrome representing a 27-fold increased risk of developing an ALS-like disorder in that particular HIV-1 patient population [162]. Overall, patients were younger than the typical ALS population, and onset was characteristically in a monomelic pattern followed by rapid spread to other regions over a period of weeks, characterized by UMN and LMN involvement, with fasciculations, cramps, and bulbar symptoms. Two patients also had rapidly progressive dementia, suggesting an additional diagnosis of AIDS–dementia complex. Sensory and sphincter disturbances were not apparent. CSF protein levels were sometimes mildly increased, and lymphocytic pleocytosis was evident in three patients, but all remaining laboratory results (HIV-1 seropositivity apart) were negative. EDX revealed widespread anterior horn cell disorder in the absence of demyelinating conduction block, and MRI in one patient showed diffuse white-matter signal increase suggestive of AIDS–dementia complex. In each case, antiretroviral therapy was beneficial either in stabilizing or curing the disease, but subsequent cases have been described that failed to recover despite treatment [117]. Another case report found similar clinical features in a 32-year-old HIV-positive patient who responded to antiretroviral therapy, and resolution of motor symptoms coincided with a lack of detectable HIV in plasma and CSF. MRI abnormalities also resolved almost completely [163]. Flail-arm ALS-like variants have also been described in HIV, with MRI signal changes in the anterior cervical spinal cord.

Table 20.5 Prognostic indicators in ALS

Better prognosis	Worse prognosis
Younger (<50 years)	Older
Spinal onset	Bulbar onset
Progressive muscular atrophy	Dyspnea onset
Primary lateral sclerosis	Some familial forms
Flail arm	
Slow deterioration	Rapid deterioration
Normal compound muscle action potentials	"Low motor–normal sensory"
No decrement on repetitive nerve stimulation	Decrement on repetitive nerve stimulation
Mild at diagnosis	Severe at diagnosis
Long duration from onset to diagnosis	Short duration from onset to diagnosis
Well nourished	Malnourished
Psychological well-being	Psychological distress
Normal serum chloride	Low serum chloride
Fasciculations mild or absent	Fasciculations widespread
Attends multidisciplinary care	

Natural History and Prognosis

Despite the recent advances in understanding the natural history of ALS, it remains difficult to accurately predict the course and prognosis in individual patients (Table 20.5) [16]. Up to 30 % of anterior horn cells may be lost by the time a patient with ALS actually presents with weakness, which suggests that ALS may be subclinical for months or even years before symptom onset. During this preclinical stage, the rate of denervation may be balanced by the rate of collateral reinnervation, but the rate of denervation eventually supercedes. Original thinking was that the pattern of decline was linear from onset (Fig. 20.7) [6, 16], but recent work has shown that deterioration in ALS is nonlinear: the early and late phases of the illness show the most rapid rates of decline. Older age and bulbar signs are associated with a steeper decline and, along with more rapid initial rate of decline, predict survival [164]. When onset is in one arm, the progression of disease is typically to the contralateral arm, then the ipsilateral leg,

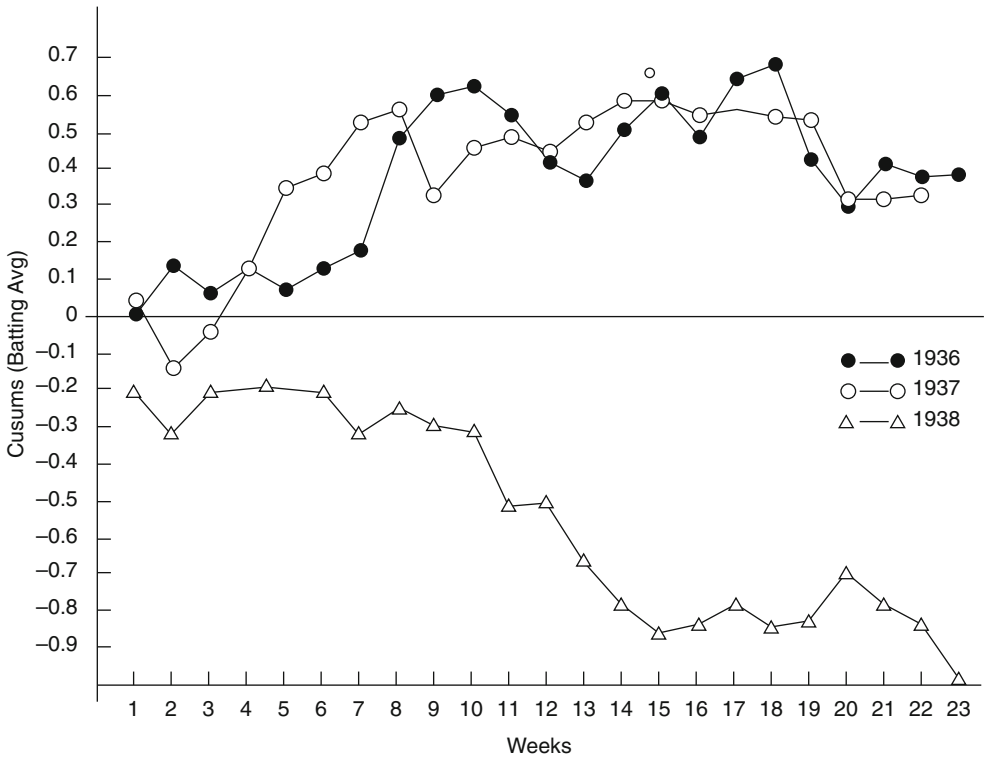

Fig. 20.7 Decline in function over time in amyotrophic lateral sclerosis as depicted by this graph representing cumulative sum (CUSUM) statistical analysis of Lou Gehrig's batting average on a weekly basis from 1936 to 1938. Note the linear decline in function in 1938 (Reproduced with kind permission from Kasarskis and Winslow [6]) (Note: a recent study suggests that progression is nonlinear. Gordon et al. [164])

contralateral leg, and, finally, the bulbar region. With lower extremity onset, a similar pattern of progression follows, the bulbar region being affected last. Bulbar-onset ALS progresses first to the arms and then to the legs [17, 165]. Mean duration of the illness from symptom onset to death is approximately 3 years (mean duration ranges from 23 to 43 months). Roughly 20 % of patients live 5 years and 10 % of patients follow a more benign course, surviving for more than a decade [16].

When one analyzes the cumulative data from several different studies using mean survival times, it is evident that PLS harbors the best prognosis of all types of ALS, with a mean survival time of 224 months in one study and 168 (14 years) in another [17, 166, 167]. By definition, PMA indicates a disorder limited to lower motor neurons for more than 4 years and thus harboring a relatively good prognosis with one series of patients living a mean of 159 months from clinical onset [17, 72]. There are conflicting data on the prognosis of bulbar-onset ALS; while it is often associated with a shorter survival (disease duration has been reported to be between 12 and 27 months), it is argued that one must factor in the generally older age and many patients may be referred to inappropriate clinics prior to diagnosis. A recent study showed that the time to anarthria predicted loss of ambulation which in turn predicted a further 3-month survival [18]. The many forms of familial ALS do not portend a uniform prognosis: it is important to try to identify the causative mutation to allow more accurate prognostication. Both the flail-leg (pseudoneuritic) and flail-arm presentations are associated with longer survival [75].

When dyspnea is the presenting feature of ALS, there is a statistically significant shortening of disease duration. Moreover, a decline in pulmonary function, as tested by serial forced vital capacities, is a strong predictor of a poor prognosis [16, 40]. The severity and duration of disease at presentation also have prognostic implications, with more severe disease portending a worse prognosis and a long interval between onset and diagnosis being more favorable [16]. The ALS CNTF Treatment Study Group identified low serum chloride as a poor prognostic indicator, reflective of a compensatory metabolic response to respiratory acidosis that occurs in the later stages of the disease [168]. The role of psychological well-being on survival has also been investigated with indicators that psychological distress significantly predicts a less favorable prognosis [16]. A "generalized low motor–normal sensory" pattern seen on nerve conduction studies, a decremental response on repetitive nerve stimulation, and a rapid rate of decline of MUNE (motor unit number estimation) are all associated with poorer prognosis. There is limited evidence to support the lack of fasciculations as being prognostically favorable. Malnutrition with low body mass index is an independent risk factor for poor outcome [169].

Treatment and Clinical Trials

The past two decades have yielded theories of ALS pathogenesis each with potential for translation into future therapeutics. Interventions to counter nuclear protein

mislocalization may show promise as may agents involved in cell trafficking/signaling, inflammatory responses, excitotoxicity, and mitochondrial regulation. Clinical trials in ALS have examined a broad spectrum of drugs for their potential anti-glutamatergic activity (e.g., talampanel, lamotrigine, branched-chain amino acids, topiramate, dextromethorphan, and gabapentin) and neuroprotective and/or antioxidant effect (vitamin E, L-deprenyl, *N*-acetylcysteine, xaliproden Sanofi SR57746A), most with negative results. In addition, several recombinant neurotrophic factors (including ciliary neurotrophic factor, brain-derived neurotrophic factor, insulin-like growth factor (IGF-1, myotropin), and glial cell–derived neurotrophic factor) have been studied in well-designed trials, but without significant clinical efficacy. A phase III trial of IGF-1 polypeptide is underway. Other agents, ultimately non-efficacious in ALS, include creatine, coenzyme Q10, minocycline, rapamycin, ceftriaxone, celecoxib, glatiramer acetate, tamoxifen, minocycline, TCH346, ONO 2506 PO, and lithium. Further details regarding ongoing trials are available at www.wfnals.org.

Despite high cost and modest efficacy, riluzole, with a modest effect on prolonging life in ALS patients, remains the only approved agent (Fig. 20.8) [172]. Its mechanism of action is not completely clear, but may include modification of N-methyl-D-aspartate (NMDA) receptor-mediated responses, stabilization of the inactivated state of voltage-dependent sodium channels, and inhibition of glutamate release from presynaptic terminals while increasing extracellular glutamate uptake. When taken for 18 months (in patients with clinically probable or definite El Escorial ALS, with symptoms less than 5 years, FVC >60 % and age <75 years), 100 mg (taken as 50 mg twice daily) probably prolongs median survival by 2–3 months [173]. Preliminary developments in areas of stem cell therapies, RNA interference, viral vector-mediated gene therapy, and immunotherapy offer promise of novel therapeutic strategies. Based on the likely role of mitochondrial dysfunction in ALS pathogenesis, dexpramipexole, the putative mitochondrial modulator (KNS-760704) has undergone preliminary trials (http://clinicaltrials.gov), which suggest safety and tolerability and possible attenuation of ALS functional rating scale decline, thus supporting further testing [174].

Although it is difficult, care must be taken to break the diagnosis of ALS in such a way that the patient and the family understand the diagnosis and its implications but do not feel that hope has been taken away. Thus, one should provide sufficient information regarding the disease itself, including treatment trials and research progress.

It is vitally important to maintain patient autonomy in all decision-making processes and, at the appropriate time, to adequately discuss difficult topics, such as advance directives and issues regarding terminal care. Those patients with more recent diagnoses and with more rapid declines in pulmonary function are more likely to seek interventions such

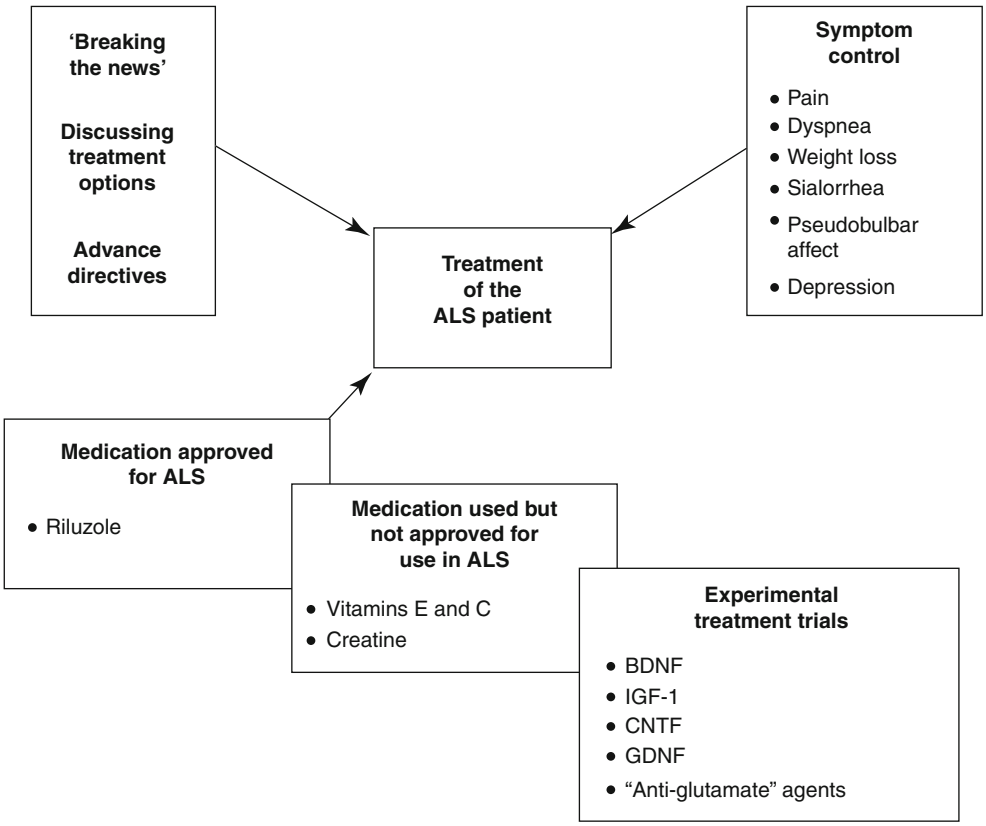

Fig. 20.8 Simplified algorithm for the treatment of amyotrophic lateral sclerosis (For a more detailed discussion, see Refs. [170, 171])

as ventilatory assistance and enteral feeding tubes. Overall, it is best to impart information, particularly that pertaining to prognosis, in a stepwise manner and not to overwhelm the patient as soon as the diagnosis is made. There is no specific treatment currently available that halts or reverses the disease, but there are several paths to optimally manage the many distressing symptoms of ALS. The recommendations for the symptom management of ALS are clearly defined in the practice parameter report by the Quality Standards Subcommittee of the American Academy of Neurology [170, 171].

Symptom Management

Sialorrhea, Pseudobulbar Affect and Depression

Daytime sialorrhea may be treated with anticholinergic preparations such as benztropine, transdermal hyoscine, glycopyrrolate, trihexyphenidyl, and atropine or, as is more commonly practiced, by utilizing the anticholinergic properties of the tricyclic antidepressants (TCADs). In order to reduce thick mucus, adding a beta-blocker, such as propranolol, may be helpful. Mechanical insufflation–exsufflation further enhances clearance of mucous plugs. Alternative approaches include injection of botulinum toxin A into the parotid glands which, by blocking autonomic cholinergic fibers subserving secretomotor function, may lead to a substantial reduction in saliva production and parotid irradiation [175, 176].

Pseudobulbar affect may be effectively controlled with tricyclic antidepressant (TCAD) treatment although one may also use a selective serotonin reuptake inhibitor (SSRI), such as fluvoxamine or quinidine/dextromethorphan. Depression, with or without anxiety, may be treated with a variety of antidepressant preparations such as the TCADs and SSRIs, whereas isolated anxiety may be responsive to benzodiazepines or buspirone. Patients may have pseudobulbar, depressive, and sialorrheic symptoms simultaneously, and it is often possible to treat all complaints with one medication.

Nutrition

Attention must be paid to the nutritional needs of the patient. Particularly with advancing dysphagia, assessment of swallow at the earliest possible stage is advised, in order to devise strategies to maximize caloric intake, prevent dehydration, and reduce aspiration risk. Initial management should focus on appropriate forward head positioning, chin tuck, thickening of liquids, and dietary supplementation. As dysphagia worsens and the patient loses more weight, the physician should recommend a percutaneous endoscopic gastrostomy (PEG), a procedure that may help maintain weight [171], enhance patient quality of life, and also prolong survival by 1–4 months. To minimize risks, evidence suggests that PEG should be performed before vital capacity (VC) falls below 50 % of predicted [177]. Although it may be possible to insert PEG with noninvasive ventilator (NIV) assistance, radiologically inserted gastrostomy (RIG) or percutaneous radiological gastrostomy (PRG) may be a safer alternative in some patients [178]. Importantly, patients who receive a PEG or RIG tube can continue to eat by mouth: the purpose of enteral feeding is to provide calories and fluid. Aspiration is a continued risk to the patient even after PEG tube insertion, and if recurrent aspiration of PEG contents becomes a persistent problem, one can either recommend percutaneous enteral jejunostomy (PEJ), which further reduces (but still does not eliminate) the risk, or a tracheostomy. In aphonic patients with recurrent aspiration, one could also consider conservative laryngectomy or laryngeal diversion. Most guidelines state that supplementary enteral feeding should be considered when body weight falls by > 10 % of the pre-diagnostic or baseline weight [179].

Pain, Spasticity, and Muscle Cramps

Pain, commonly from pericapsulitis, bursitis, cramps, or spasticity, may pose a significant problem in advanced stages of ALS, and the physician must be aggressive in controlling such discomfort. This should start with physical therapy, using passive joint-stretching techniques, followed by treatment with nonsteroidal anti-inflammatory drugs (NSAIDS). Various heating agents, including diathermy and ultrasound, are useful in pain management and in performance of range-of-motion exercises. In addition, transcutaneous electrical nerve stimulation (TENS) is often effective in relieving joint and connective tissue–related pain. Lancinating pains may be responsive to carbamazepine, phenytoin, clonazepam, and amitriptyline, but if pain remains poorly controlled, the physician should not be hesitant to use opioids and, particularly in the preterminal stages, morphine or a fentanyl patch. Several agents, such as baclofen, tizanidine, benzodiazepines, and dantrolene either alone or in combination, may be effective in managing spasticity although patients may experience additional weakness as a troublesome side effect. When cramps are severe, one may employ muscle-stretching exercises in combination with quinine sulfate, baclofen, carbamazepine, diazepam, or phenytoin. In the preterminal phase of ALS, the patient may suffer considerably from distressing dyspnea which can be managed using benzodiazepines, opiates, supplemental oxygen, and, for terminal restlessness, chlorpromazine.

Mobility and Assist Devices

With advancing disease, it is important to continually make adjustments so as to maximize patient function and independence. A number of adaptive devices are available to assist in this regard, including AFO braces for foot drop, specialized neck-support collars for head drop, and various hand/wrist

splints. Increasingly sophisticated communication assist devices are becoming available to aid anarthric patients. Likewise, there are many kinds of wheelchairs, including motorized models that may be customized for each patient's needs. Home assessments by nurses, occupational therapists, and physical therapists are of great benefit when choosing the optimal equipment. Apart from assist devices, it is important that the patient initiates an appropriate program of therapeutic exercise with particular focus on range-of-motion stretching maneuvers. There is some concern that excessive exercise to the point of fatigue may be deleterious and may even be an underlying precipitant of the disease itself, although this has not been borne out in the literature.

Respiratory Function

Dyspnea-onset ALS and a progressive decline in pulmonary function portend a poorer prognosis, but visible signs of early pulmonary compromise may go unnoticed until an adverse event, such as aspiration pneumonia, occurs. Measuring the FVC at regular intervals serially assesses declining pulmonary function and assists the patient and the physician in appropriately projecting ahead. Whether or not the patient wishes for mechanical ventilation should be planned as early as possible. Most patients and physicians prefer the noninvasive approach.

Erect forced vital capacity (FVC) is the most commonly measured index of pulmonary function in ALS, but supine FVC provides a more accurate assessment of diaphragmatic weakness. To detect nocturnal hypoventilation, maximal inspiratory pressure (MIP) and nocturnal oximetry may be more effective. Trans-diaphragmatic sniff pressure (sniff Pdi) and the Sniff nasal inspiratory pressure (SNIP) are also useful indicators of hypercapnia and nocturnal hypoxemia [171]. SNIP is a good measure of diaphragmatic strength and is probably more accurate than vital capacity, although both measurements underestimate respiratory function in patients with bulbar impairment. A SNIP of 32 % (~25 cm H2O) or less is highly predictive of respiratory failure [180–183]. Observational studies and a randomized controlled trial show that NIV improves survival and quality of life. In patients with severe bulbar impairment, NIV improves sleep-related symptoms, but is unlikely to confer a large survival advantage [184]. Sociocultural factors (age, gender, marital status) influence the probability of receiving NIV, and these obstacles should be addressed to encourage NIV use in all ALS patients with respiratory failure [185].

Although evidence exists that NIV improves quality of life and may prolong survival in ALS, it does not prolong life indefinitely, and patients still face the difficult decision of whether to use an invasive ventilator. While invasive ventilation may prolong a patient's life for many years, the patient may develop additional "atypical" signs of disease such as overt cognitive decline, extraocular muscle palsies, and sphincter disturbance, which may later place a great burden upon patient and family. When initiating ventilatory therapy, there should be an agreement as to when, or if, it should be withdrawn. Decisions regarding withdrawal of ventilatory support, or augmentation when noninvasive means of ventilatory assistance are insufficient, must be based on effective and compassionate end-of-life care. In the event of initiating ventilatory withdrawal, sufficient opiates and anxiolytics should be used to minimize patient discomfort.

Because ALS is a progressive neurodegenerative disease with a predictable clinical course, palliative care should be initiated at, or soon after, diagnosis. The majority of skeletal muscles are eventually affected, and multiple ensuing problems require multidisciplinary input, including symptomatic therapy, rehabilitation to maintain muscle function, nutritional and respiratory support, communication device introduction, and psychological support for both patient and family or caregivers. Social, ethical, financial, and legal issues, including advance directives, should be addressed long before decisions regarding enteral feeding and assistive ventilation are required. Management goals must be reassessed regularly [186]. Hospice care, at home or in a residential hospice, provides highly effective palliative services to patients and families. Its philosophy strongly affirms life, promoting maintenance of independence and dignity as much as possible [187].

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