Amyotrophic Lateral Sclerosis

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Orla Hardiman

Abstract Amyotrophic lateral sclerosis or motor neuron disease is a progressive motor system degeneration. Extra motor involvement also occurs, primarily in the form of executive dysfunction. Up to 15% of those with ALS also develop frontotemporal dementia. The pathophysiology of ALS is not well understood. Five percent of cases have a positive family history, and a number of causative and "at risk" genes have been identified. Diagnosis is clinical, and investigations are aimed at excluding other treatable conditions. Optimal management of ALS requires a multidisciplinary team. Most ALS patients develop respiratory failure, and early intervention with noninvasive ventilation can improve survival and enhance quality of life. Patients with ALS should be encouraged to consider an advance directive regarding their end of life.

Keywords ALS • MND • Pathogenesis • Diagnosis • Multidisciplinary management • End of life

Introduction

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is the commonest neurodegenerative condition of the young and middle aged. The disease is characterized by progressive upper and lower motor neuron degeneration. Mean life expectancy is 3–5 years from first symptom. Although primarily a disorder of the motor system, ALS also has nonmotor features and can overlap clinically and pathologically with other neurodegenerative conditions including frontotemporal dementia (FTD). Once symptoms develop, the course of ALS is progressive, and death is usually from respiratory failure. Although treatment options are limited, multidisciplinary management can preserve quality of life and interventions such as noninvasive ventilation can improve survival.

O. Hardiman
HRB Clinician Scientist, Consultant Neurologist and Clinical Professor,
Department of Neurology, Beaumont Hospital and Trinity College, Dublin, Ireland
e-mail: orla@hardiman.net

O. Hardiman and C.P. Doherty (eds.), *Neurodegenerative Disorders*,
DOI: 10.1007/978-1-84996-011-3_7, © Springer-Verlag London Limited 2011

Clinical Features

The clinical onset of ALS is usually asymmetric. The first symptom may be a gait disturbance (e.g., tripping, dragging one leg) or difficulty with fine movements in the upper extremities, e.g., fastening buttons. As motor neurons are affected segmentally, clinical presentation depends on where in the neuroaxis the disease is first manifest. Up to 25% of patients present with bulbar symptoms such as dysarthria and dysphagia and 1–5% present with respiratory failure. The site of disease onset is of prognostic significance, as limb onset carries a better prognosis than bulbar onset, and lower limb onset carries a better prognosis than upper limb onset. Respiratory onset disease carries the worst prognosis.

People with ALS almost never describe fasciculations as a key part of their presenting symptomatology, and people presenting with fasciculations in the absence of muscle weakness or other neurologic signs rarely have ALS.

The clinical hallmark on neurological examination is the presence of both upper and lower motor neuron signs that are not attributable to other causes. A combination of upper and lower motor signs occurring concomitantly at the same spinal level s (e.g., brisk reflexes in a weak, fasciculating limb) should raise a differential diagnosis of ALS, although cervical spondylotic myelopathy could also produce this clinical picture. Bladder function is not usually impaired in the early stages of the disease. Up to one quarter of patients complain of minor sensory symptoms, however formal sensory examination is generally normal.

The time from symptom onset to diagnosis is usually in the order of 9–15 months. Many people will have seen two or three other specialists before they are correctly diagnosed.

A recognizable phenotype of frontotemporal dementia (FTD) occurs in up to 15% of patients with ALS. This is characterized by personality change, irritability, obsessions, poor insight, and pervasive deficits on frontal executive tests. A milder form of cognitive impairment occurs in up to 50% of patients with ALS, and can include subtle executive deficits, apathy, verbal fluency deficits, and changes in memory. Behavioral change may also be reported by a spouse or relative and may not be apparent during formal clinical interview. Cognitive dysfunction can precede or follow the onset of motor symptoms.

There is currently no definitive screening test for cognitive impairment in ALS. Verbal fluency is a sensitive marker of cognitive impairment in ALS, and a simple 2 min word-generation test can help to identify patients in whom a more detailed neuropsychological evaluation may be required. Patients with severe deficits in verbal fluency are more likely to exhibit frontal and executive deficits on more formal testing although these tests are also predicated on premorbid intellectual ability. Short batteries of tests, such as the MMSE, are not sensitive to frontotemporal syndromes and should not be used for diagnostic purposes.

In patients with features of frontotemporal dementia, behavioral change can be assessed using carer-based instruments such as The Neuropsychiatric Inventory or Frontal Systems Behavioral Scale. These questionnaires are completed by caregivers and can convey how the patient functions on a day-to-day basis compared with his or her premorbid status. However, cognitive impairment may be underestimated in the absence of a complete neuropsychological battery.

Once symptoms and signs of ALS develop, the condition progresses. Functional decline can be measured using the revised ALS Functional Rating Scale (ALSFRS-R) (Table 7.1).

Table 7.1 ALSFRS-revised

1. Speech	
4	Normal speech
3	Detectable disturbance
2	Intelligible without repeating
1	Speech with nonverbal communication
0	Loss of useful speech
2. Salivation	
4	Normal
3	Slight but definite excess of saliva
2	Moderate excessive saliva, minimal drooling
1	Marked excessive of saliva, some drooling
0	Marked drooling, requires constant tissue
3. Swallowing	
4	Normal eating habits
3	Early eating problems, occasional choking
2	Dietary consistency changes
1	Needs supplemental tube feeding
0	Nil orally
4. Handwriting	
4	Normal
3	Slow or sloppy, all words legible
2	Not all words legible
1	Able to grip pen but cannot write
0	Unable to grip pen
5. Cutting food and handling utensils	
4	Normal
3	Slow and clumsy but no help needed
2	Can cut most foods, although clumsy and needs some help
1	Food must be cut by someone else
0	Needs to be fed
6. Dressing and hygiene	
4	Normal
3	Independent but decreased efficiency
2	Some help with closures and fasteners
1	Provides minimal assistance to caregiver
0	Unable to perform any task
7. Turning in bed	
4	Normal
3	Slow and clumsy
2	Can turn alone with difficulty
1	Can initiate but cannot turn or adjust sheets
0	Total dependence

(continued)

Table 7.1 (continued)

8. Walking	
4	Normal
3	Early ambulation difficulties
2	Walks with assistance
1	Non ambulatory, functional movement
0	No purposeful leg movement
9. Climbing Stairs	
4	Normal
3	Slow
2	Mild unsteadiness / fatigue
1	Needs assistance
0	Cannot do
10. Dyspnea	
4	None
3	Occurs when walking
2	Occurs when eating, bathing or dressing
1	Occurs at rest
0	Considerable difficulty
11. Orthopnea	
4	None
3	Some difficulty, does not routinely use more than two pillows
2	Needs extra pillows to sleep
1	Only sleeps sitting up
0	Unable to sleep
12. Respiratory insufficiency	
4	None
3	Intermittent use of noninvasive ventilation
2	Continuous use of noninvasive ventilation at night
1	Continuous use of noninvasive ventilation day and night
0	Mechanical ventilation via tracheostomy

Most patients die within 3–5 years of diagnosis. Up to 10% of patients experience a more protracted disease course, and may live for up to 10 years from the time of first symptom.

Variants of ALS include primary lateral sclerosis (PLS), in which clinical signs are confined to upper motor neurons, and progressive muscle atrophy, in which signs are confined to the lower motor neuron. Diagnostic criteria for PLS require the presence of signs for a minimum of 3 years. These ALS variants can be difficult to diagnose in the early stages, and prognosis is generally better than in typical ALS.

Restricted forms of ALS have also been described, including flail arm and flail leg syndromes, and monomelic disease. The former two are more common in men, and carry a better prognosis than typical ALS.

Table 7.2 Variants of ALS/MND

Disease	Clinical features	Other comments	Median survival
ALS	Both upper and motor neuron signs in multiple spinal segments	Most common adult-onset form of motor neuron disease	3–5 years
Primary lateral sclerosis	Upper motor neuron signs only	Many patients eventually develop clinical or electrophysiological signs of LMN involvement. ALS develops in up to 77% within 3–4 years	For those who remain with a diagnosis of PLS, median survival =20 years or more
Progressive muscular atrophy	Lower motor neuron signs only	Variable evolution to ALS	5 years, a subset survive 20 years or more
Progressive bulbar palsy	Speech and swallowing affected initially due to LMN involvement of CN IX, X, XII.	Symptoms include dysarthria, dysphagia, and dysphonia. Aspiration pneumonia is usually the terminal event	2–3 years
Bulbospinal muscle atrophy (Kennedy's disease)	Speech and swallowing affected, proximal limbs	X-linked recessive inheritance pattern. Pure lower motor neuron condition due to trinucleotide repeat in androgen receptor	10 years or more

CN cranial nerves, *UPM* upper motor neuron, *LMN* lower motor neuron

Other variants include bulbospinal muscular atrophy (Kennedy's disease). This X-linked disorder is due to an expansion of trinucleotide repeats in the androgen receptor. The clinical features include slowly progressive lower motor neuron signs in bulbar and proximal limbs. Fifty percent of cases have gynecomastia. Progression is usually slower than in typical ALS. Nerve conduction studies can be helpful as, in contrast to ALS, the sensory nerve action potentials may be absent in Kennedy's disease. (Table 7.2)

The majority of ALS patients die from respiratory failure. Prognostic indicators include time from first symptom to diagnosis (longer duration carries a better prognosis), presence of dementia (poorer prognosis), bulbar or respiratory onset disease (poorer prognosis), older age of onset (poorer prognosis), marked weight loss (poorer prognosis), and presence of pure upper or pure lower motor syndromes (better prognosis) (Table 7.3).

Discussing the Diagnosis

Once the diagnosis has been established, the patient should formally meet with an experienced doctor who has been involved in the care, to discuss the outcome of the investigations. Specific techniques should be used as outlined in Table 7.4, including the provision of a quiet space and adequate time to discuss the diagnosis. The patient should be accompanied by a

Table 7.3 Prognostic indicators

Poor prognostic indicators
Short interval between first symptom and diagnosis
Bulbar onset disease
Respiratory onset disease
Malnutrition/hypermetabolism
Rapidly progressive decline in ALSFRS
Presence of dementia
Familial disease (some SOD1 mutations)
Beneficial vascular risk profile
Increased homocysteine
Vital capacity <50% of normal
Sniff nasal inspiratory pressure <40 cmH_2O
Good prognostic indicators
Long interval between first symptom and diagnosis
Lower limb onset
Flail arm/flail leg syndrome
Upper motor neuron predominant disease
Lower motor predominant disease
Familial disease (some SOD1 mutations)
Age of onset <50 years

Table 7.4 How should a physician tell the patient that they have ALS

Task	Recommendations
Location	Off the ward, in a quiet room Not in an out-patient clinic
Participants	Senior clinician Patient Family member Nursing staff
Breaking the news	Ask what the patient/family knows about their condition Approach the diagnosis with sensitivity Use diagrams to help explain the concept of upper and lower motor neurons Be honest about prognosis Acknowledge the distress that the diagnosis causes Allow plenty of time for questions Allow time for reflection
Hope and reassurance	Provide hope: up to 10% of patients survive for > 10 years Identify positive prognostic indicators Explain that support is available, and that the patient and family are not alone Reassure that as the condition progresses, interventions can help to maintain independence, quality of life, and dignity Reassure that decline occurs gradually Provide information about voluntary organizations Discuss likely opportunities to participate in research and clinical trials
Honesty	Be honest but empathic
Communication	Simple language, no jargon

close friend or family member. The level of information the patient has about the disease should be explored. Some patients have specific concerns including a fear of choking to death; reassurance can be provided about these and other anxieties relating to the progress of the disease. Patients should be provided with a follow up appointment within 2–4 weeks of diagnosis. Some patients seek a second opinion. This should be facilitated.

Epidemiology

The incidence of ALS/MND in Europe is approximately 2 per 100,000 and the overall lifetime risk is approximately 1:400. In populations of non-European or mixed ethnicity, the frequency of ALS is lower. While the reasons for this difference remain unclear, preliminary evidence suggests that genetic admixture may be protective. Careful evaluation of populations over a long period of time has indicated that the adjusted age-specific incidence of the disease is not increasing.

ALS is more common in males than females by a ratio of approximately 1.5:1. This disparity is mostly due to the increased frequency of spinal-onset ALS in men. In contrast to Parkinson's disease and Alzheimer's disease, the risk of developing ALS peaks between the ages of 50–75, and declines thereafter. This suggests that ALS is not a disease of aging, but a disease for which age is one of a number of risk factors.

As ALS is a rare disease, environmental factors that confer increased risk have been difficult to identify. Case-controlled studies seeking to establish exposure risks are often inadequately powered and confounded by methodological errors. High incidences of ALS in Guam and the Kii Peninsula in Japan have been associated with cyanobacterial neurotoxins including BMAA, although definitive evidence in this regard is lacking. Clustering of ALS has been identified in certain occupations including Italian soccer players. The factors that lead to this apparent increased risk remain to be determined. Other environmental factors that have been associated with ALS have included smoking, exposure to pesticides and organic toxins, and electromagnetic radiation. With the exception of smoking, definitive evidence of risk remains to be established and will require large unbiased population-based case-controlled studies for confirmation.

Genetics

Approximately 5% of ALS is familial with a Mendelian pattern of inheritance. A total of 12 genes and loci of major effect have been identified. (Table 7.5) The majority are autosomal dominant in inheritance pattern.

Mutations in superoxide dismutase (SOD1) account for up to 20% of all familial ALS, and up to 5% of apparently sporadic disease. Mutations in two different DNA/RNA binding proteins, TDP-43 and FUS/TLS, account for a further 15% of familial ALS. Both TDP-43 and FUS code for proteins involved in gene regulation including transcription, RNA splicing, RNA transport, and translation, and in the regulation and processing of small regulatory RNAS (microRNAs). Mutations in another RNA regulatory protein ANG accounts for up to 1% of sporadic cases. OPTN, coding for optineurin, is a causative gene

Table 7.5 Known causative genes/loci in ALS

Name	Gene	Locus	Protein
ALS1	SOD1	21q22.1	Cu/Zn Superoxide dismutase
ALS2	ALS2	2q33–35	Alsin
ALS3		18q21	
ALS4	SETX	9q34	Senataxin
ALS5		15q15-q22	
ALS6	FUS	16q15-q22	FUS
ALS7		20ptel	
ALS8	VAPB	20q13.33	VAMP-associated protein
ALS9	ANG	14q11	Angiogenin
ALS10	TARDBP	1q36	Tar DNA-binding-protein 43
	OPTN	10p14	Optineurin
ALS-FTD		9q21–22	
ALS-FTD		9p13.2–1,3	

of primary open-angle glaucoma. ALS-causing mutations of OPTN abolish the inhibition of activation of nuclear factor kappa B, and alter the cytoplasmic distribution of optineurin. The frequency of OPTN mutations in familial and sporadic ALS remains to be determined. Of the known genes, only SOD1, TDP-43, OPTN, ANG, and FUS mutations have been associated with typical ALS; the remainder are associated with unusual phenotypes or have been described in small numbers of kindred.

Ninety five percent of people diagnosed with ALS have no family history and are classified as having sporadic disease. Family aggregation studies have identified an overlap between ALS and some more common neurodegenerations, suggesting the existence of susceptibility genes that may increase the overall risk of neurodegeneration within kindreds.

Candidate gene studies have identified a number of "at risk" genes that increase disease susceptibility, although the relative contribution of each identified gene rarely exceeds an odds ratio of 2.0, and in most cases, the mechanism by which the risk is conferred remains to be elucidated (Table 7.6).

Genome-wide association (GWA) studies in ALS have been disappointing, as no single gene of major effect has been identified. Studies have lacked power related to sample size, and "hits" have been accordingly difficult to replicate in a second population. However, increased international collaboration coupled with the combination of detailed clinical phenotyping with next-generation bioinformatic technology is likely to provide a wealth of new information about ALS pathophysiology. This, in turn, will provide exciting new avenues for developments in disease therapeutics.

Genetic Testing

Because most ALS is nonfamilial, there is currently little advantage in testing sporadic individual patients for known gene mutations. Genetic testing should only be undertaken in known familial disease, where the presence of mutations in known genes might accelerate the diagnostic process. Genetic counseling is recommended prior to testing.

Table 7.6 Known susceptibility genes for ALS

Gene	Functional significance
Oxidative stress	
SOD1	Cytoplasmic antioxidant soluble form may become neurotoxic
HFE	Regulator of iron metabolism
Cytoskeleton, *microtubule*, *axonal transport*	
MAPT	Microtubule protein disruption, involved in other neurodegenerative diseases
NEFH	Neurofilament protein, mutations alter axonal transport
PRPH	Intermediate filament, transgenic mice develop motor neuron degeneration
DCT1	Disruption in dynein/dynactin complex alters axonal transport, produces phenotype in mice
KIFAP3	Kinesin-associated protein, modulates survival
Metabolism	
PON 1–3	Paraoxonases are important detoxifying enzymes. Association in five different populations, but different haplotypes implicated in different ancestral populations
Progranulin	Gene of major effect in FTD. Coding variations associated with ALS in some populations, similar in function to angiogenin
DNA/RNA repair	
ANG	RNA ribonuclease and hypoxia responsive agent; overlap in function with VEGF and progranulin
APEX	DNA repair enzyme
SMN1, SMN2	Affects RNA splicing, gene of major effect in spinal muscular atrophy
TDP-43	RNA regulator
ELP 3	RNA polymerase
Excitotoxicity	
UNC13A	Also links to familial ALS FTD
Unknown	
9p13.2–21,3	

Presymptomatic genetic testing should only be performed in first-degree adult blood-relatives of patients with a known gene mutation. As many mutations in ALS are incompletely penetrant, the identification of a mutation in an asymptomatic relative cannot accurately predict development of the disease. Testing should be performed on a strictly volunteer basis and should follow extensive genetic counseling.

Overlap Syndromes

Up to 15% of patients with ALS have frontotemporal dementia (FTD), and up to 30% of those with FTD have neurophysiologic evidence of anterior horn cell degeneration (see Chap. 6). A smaller percentage (2–5%) of patients with ALS has evidence of

other forms of dementia, including features of Alzheimer's disease. Patients with ALS are more likely to have a family history of neurodegenerative disease, suggesting common genetic susceptibilities. Parkinsons and dementia have been described in Guam, and the Kii peninsula in Japan. Outside of these areas, occasional patients with extrapyramidal syndromes and anterior horn cell degeneration have been reported and a small minority of ALS patients are ataxic. Rarely, Huntington's disease can present with amyotrophy (see Chap. 8).

Diagnostic Criteria

Formal diagnosis of ALS is based upon clinical criteria that include the presence of upper motor neuron (UMN) and lower motor neuron (LMN) signs, progression of disease, and the absence of an alternative explanation. There is no single diagnostic test that can confirm or entirely exclude the diagnosis of motor neuron disease.

The *El Escorial* criteria were developed in 1990 by the World Federation of Neurology (WFN) for research and clinical trial purposes. These guidelines were subsequently revised in Airlie House in April 1998 (Table 7.7).

Both sets of criteria are based on the degree of certainty of diagnosis, which in turn is based on clinical assessment and the presence of upper and lower motor neuron signs together in the same topographical anatomic region in the brainstem, cervical, thoracic, or lumbosacral spinal cord. Although not validated at the time of inception, a number of inter-rater reliability studies have shown that among experts, the criteria are in general uniformly applied and reproducible. Notwithstanding, the criteria have been criticized as being too restrictive, as up to 10% of patients with ALS remain within the "possible" category at the time of death and are thus excluded from most clinical trials, which require a diagnosis of "probable" " or "definite" ALS. The *El Escorial* and Airlie House criteria are not helpful in day-to-day management of ALS and should be reserved for classification of patients for research purposes.

Differential Diagnosis of ALS

Some conditions can closely resemble ALS and should be actively considered in the differential diagnosis. Consideration of the "mimic syndromes" is important, as the diagnosis of ALS is based primarily on clinical examination, supported by a series of laboratory investigations to exclude other conditions.

The majority of likely mimic syndromes are listed in Table 7.8. In practice, the most frequent conditions mistaken for ALS are multifocal motor neuropathy with conduction block and cervical spondylotic myelopathy.

Based on these studies, factors that should lead to revision of the diagnosis of ALS can be divided into two broad categories:

Table 7.7 El Escorial and Airlie House criteria for diagnosis of ALS

1. The presence of:
   (a) Evidence of LMND degeneration by clinical, electrophysiological, or neuropathological examination
   (b) Evidence of UMN degeneration by clinical examination; and
   (c) Progression of the motor syndrome within a region or to other regions, as determined by history or examination;

and:

2. The absence of:
   (a) electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN or UMN degeneration; and
   (b) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

El Escorial Criteria

Definite ALS: UMN and LMN signs in three regions.

Probable ALS: UMN and LMN signs in at least two regions with UMN signs rostral to (above) LMN signs.

Possible ALS: UMN and LMN signs in one region, UMN signs alone in two or more regions, or LMN signs above UMN signs.

Suspected ALS: LMN signs only in two or more regions.

Airlie House (*modified*) *criteria*

Clinically definite ALS: clinical evidence alone of UMN and LMN signs in three regions.

Clinically probable ALS: clinical evidence alone of UMN and LMN signs in at least two regions with some UMN signs rostral to (above) the LMN signs.

Clinically probable—laboratory-supported ALS: clinical signs of UMN and LMN dysfunction are in only one region, or UMN signs alone in one region with LMN signs defined by EMG criteria in at least two limbs, together with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

Possible ALS: clinical signs of UMN and LMN dysfunction in only one region, or UMN signs alone in two or more regions; or LMN signs rostral to UMN signs and the diagnosis of clinically probable—laboratory-supported ALS cannot be proven.

Suspected ALS: this category is deleted from the revised El Escorial Criteria.

Failure of symptom progression – In general, patients with common mimic syndromes do not progress as rapidly as those with ALS, and tend to survive for longer periods.

Atypical history or symptoms – Common clinical features that lead to a reconsideration of the diagnosis of ALS include the presence of isolated upper or isolated lower motor neuron signs (leading to possible diagnoses of hereditary spastic paraparesis, multiple sclerosis, and motor neuropathy, respectively); the development of sensory complaints or bladder involvement (leading to diagnoses of myelopathy or demyelinating disease); the absence of upper motor neuron signs rostral to lower motor neuron signs; or the absence of bulbar signs in patients with prominent spinal signs (leading to a diagnosis of cervical myelopathy); and a family history of males only affected, and no male-to-male transmission (suggesting X-linked bulbospinal muscle atrophy (Kennedy's disease). The presence of asymmetric weakness and wasting in a C8 T1 distribution in a young man should raise the possibility of Hirayama disease (Table 7.9).

Table 7.8 Differential diagnosis of MND

Hereditary	• Kennedy's disease • Hereditary spastic paraparesis • Acid maltase deficiency • Facioscapulohumeral muscular dystrophy • Adrenomyeloneuropathy • Huntington's disease • Hexosaminidase deficiency
Metabolic/toxic	• Hyperthyroidism • Hyperparathyroidism • Heavy metal intoxication • Lathyrism • Organophosphate toxicity
Immune/inflammatory	• Multifocal motor neuropathy with conduction block • Chronic inflammatory demyelinating polyneuropathy • Myasthenia gravis • Inclusion body myositis • Polymyositis • Multiple sclerosis • Paraneoplastic disorders
Structural	• Cervical spondylotic myelopathy • Syringomyelia/bulbia • Post-irradiation myelopathy/plexopathy • Tumor • Cerebrovascular disease
Other neurodegenerative diseases	• Corticobasal degeneration • Multiple system atrophy • Progressive supranuclear palsy • Parkinson's disease • Huntington's disease
Other motor neuron diseases	• Primary lateral sclerosis • Progressive muscular atrophy • Spinal muscular atrophy • Post-polio spinal muscle atrophy • Benign fasciculation syndrome • Hirayama disease

Table 7.9 Clinical features that should prompt a search for mimic syndromes

• History of poliomyelitis
• Family history with no affected females and no male-to-male transmission
• Symmetrical signs
• Pure upper or pure lower motor neuron syndrome
• Upper motor signs caudal to lower motor neuron signs, with no bulbar involvement
• Development of sensory signs
• Development of sphincter disturbances

Diagnostic Tests

There is no definitive diagnostic test for ALS. The combination of suggestive clinical signs with negative laboratory and imaging studies supports the diagnosis. Progression of the condition is a prerequisite for diagnosis (Fig. 7.1).

Essential Investigations

Routine laboratory investigation of a patient with apparently "typical" ALS should include ESR, serum and urine protein electrophoresis, thyroid function tests, and serum calcium and phosphate (Table 7.10).

CSF analysis should be performed. CSF protein levels above 80 mg% are unusual and should prompt a search for other pathology, particularly for the presence of an associated lymphoproliferative disease. Heavy metal screen should be performed in those with a potential history of exposure. Hexosaminidase A and B activity should be tested in patients of Ashkenazi Jewish extraction.

Neurophysiologic studies can assist in the diagnosis by demonstrating ongoing denervation (fibrillation potentials and positive sharp waves) and reinnervation (large polyphasic units) in affected and clinically unaffected limbs, with normal sensation, and normal or near-normal motor nerve conduction velocities. For corroboration of diagnosis, the distribution of denervation-associated changes on EMG should be outside the anatomic territories of peripheral nerves and roots. At least two proximal and two distal muscles in each of the four limbs should be sampled by EMG.

Prolonged F response and the presence of conduction block should suggest an alternative diagnosis, such as multifocal motor neuropathy. Sensory nerve action potentials (SNAPs) are preserved in ALS. Abnormalities in SNAPs should prompt a search for an alternate diagnosis. In males, the possibility of Kennedy's disease should be considered.

Electrophysiological results should be evaluated in conjunction with the clinical and other ancillary findings. A recent algorithm to enhance the electrophysiologic criteria for ALS diagnosis (The Awaji Algorithm) has been published by de Carvehlo et al. (see Further Reading at the end of this chapter).

At present, there are no validated, reliable, and accessible neurophysiologic investigations to establish the presence of upper motor neuron dysfunction, although a number of recent studies using transcortical magnetic stimulation have suggested increased cortical excitability in ALS. At present, none of the measures of central motor function in ALS is likely to be useful for monitoring patients in a clinical trial setting.

Neuroimaging studies should be used to exclude other conditions that may cause UMN and/or LMN signs. Advanced neuroimaging in ALS is unlikely to be useful in primary diagnosis of ALS, or as an easily available biomarker of progression. However, detailed neuroimaging using modern scanners has potential as a research tool to further characterize anatomic pathways involved in ALS.

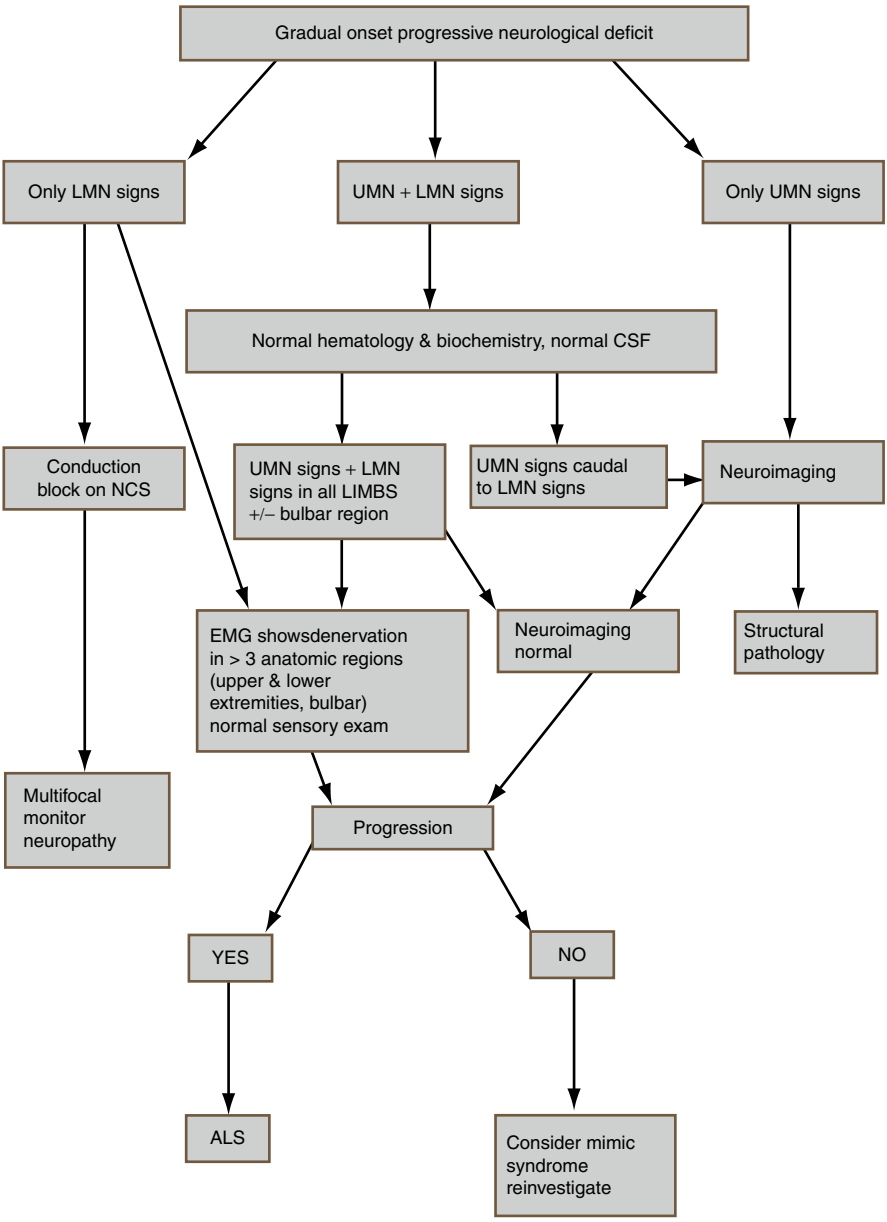

Fig. 7.1 Diagnostic algorithm for ALS (*UMN* upper motor neuron, *LMN* lower motor neuron, *NCS* nerve conduction studies)

Table 7.10 Essential investigations

Blood erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
Hematological screen
ASAT, ALAT, LDH
TSH, FT4, FT3 hormone assays
Vitamins B12 and folate
Serum protein electrophoresis
Serum immunoelectrophoresis
Creatine kinase (CK)
Creatinine
Electrolytes (Na^+, K^+, Cl, Ca^{2+}, PO_4^{3})
Glucose
Hexoaminidase A and B assay (where clinically indicated)
Ganglioside GM-1 antibodies (where clinically indicated)
Serology (*Borrelia*, virus including HIV) (where clinically indicated)
CSF Cell count, protein, glucose
Neurophysiology: EMG, nerve conduction velocity
Radiology MRI/CAT (head/cervical, thoracic, lumbar)
Chest x-ray

Biomarkers in ALS

There is a growing interest in identifying biomarkers for diagnosis, progression, and prognosis in ALS. To date, no biomarker has been of sufficient sensitivity and specificity to incorporate into clinical practice. Although protein profiling in CSF has yielded findings that are of interest, standardized handling of spinal fluid will be required to ensure reproducibility of results. Neuroimaging and quantitative neurophysiological techniques such as motor unit number estimation (MUNE) are considered to have potential but are both cost- and labor intensive. Disease signatures may also be possible using transcriptomics and metabolomics. However, it is likely that further subcategorization based on clinical phenotype will be necessary to generate reproducible biomarkers.

Management of Progression of ALS

Evidence-based guidelines for clinical management have been published by the European Federation of Neurological Sciences and by the American Academy of Neurology. (See Further Reading at the end of this chapter.) Both sets of guidelines emphasize the importance of multidisciplinary care, which provides the cornerstone of ALS management. The multidisciplinary team should include a neurologist, a respiratory physician, a palliative care physician, and allied professions including physiotherapy, occupational therapy, speech and language therapy, nutrition, and medical social services (Table 7.11 see also Chap. 13). Those who received care at a multidisciplinary clinic have a better prognosis

Table 7.11 Multidisciplinary team for ALS management

Neurologist	Diagnosis, disclosure of diagnosis,treatment and symptom management, initiation of respiratory and nutritional interventions, and unbiased information regarding research developments
Family doctor	Symptom control, drug monitoring, liaison with other teams
MND specialist nurse	Point of contact for patients and families, coordination of care, home visits, practical advice regarding accessing support services, patient advocacy
Speech and language therapist	Evaluation and monitoring of dysphagia and aspiration, speech therapy, and advice regarding communication devices
Occupational therapist	Optimization of the patient's environment. Advice re safety awareness, adaptive and splinting devices, activity modification, driving, energy conservation, home modification
Dietitian/nutritionist	Evaluation of nutritional status and the need for tube feeding, management of dysphagia, management of enteral feeding
Physiotherapist	Evaluation of muscle strength and function, advice re walking aids and orthoses, management of spasticity, safety awareness
Social worker	Advice and counseling re employment, change in lifestyle and financial issues, support for carers
Palliative care	Symptom control, pain management, maintenance of quality of life, preservation of dignity
Psychiatry and neuropsychology	Evaluation and management of cognitive impairment/dementia, adjustment disorders, anxiety and depression
Respiratory physician	Assessment of respiratory dysfunction, initiation of noninvasive ventilation, monitoring of noninvasive ventilation

than those attending a general neurology clinic, and because symptoms are addressed and treated early, management in a specialized setting is also more cost effective.

Despite a large number of clinical trials of various agents, the anti-glutamate agent Riluzole remains the one evidence-based disease-modifying drug for ALS. Patients with ALS should be offered Riluzole at the time of diagnosis, as clinical trials have repeatedly demonstrated that early treatment with Riluzole can increase survival by a mean of approximately 3 months.

Symptomatic Therapies

The aim of symptomatic therapy is to improve the quality of life of the patient and carer. The commonest symptoms and their management are outlined below.

Cramping and Spasticity

Cramping can be treated with massage and physiotherapy. Quinine sulfate (200 mg) is also effective, as are phenytoin, carbamazepine, and benzodiazepines.

Spasticity can be treated with physiotherapy and hydrotherapy. Baclofen and tizanidine are effective pharmacologic agents.

Sialorrhoea and Bronchial Secretions

Sialorrhoea (drooling or excessive salivation) is distressing to patients, and increases the risk of oral infections. It is associated with dysphagia, and a failure to effectively handle salivary secretions.

Sialorrhoea can be difficult to manage, although patients and carers can be trained to use a portable suction machine. Treatments include amitriptyline (25–50 mg), oral or transdermal hyoscine, atropine drops, or glycopyrrolate. For more severe sialorrhoea, botulinum toxin can be effective, as can salivary gland irradiation.

Bronchial secretions can be treated with mucolytics and nebulized beta adrenergic antagonists and/or anticholinergics. In some instances, use of mechanical cough-assisting devices (insufflator-exsufflator) can be beneficial.

Pseudobulbar Affect

Pathological weeping or laughing occurs in up to 50% of patients. A combination of dextromethorphan and quinidine may be beneficial, although treatment may be limited by side effects. Fluvoxamine, amitriptyline, and citalopram can also be of benefit.

Anxiety and Depression

Counseling for patients and carers is useful in managing the reactive depression associated with recent diagnosis. For more protracted depression, SSRIs can be helpful. Anxiety can be treated with benzodiazepines or buproprion.

Pain

Pain is not uncommon in ALS. Treatment should begin with simple analgesics such as paracetamol, followed by weak opioids such as tramadol, followed by strong opioids such as morphine or ketobemidone.

Communication

Dysarthria progressing to mutism occurs in bulbar ALS. As dysarthria develops, patients should be reviewed by an experienced speech and language therapist. The goal should be to optimize the communication both for the patient and the carer. Prosthetic treatments (palatal lift and/or palatal augmentation prosthesis) can be helpful to improve articulation. Augmentative and alternative communication (AAC) devices can be used in those with

intact cognition. Useful technological advances include brain–computer interfaces and thought translation devices, though these are not yet widely available.

Respiratory Insufficiency

The majority of ALS patients die of respiratory failure, and the presence of respiratory muscle weakness is an independent predictor of quality of life. Symptoms of respiratory insufficiency may be subtle. Patients should be asked directly about dyspnea, orthopnea, disturbed sleep (sleep fragmentation due to hypoventilation), nightmares, morning headaches, daytime somnolence and fatigue, poor concentration/memory, and nocturia. Assessment of respiratory insufficiency includes history and examination, pulmonary function tests, and overnight pulse oximetry and early morning arterial blood gases.

Forced vital capacity is most widely used in the assessment to respiratory insufficiency in ALS but limitations include insensitivity to significant changes in respiratory function partly because the shape of the lung pressure–volume curve, and difficulties in performing the test due to muscle weakness or apraxia. Sniff nasal inspiratory nasal pressure (SNIP) is a more accurate measure of declining respiratory function, although its use is also limited by apraxia. SNIP is particularly useful in patients with bulbar involvement since a face mask is not required. The SNIP correlates well with diaphragm strength and nocturnal hypoxemia and is sensitive to changes in respiratory muscle strength. A SNIP of <40 cm H2O had a higher sensitivity for predicting 6 month mortality compared with a FVC of <50%.

Transcutaneous carbon dioxide/oxygen sensor can be useful during home visits as it avoids the need for regular arterial blood gases. While not used as a primary tool in the assessment of the need for noninvasive ventilation, it can be a useful adjunct (Table 7.12).

Noninvasive positive pressure ventilation (NIPPV) should be introduced early. Current recommendations are that NIPPV should be offered to any patient with respiratory symptoms and vital capacity less than 50% of predicted, a SNIP of less than 40 cm H_2O, or where symptoms of respiratory insufficiency are associated with nocturnal hypoxemia. An elevated early morning blood CO_2 level is an absolute indication.

Table 7.12 Indications for initiation of noninvasive ventilation

European consensus criteria for NIV (European ALS/MND Consortium and European Neuromuscular Centre workshop on noninvasive ventilation in MND, May 2002)	
Suggested criteria for noninvasive ventilation	
Symptoms related to respiratory muscle weakness. At least one of	Dyspnea, orthopnea, disturbed sleep (not caused by pain), morning headache, poor concentration, anorexia, excessive daytime sleepiness (ESS > 9)
and	
Evidence of muscle weakness	FVC ≤ 80% or SNIP ≤ 40 cm H20
and	
Evidence of either	Significant nocturnal desaturation on overnight oximetry or Morning ear lobe gas pC02 ≥ 6.5kPa

NIPPV extends survival, particularly in those who are compliant with ≥ 5 h of NIPPV each day and those without severe bulbar dysfunction. Treatment with NIPPV also improves quality of life (QOL) in patients without increasing caregiver burden or stress. Some patients have difficulty tolerating NIPPV. Factors that adversely affect the ability of patients to tolerate NIPPV include the presence of bulbar symptoms, the ability to manually adjust the mask, and the presence of cognitive impairment. Pulse oximetry should be performed following commencement on NIPPV, and patients should be reviewed at regular intervals by a respiratory physician to ensure that the pressure settings are optimized.

Weight Loss and Nutritional Support

Weight loss and malnutrition are common features of ALS. Nutritional decline can occur in the context of evolving dysphagia. In those without significant bulbar features, weight loss can result from difficulties in finishing meals because of upper extremity weakness. Weight loss may also be due to hypermetabolism, particularly in those with respiratory compromise. Dysphagia increases the risk for insufficient calorie intake, aspiration, and choking. Dysphagia can be evaluated using bedside clinical scales and with videofluoroscopy and fiber-optic examination. Management includes modification of food and fluid consistency, postural advice (e.g., chin tuck: flexing the neck forward on swallowing to protect the airway), and parenteral feeding by gastrostomy.

Gastrostomy placement is indicated for those who have symptomatic dysphagia or significant weight loss. Advantages include improved nutrition, although the survival effect is likely to be marginal. Radiologically inserted gastrostomy (RIG) is preferred over endoscopic gastrostomy in patients with pronounced bulbar symptoms and/or respiratory compromise. If there is evidence of respiratory insufficiency, noninvasive ventilation should be introduced before gastrostomy (Fig. 7.2).

Management of Cognitive Impairment in ALS

Most studies of treatment of FTD are relatively small and uncontrolled. The management of cognitive decline in ALS is accordingly difficult. Off-label use of medications more commonly includes donepezil, rivastigmine, galantamine, and memantine.

SSRIs are commonly used for aggression, agitation, disinhibition, and depression in FTD. Treatment with SSRI is well tolerated, and they are currently the drugs of choice for behavioral control in FTD. Nocturnal agitation can be treated with low-dose olanzapine, rispiridone, or quetiapine. Comanagement with neuropsychiatry is recommended.

Quality of Life

Quality of life (QOL) is determined by the pleasure and satisfaction an individual draws from living. Health-related QOL is determined by the impact of an individual's health on their experience of living. In ALS, health-related QOL declines commensurately with

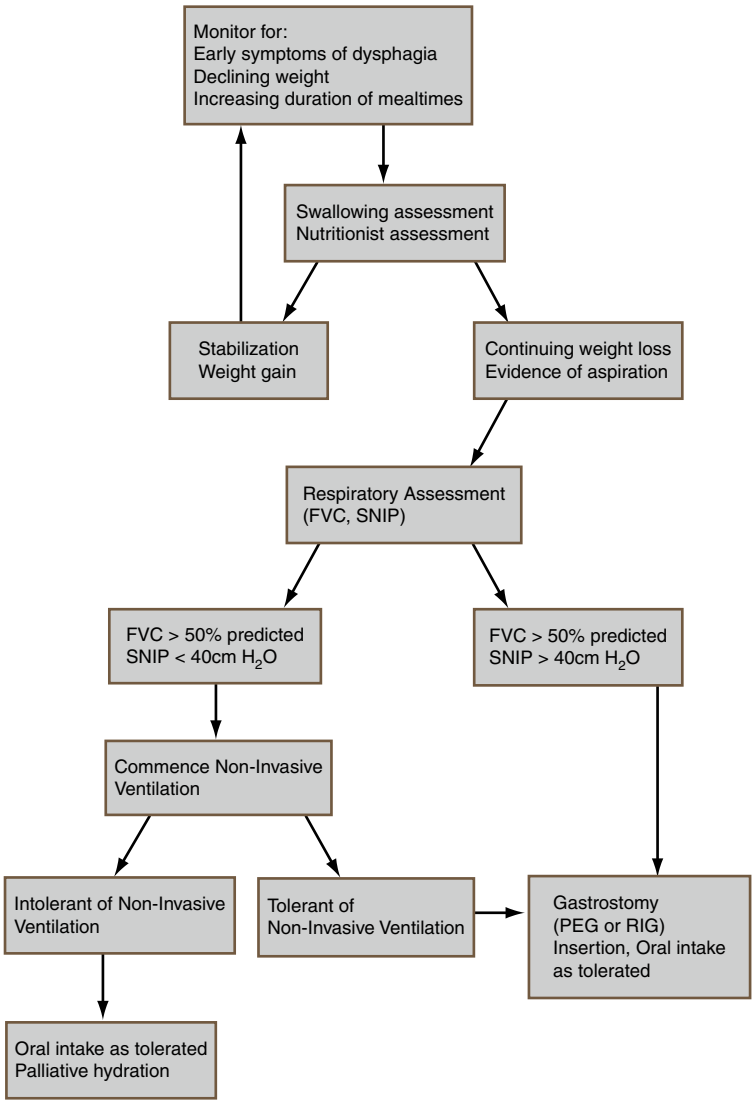

Fig. 7.2 Algorithm for management of nutritional decline in ALS (*FVC* forced vital capacity, *SNIP* sniff nasal inspiratory pressure, *PEG* percutaneous endoscopic gastrostomy, *RIG* radiologically inserted gastrostomy)

physical decline, and high levels of psychological distress can occur. However, self-assessed QOL, as measured by scales in which the individual selects what is most important to them (e.g., the Schedule for Evaluation of Individual Quality of Life (SEIQoL)), does not generally decline in ALS. Moreover, the majority of patients with ALS do not exhibit high scores on depression and anxiety scales. This is because most individuals perform a psychological shift toward domains that can continue to be enjoyed despite the

evolution of neurological deficits. Recognition of the ability of patients to undertake this psychological shift is an important aspect of caring for those with ALS and should be recognized by health professionals, as perceived QOL may impact on decision-making, both by the patient and the health care professional.

Carer Burden

A diagnosis of ALS impacts the entire family. The role of the patient within the family may change – the breadwinner may become a dependent and the primary carer within the family may become the person requiring most care. These changes can have a major destabilizing effect on intimate relationships.

As the condition progresses, there is an increasing and often unacknowledged burden on the primary carer, both from a physical and emotional perspective. Many studies have shown that the self-reported QOL of carers may be lower than that of patients. The burden of care may be increased considerably when the patient is cognitively impaired. Supportive strategies including counseling for family members should be available. In the later stages of illness, regular respite and psychological support should be available for the primary carer.

Palliative Care and End-of-Life Decisions (See also Chap. 13)

ALS is an inexorably progressive condition that significantly reduces life expectancy. A palliative care approach should be taken from the time of diagnosis. The aim of palliative care is to maximize QOL of patients and families by relieving symptoms, providing emotional, psychological, and spiritual support as needed, removing obstacles to a peaceful death, and supporting the family in bereavement. From the time of diagnosis, patients should be provided with a realistic projection of the trajectory of their disease. As the condition progresses, they should be encouraged to consider an advance directive regarding their end of life. Candid discussions about the relative merits and demerits of full mechanical ventilation should take place in a planned manner, and in a comfortable and quiet setting. Assurances should be provided that palliative care strategies can control symptoms in the terminal phase of the illness. Opioids and benzodiazepines (where necessary for anxiety) can be used for symptomatic treatment of dyspnea. Pain should be managed with opioids. Neuroleptics can be used for treating terminal restlessness and confusion due to hypercapnia.

Most Important Recent Advances

While ALS was originally considered to a pure motor system degeneration, ongoing research in cell and molecular biology suggests that the pathophysiology of ALS and FTD are closely intertwined. A number of genes are known to cause both ALS and FTD (Table 7.13). Advances in neuroimaging and neuropathology have demonstrated

Table 7.13 Genes causing ALS and FTD

Chromosome 17q 21–22; MAPT gene	Disinhibiton-dementia-Parkinson-amyotrophy complex (DDPAC): semantic language abnormalities
Chromosome 9p 13.2–21.3	Motor symptoms followed by personality and behavioral abnormalities between 4th and 7th decades
Chromosome 9q21-q22	Five with ALS and mild cognitive impairment, 9 pure FTD, ALS and/or ALS/FT
9p13.3–12, valosin-containing protein	Autosomal dominant inclusion body myopathy, Paget's disease of bone, FTD
3p12, CHMP2B	FTD and later motor syndrome (not typical ALS)
Point mutation (R1101K) in the DCTN1 gene	FTD and ALS segregate as separate traits
TDP-43	ALS-FTD
FUS	ALS-FTD
SOD1	ALS-FTD (rarely)
ANG	ALS-FTD (rarely)
Progranulin	Mostly FTD, polymorphisms associated with phenotype in ALS

involvement of regions of the brain outside the motor system in ALS. Detailed neuropsychological assessment of ALS patients has also identified corresponding changes in up to 50% of patients, with evidence of frontotemporal dementia in up to 15%. These advances have radically changed the perspective of clinicians and researchers, and have opened new and exciting frontiers in research.

Although effective disease-modifying drugs for ALS remain elusive, much progress has been made in understanding and managing the disease. From a laboratory perspective, there has been a veritable explosion of new genes that are implicated in ALS and ALS/FTD. This has led to the important observation that disruptions in RNA processing may contribute to disease pathogenesis. SOD1 mouse models have identified the pivotal importance of glial tissue in the pathogenesis and progression of the disease. However, the limitations of the murine SOD1 model of ALS have also become apparent, and new guidelines are under consideration to harmonize mouse studies. Moreover, the identification of new genes has provided a timely opportunity to generate new animal models, including a mutant TDP-43 transgenic mouse.

From a clinical perspective, it is now increasingly recognized that the incidence and, possibly, the phenotype of ALS is likely to differ across populations – this important observation opens new avenues of comparative epidemiologic and population genetics research.

Although clinical trials have been disappointing, there have significant developments in clinical trial design and an improved recognition of the pitfalls in attempting to translate positive findings from laboratory animals into humans. It is now acknowledged that the failure of some of the more promising compounds in Phase II and III trials may have

reflected a relative paucity of preclinical data regarding the biological activity of the therapy. This has been coupled, in some instances, with a failure to identify the appropriate dose range for testing.

Notwithstanding the disappointing outcome of recent trials, clinical management has significantly improved in the recent past. There is now robust evidence to indicate that survival is enhanced by attendance at a multidisciplinary clinic. Close attention to respiratory status has led to increasing use of noninvasive ventilation, with attending survival benefits of up to 9 months.

The pace of research in ALS has increased considerably in the past decade; the coming decade is likely to yield exciting results both in clinical management and in helping to understand underlying disease pathophysiology.

Most Important Developments in the Coming Years

ALS research is poised on the brink of some major and exciting advances both in clinical and basic science research. ALS researchers throughout the world are coalescing to form a variety of consortia that will pool and maximize both resources and expertise. The close biological relationship between ALS and FTD will continue to provide insights into disease pathogenesis. The recent recognition of the likely importance of RNA regulation in both diseases will have wide-ranging implications in research in molecular and cell biology.

Translation of potential therapeutic agents from animal to human models of disease will benefit from the lessons learned over the past decade. New clinical trials in ALS will be underpinned by a detailed knowledge of drug activity, bioavailability, and efficacy in both the preclinical and clinical setting, coupled with robust proof of biological activity in the target tissue.

The new fields of transcriptomics and metabolomics are likely to be harnessed in the quest for biomarkers. Advances in high-resolution neuroimaging is also likely to be helpful in tracking disease progression, as will advances in neurophysiology and neurophysics. And finally, brain–computer interfaces will help to provide improved aids by using EEG signals recorded from the scalp to enable patients to both communicate, and to interact with their environment using modern robotics.

Further Reading

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