

Amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is an idiopathic, fatal neurodegenerative disease of the human motor system. In this Seminar, we summarise current concepts about the origin of the disease, what predisposes patients to develop the disorder, and discuss why all cases of ALS are not the same. In the 150 years since Charcot originally described ALS, painfully slow progress has been made towards answering these questions. We focus on what is known about ALS and where research is heading—from the small steps of extending longevity, improving therapies, undertaking clinical trials, and compiling population registries to the overarching goals of establishing the measures that guard against onset and finding the triggers for this neurodegenerative disorder.

Introduction

Since the 1990s, there has been growing scientific and clinical interest in amyotrophic lateral sclerosis (ALS). Advances in our understanding of the glutamate neurotransmitter system and the discovery of causal genes linked to the development of familial ALS have stimulated research interest, problems associated with clinical heterogeneity have been identified, and survival in ALS is now understood to be dependent on several factors, including clinical presentation (phenotype), rate of disease progression, early presence of respiratory failure, and the nutritional status of patients.

Extending life expectancy in ALS seems to be dependent on improving our understanding of its pathogenesis, which will lead to the development of early and specific diagnostic methods. There is a crucial need to formulate therapies that not only slow disease progression, but also deal with the secondary consequences of malnutrition and respiratory failure. At present, no definitive diagnostic test or biomarker for ALS exist, and neurologists rely on only clinical criteria for diagnosis. The development of novel biomarkers to objectively assess disease progression holds the promise of greatly refining therapeutic trial design and reducing trial costs. Furthermore, the power of population registries is being increasingly recognised as an essential adjunct to improved clinical assessment techniques. These collaborative endeavours will inevitably lead to a better understanding of ALS and its often

unpredictable progression, and will lead to the development of guidelines for improved care of patients. In this Seminar, we provide an up-to-date overview of the key developments across the ALS specialty.

Epidemiology and molecular genetics

Several factors have complicated epidemiological studies in ALS, including determination of a specific date of disease onset and the potentially long duration between onset of pathological changes and manifestation of clinical disease. This prodromal period between disease onset and presentation of symptoms possibly indicates the redundancy of neuronal populations. As a consequence, a range of epidemiological studies with rigorous designs and the use of unbiased patient cohorts have provided varying levels of evidence in support of different causative mechanisms of disease.^{1,2} Population-based studies have established that the incidence of ALS in Europe is fairly uniform at 2·16 per 100 000 person-years.³ Although ALS affects people worldwide, an exact incidence of this disease is not yet known.⁴ Men have a higher incidence of disease (3·0 per 100 000 person-years; 95% CI 2·8–3·3) than do women (2·4 per 100 000 person-years; 95% CI 2·2–2·6), although the incidence between men and women is about the same in familial disease. The overall population-based lifetime risk of ALS is 1:400 for women and 1:350 for men. Peak age at onset is 58–63 years for sporadic disease and 47–52 years for familial disease. Incidence decreases rapidly after 80 years of age.³

Although the ALS phenotype might seem similar across populations, there are subtle differences in clinical presentation across European registries.³ There is evidence from population-based studies that suggest that ALS is less common in individuals of mixed ancestral origin than in individuals of Spanish origin.⁴ In a population-based mortality study from Cuba,⁵ disease rates were 60% lower than in European and North American populations, lending support to previous observations of reduced frequency of ALS in those of Hispanic origin in North America.

About 5–10% of ALS is familial, with a Mendelian pattern of inheritance. To date, 13 genes and loci of major effect have been identified, many since 2009.^{6,7} Of the known genes, mutations in *SOD1* (encodes for

Search strategy and selection criteria

We searched Medline (1966, to December, 2009), EmBase (1980, to December, 2009), and the Cochrane Library using the search terms “amyotrophic lateral sclerosis” or “motor neurone disease” in combination with “diagnosis”, “epidemiology”, “fronto-temporal dementia”, “imaging”, “neurophysiology”, “management”, and “neuroprotection”. Further articles were included from reference lists, review articles, and major textbook chapters. Abstracts and reports from relevant meetings were also included. The final reference list was generated on the basis of originality and relevance to the topics covered in this Seminar. Emphasis was placed on publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications.

copper/zinc ion-binding superoxide dismutase), *TARDBP* (also known as *TDP-43*; encodes for TAR DNA binding protein), *FUS* (encodes fusion in sarcoma), *ANG* (encodes angiogenin, ribonuclease, RNase A family, 5), and *OPTN* (encodes optineurin) cause a typical clinical phenotype. Mutations in *SOD1* induce a toxic gain of function, although the pathophysiology remains unclear. Both *TDP-43*⁸ and *FUS*^{9,10} (also known as TLS [translated in liposarcoma]) are multifunctional proteins involved in gene expression and regulation, including transcription, RNA splicing, transport, and translation. *FUS* and *TDP-43* are also involved in the processing of small regulatory RNAs (microRNAs) and in RNA maturation and splicing. *ANG* is a hypoxia-responsive gene, which regulates RNA transcription.¹¹ *OPTN* is a causative gene of primary open-angle glaucoma. ALS-causing mutations of *OPTN* abolish the inhibition of activation of NF κ B, and change the cytoplasmic distribution of optineurin.

Mutations in *SOD1* account for 20% of familial ALS¹² and 5% of apparently sporadic disease. Mutations in *TARDBP* account for 5–10% of familial ALS, mutations in *FUS* for 5%, and mutations in *ANG* for about 1%.

The remaining 90% of people diagnosed with ALS are classified as having sporadic disease. For these patients, results from family aggregation studies have identified an overlap between ALS and common neurodegenerative disorders, suggesting the existence of susceptibility genes that might increase the overall risk of neurodegeneration among relatives.¹³ However, attempts to establish the complex genetic basis for sporadic ALS by identifying susceptibility genes have had little success. Results from candidate gene studies have identified several susceptibility genes,⁷ although the relative contribution of every identified “at risk” gene rarely exceeds an odds ratio of 2.0, and the mechanism by which risk is conferred is not known.

Despite the disappointing findings in several recent genome-wide association studies of sporadic ALS,⁴ a few possible genes have been identified. The main problem has been low power due to small sample sizes, with candidates being accordingly difficult to replicate in a second population.⁷ The recent identification of two new susceptibility genes through collaborative research¹⁴ suggests that further genes and pathways could be identified with increasingly effective cooperation between research groups. However, the poor track record of whole-genome association studies has led to a reconsideration of the “common disease, common variant” hypothesis in favour of a “common disease, multiple rare variant” hypothesis.

Clinical phenotypes and prognosis

The varied presentations of ALS¹⁵ are also crucial to the understanding and development of measures of disease progression.¹⁶ The identification of specific phenotypes has important implications for patients,

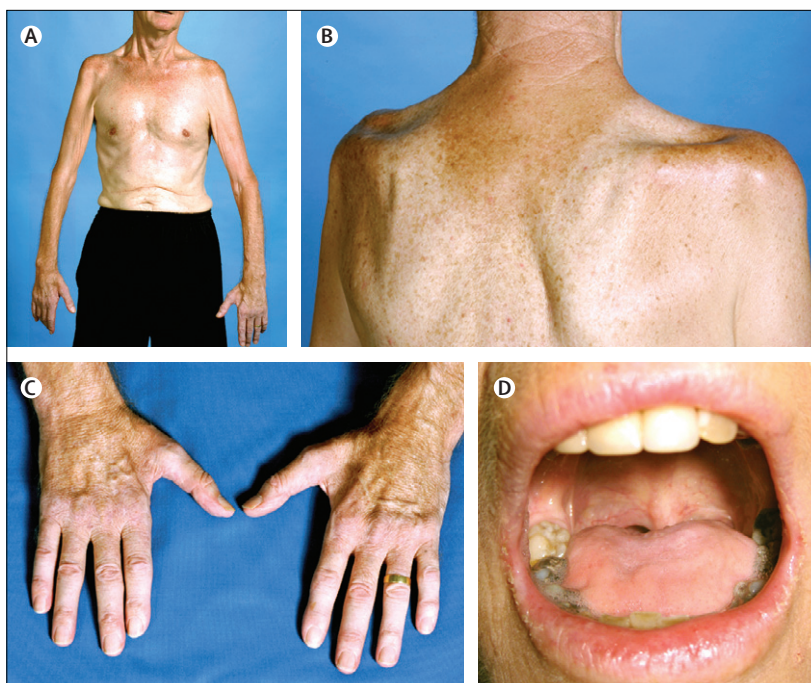


Figure 1: Clinical features of muscles wasting in a patient with ALS

Proximal and symmetrical upper limb wasting (A) results in an inability to lift arms against gravity (“man-in-the-barrel” or flail-arm variant ALS). Note the recessions above and below the scapular spine (B), indicating wasting of supraspinatus and infraspinatus muscles, as well as substantial loss of deltoid muscle. As a consequence, the glenohumeral joint becomes prominent, and prone to subluxation. (C) Disproportionate wasting of the thenar muscles combined with the first dorsal interossei, the so-called “split-hand”, is a typical feature in ALS.¹⁷ Although the mechanisms underlying this disproportionate wasting of hand muscles are unclear, a corticomotoneuronal origin has been proposed.¹⁷ Specifically, the thenar muscles and first dorsal interossei receive more extensive corticospinal connections and thereby might be prone to glutamate-mediated excitotoxicity.¹⁸ (D) Substantial wasting of the tongue muscles in bulbar-onset ALS. Note the absence of palatal elevation present on vocalisation. Difficulty with mouth opening and dysphagia might require supplementary feeding through a percutaneous endoscopic gastrostomy. In further support of a corticomotoneuronal hypothesis, the tongue is often disproportionately affected in comparison to other oropharyngeal musculature in patients with bulbar-onset ALS. As with the thenar muscles in the hand, the tongue receives more extensive cortical input than other muscle groups in the oropharyngeal area. ALS=amyotrophic lateral sclerosis.

particularly with regards to prognosis and survival, but also for their enrolment in clinical trials.

The main presentations of ALS include: (1) limb-onset ALS with a combination of upper and lower motor neuron (UMN and LMN) signs in the limbs; (2) bulbar-onset ALS, presenting with speech and swallowing difficulties, and with limb features developing later in the course of the disease (figure 1); (3) the less common primary lateral sclerosis with pure UMN involvement; and (4) progressive muscular atrophy, with pure LMN involvement.¹⁹

The clinical hallmark of ALS is the presence of UMN and LMN features involving brainstem and multiple spinal cord regions of innervation. Patients can present with bulbar-onset disease (about 25%) or limb-onset disease (about 70%), or with initial trunk or respiratory involvement (5%), subsequently spreading to involve other regions.²⁰ Atypical modes of presentation can include weight loss, which is an indicator of a poor prognosis, cramps and fasciculations in the absence of muscle

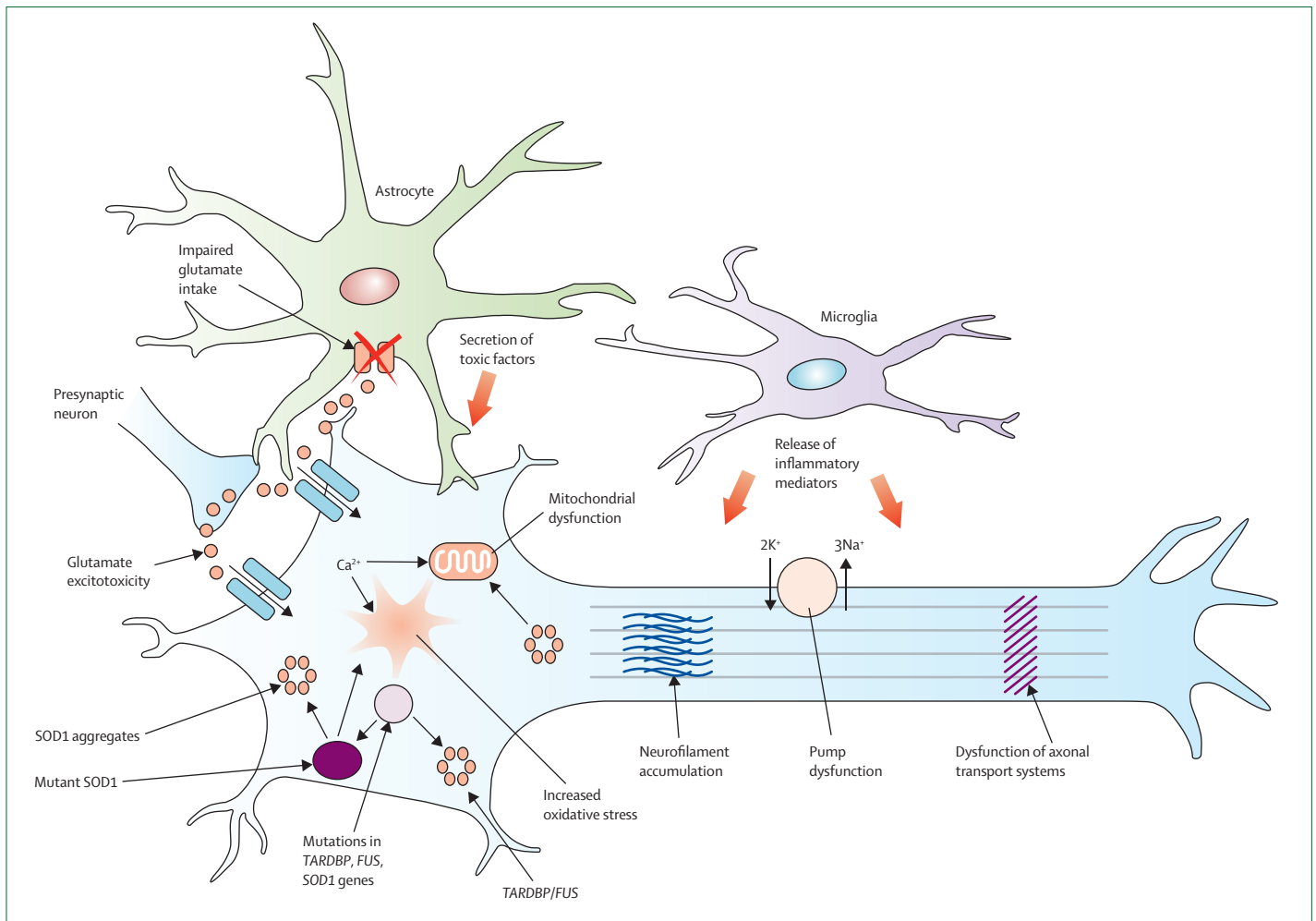


Figure 2: Cellular and molecular processes mediating neurodegeneration in ALS

The mechanisms underlying neurodegeneration in ALS are multifactorial and operate through inter-related molecular and genetic pathways. Specifically, neurodegeneration in ALS might result from a complex interaction of glutamate excitotoxicity, generation of free radicals, cytoplasmic protein aggregates, SOD1 enzymes, combined with mitochondrial dysfunction, and disruption of axonal transport processes through accumulation of neurofilament intracellular aggregates. Mutations in *TARDBP* and *FUS* result in formation of intracellular aggregates, which are harmful to neurons. Activation of microglia results in secretion of proinflammatory cytokines, resulting in further toxicity. Ultimately, motor neuron degeneration occurs through activation of calcium-dependent enzymatic pathways. ALS=amyotrophic lateral sclerosis.

weakness, emotional lability, and frontal lobe-type cognitive dysfunction.²¹

In terms of presentation, UMN disturbance involving the limbs leads to spasticity, weakness, and brisk deep tendon reflexes. By contrast, LMN limb features include fasciculations, wasting, and weakness. Bulbar UMN dysfunction results in spastic dysarthria, which is characterised by slow, laboured, and distorted speech, often with a nasal quality.²² The gag and jaw jerk can be pathologically brisk. Bulbar LMN dysfunction can be identified by tongue wasting, weakness, and fasciculations, accompanied by flaccid dysarthria and later dysphagia. Flaccid dysarthria results in nasal speech caused by palatal weakness, hoarseness, and a weak cough.²²

ALS is relentlessly progressive—50% of patients die within 30 months of symptom onset and about 20% of

patients survive between 5 years and 10 years after symptom onset.²³ Older age at symptom onset, early respiratory muscle dysfunction, and bulbar-onset disease are associated with reduced survival, whereas limb-onset disease, younger age at presentation, and longer diagnostic delay are independent predictors of prolonged survival.²³

Some ALS subtypes tend to lead to a better prognosis. Specifically, flail-limb variant ALS (figure 1A, figure 1B) and progressive muscular atrophy, both predominantly LMN forms, are characterised by slower progression than other forms of ALS.^{23,24} In the pure bulbar palsy phenotype, which typically affects women older than 65 years of age with disease remaining localised to oropharyngeal musculature and with UMN features predominating,²³ the prognosis varies from 2–4 years. Additionally, patients with primary lateral sclerosis progress more slowly than do patients with classic

ALS.^{19,23} A definite diagnosis of primary lateral sclerosis should be delayed for at least 4 years from disease onset, given that development of LMN signs can occur even if the initial presentation appears that of a pure spastic syndrome.²⁵ Distinguishing these phenotypes from the typical ALS phenotype has implications for clinical trials of putative disease-modifying therapies.

Fatigue and reduced exercise capacity are common symptoms in ALS²⁶ and, ultimately, most patients need assistance with activities of daily living. Dysphagia develops in most patients with ALS, with consequent weight loss and malnutrition associated with poor prognosis.²⁷ Respiratory compromise eventually develops in most cases of ALS, leading to exertional dyspnoea, orthopnoea, hypoventilation with resultant hypercapnia, and early morning headaches.²⁸ Death becomes imminent once patients develop dyspnoea at rest. Progressive weakening of the respiratory muscles leads to respiratory failure, often precipitated by pneumonia.

Overlap with frontotemporal dementia

The recent identification of TDP-43-positive ubiquitinated cytoplasmic inclusions in almost all cases of ALS, and more than half of patients with frontotemporal dementia (FTD), has rekindled interest in the overlap between these progressive neurodegenerative syndromes.²⁹ Although reported in early descriptions, overt cognitive symptoms and frank dementia were previously thought to be uncommon symptoms of ALS. Conversely, a few patients with FTD develop ALS.³⁰ Familial clustering of both disorders is also well recognised, with cases of FTD or ALS or coincident FTD-ALS presenting in families. The genes that cause these familial clusters are not yet known, but results from linkage studies have identified a common locus on chromosome 9.^{31–35}

Cognitive deficits might initially have a subtle appearance and are often overlooked, but with appropriate cognitive and neuropsychological assessment, 20–50% of patients with ALS fulfil the consensus criteria for probable or definite FTD.³⁶ The most commonly encountered deficits involve executive function,³⁷ either affecting language or personality, with the cognitive profile most closely resembling that of behavioural-variant FTD. In terms of clinical implications, problems with judgment, impulsivity, and a general deterioration in the ability to undertake routine daily tasks can develop into difficult problems with management of patients.³⁸ Impaired verbal fluency, which is more prominent in patients with pseudobulbar disease, inevitably hinders the simple task of patients being able to communicate their needs. Cognitive, and particularly executive dysfunction, can also adversely affect patient compliance with treatment, decision-making abilities, and potentially raise ethical and medico-legal concerns.³⁷

In further support of overlap between these two diseases, structural abnormalities, and specifically frontotemporal atrophy, have been identified by voxel-

Panel 1: Controversy in ALS—where does the disease begin?

- Despite Charcot's initial observation of concomitant UMN and LMN pathological changes in ALS, the question of where ALS begins has not been established. Resolution of this question might enhance the understanding of the pathophysiology of ALS and has diagnostic and therapeutic importance.
- The "dying-forward" hypothesis proposes that ALS is mainly a disorder of corticomotoneurons, which connect monosynaptically with anterior horn cells, mediating anterograde degeneration of anterior horn cells via glutamate excitotoxicity.
- Support for a dying-forward hypothesis includes:
 - Results from transcranial magnetic stimulation studies documenting that cortical hyperexcitability is an early feature in patients with sporadic ALS and precedes the clinical onset of familial ALS.
 - Clinical observations that: (1) motor neurons without a monosynaptic connection with corticomotoneurons, such as the oculomotor, abducens, and Onuf's nuclei, are typically spared in ALS; (2) the absence of a naturally occurring animal model of ALS is ascribed to a paucity of corticomotoneuronal-anterior horn cell connections; and (3) pure LMN forms of ALS are rare, whereas subclinical UMN involvement is invariably detected with transcranial magnetic stimulation studies.
- The "dying-back" hypothesis proposes that ALS begins within the muscle cells or at the neuromuscular junction. Specifically, there is deficiency of a motor neurotrophic hormone, which is normally released by postsynaptic cells and retrogradely transported up the presynaptic axon to the cell body where it exerts its effects.
- Support for the dying-back hypothesis includes:
 - Observations that synaptic denervation precedes the onset of motor neuron degeneration.
 - Synaptic denervation is mediated by accumulation of mutant SOD1 protein in Schwann cells.
- By contrast with the dying-forward and dying-back hypotheses, some investigators have proposed that UMN and LMN degeneration occur independently.

ALS=amyotrophic lateral sclerosis. LMN=lower motor neuron. UMN=upper motor neuron.

based morphometry MRI in patients with ALS and FTD-ALS. Bilateral atrophy of the motor and premotor cortices can develop,^{30,39} although patients with FTD-ALS typically have more severe frontotemporal atrophy than do patients with ALS alone.^{31,39} From a functional perspective, frontotemporal hypometabolism has been characterised in patients with ALS and FTD-ALS by use of 2-¹⁸fluoro-2-deoxy-D-glucose PET.³³ This frontotemporal atrophy seems to be associated with neuronal loss and cortical gliosis on post-mortem pathology. As for most patients with sporadic ALS, intraneuronal inclusions (TDP-43-positive) are present in half of patients with FTD.^{32,40} FUS-positive inclusions have been recently identified in patients with ubiquitin-positive, TDP-43-negative FTD and in patients with familial ALS caused by mutations in *FUS*^{39,40}—further emphasising the pathological overlap between ALS and FTD.

Pathophysiological mechanisms

The pathophysiological mechanisms underlying the development of ALS seem multifactorial (figure 2), with emerging evidence of a complex interaction between genetic and molecular pathways.^{41–43} ALS might be an

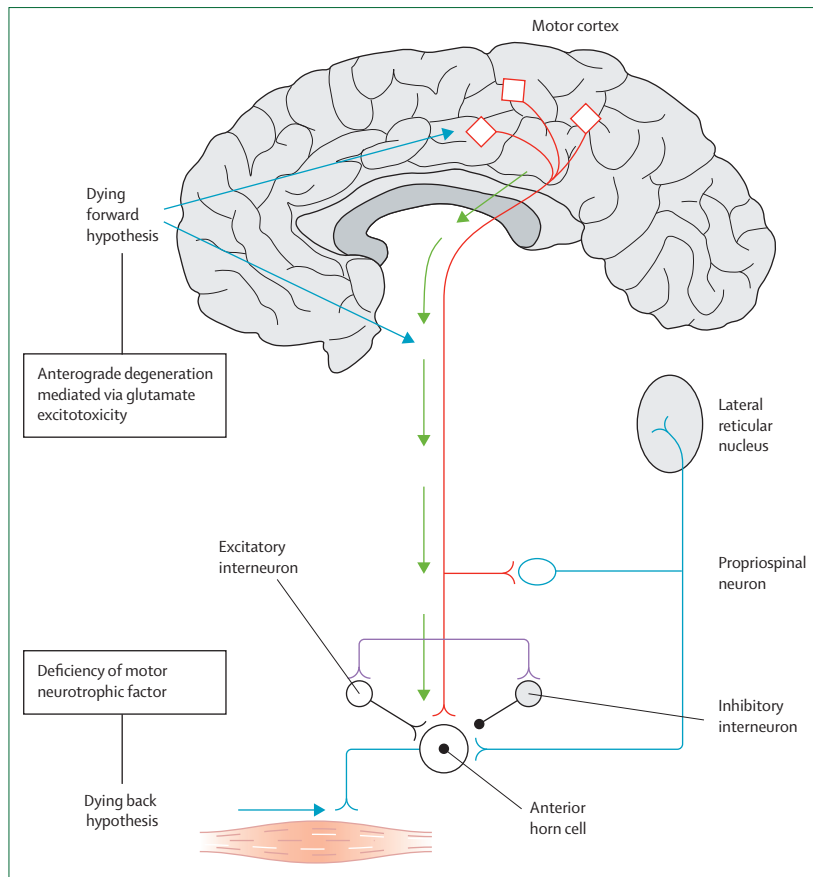


Figure 3: The “dying-forward” and “dying-back” hypotheses

adult manifestation of a developmental disorder of the human motor system. Specifically, in a Swedish case-control study,¹ low maternal age and high maternal age, and exposure to younger siblings, were associated with increased risk of developing ALS. Additionally, the development of the human motor system might potentially be perturbed during childhood by increased exposure to childhood infections, as occurs in families with young children. Various environmental risk factors for ALS have also been suggested, including a lifetime of intensive sport or physical exertion⁴⁴ and active service in the US armed forces.⁴⁵ In a retrospective study of football players from the Italian professional leagues, the standardised morbidity ratios were increased for development of ALS, particularly younger-onset disease.⁴⁶ For unknown reasons, footballers who played for more than 5 years, particularly in an active midfield position, were at highest risk of developing ALS. A cluster of ALS cases has also been reported in amateur football players from England.⁴⁷

With regards to smoking, cigarettes might have a dose-dependent effect on the subsequent development of ALS.⁴⁸ Neurotoxins, including β -methyl-amino-L-alanine, were associated with the development of an epidemic of ALS-Parkinson's disease on the island of Guam.⁴⁹ This

neurotoxic amino acid was concentrated in the brains of patients with ALS-Parkinson's disease and entered the human food chain by consumption of flying foxes. These bats, a delicacy of native Guamanians, the Chamorro, feed on cycad seeds that have high concentrations of β -methyl-amino-L-alanine.⁴⁹

No clear consensus has emerged to link *SOD1* mutations to the premature death of motor neurons. Current understanding links genetic mutations to a toxic gain of function of the *SOD1* enzyme,⁴¹ with generation of free radicals that eventually leads to cell injury and death.^{50–53} Additionally, *SOD1* mutations induce conformational instability and misfolding of the *SOD1* peptide, resulting in formation of intracellular aggregates^{51,54} that inhibit normal proteasomic function, disrupting axonal transport systems and vital cellular functions.^{50,51,55}

Glutamate-induced excitotoxicity has been implicated in ALS pathogenesis. Glutamate is the main excitatory neurotransmitter in the CNS, and binds to ionotropic N-methyl-D-aspartate (NMDA) receptors and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic membrane.^{56,57} Excessive activation of these postsynaptic receptors by glutamate, known as glutamate-induced excitotoxicity, can incite neurodegeneration through activation of calcium-dependent enzymatic pathways.^{58,59} Glutamate-induced excitotoxicity can also result in generation of free radicals, which in turn can cause neurodegeneration by damaging intracellular organelles and upregulating proinflammatory mediators.^{60,61}

The mechanism by which glutamate-induced excitotoxicity mediates motor neuron degeneration in human beings remains unclear (panel 1, figure 3). A so-called “dying-forward” process has been proposed, whereby UMN mediate anterograde degeneration of LMN by glutamate-induced excitotoxic processes.^{62,63}

In addition to glutamate-induced excitotoxicity, structural abnormalities of mitochondria, dysfunction of the sodium/potassium ion pump, autophagy, and disrupted axonal transport systems have all been implicated in the pathogenesis of ALS.^{64–70} Non-neuronal cells, such as astrocytes and microglia, might also directly contribute to neurodegeneration through mechanisms including insufficient release of neurotrophic factors, secretion of neurotoxic mediators, and modulation of glutamate receptor expression (known as non-cell autonomous neurodegeneration).⁷¹

Of further relevance, TDP-43 was recognised as a major component of ubiquitinated cytoplasmic protein aggregates in almost all patients with sporadic ALS, but not in the nucleus, as in normal neurons. Although there were questions about whether such aggregates triggered neurodegeneration in ALS, mutations in *TARDBP* were reported in 3% of familial ALS and 1·5% of patients with sporadic ALS, suggesting that TDP-43 aggregates have a central role in triggering ALS.^{8,72} Evidence for the pathogenicity of

TARDBP mutations was suggested when mutations identified in highly conserved regions of DNA were not evident in controls, and segregated with the disease.^{8,72} Given that TDP-43 binds both DNA and RNA, mutations in *TARDBP* could result in dysregulation of RNA processing.

Identification of *FUS* mutations on chromosome 16 associated with familial forms of ALS lends further support to this theory. *FUS* aggregates were not evident in patients with pathological changes in TDP-43 or SOD1, indicating a novel disease pathway.¹⁰ Although the identification of a causative effect between mutations in the *TARDBP* and *FUS* genes and ALS was a major leap in understanding ALS pathogenesis, several factors need to be resolved. Do mutations in these DNA/RNA-binding proteins indicate a toxic gain or loss of function?⁷³ Does neurotoxicity result from the misfolded proteins overwhelming the cells' protein surveillance pathways or from sequestration of vital proteins and genomic material by TDP-43 and *FUS* aggregates? And what is the association between previously established pathophysiological mechanisms and the TDP-43 and *FUS* proteins?

Diagnosis

Without a diagnostic test for ALS, clinicians mostly rely on identifying the combination of UMN and LMN signs in the same body region, with subsequent evidence of disease progression to other regions. The El Escorial criteria,⁷⁴ revised in 1997,⁷⁵ use a combination of UMN and LMN signs to establish levels of diagnostic certainty. Clinical trial investigators have tended to enrol patients with either probable or definite ALS according to the El Escorial criteria, highlighting their universality, although inclusion of these diagnostic features as enrolment criteria might be argued as restrictive.⁷⁶ Furthermore, these criteria can have poor sensitivity, particularly in the early stages of ALS when patients are most likely to benefit from therapeutic intervention.⁷⁷ Because of these criticisms, the criteria have been modified to help early diagnosis⁷⁸ and to optimise levels of diagnostic certainty, important in the clinical trial setting.⁷⁹

There is often a long delay before a definitive diagnosis is reached, partly because of the insidious onset of symptoms, with the median time to diagnosis of about 14 months.⁸⁰ Unusual clinical presentations, a low index of suspicion, and misinterpretation of neurophysiological or neuroradiological findings are common causes of diagnostic uncertainty.¹⁵ Unfortunately, diagnostic delay can lead to use of inappropriate therapies, a delay in starting appropriate pharmacological and symptomatic therapies, and problems in dealing with psychosocial factors.

The diagnosis of ALS is devastating for the patient and family members, and must be handled sensitively. Patients and family members can carry the emotional burden of an

Panel 2: Differential diagnosis of ALS and appropriate investigations

Disorders of motor neurons

- Spinal muscular atrophy (*SMN* gene deletion assay)
- X-linked spinobulbar muscular atrophy (Kennedy's disease; increased CAG repeats in DNA from blood)
- Poliomyelitis or post-polio syndrome (history, NCS, electromyography)
- Hexosaminidase A deficiency (white-cell enzyme testing)

Disorders of motor nerves

- Multifocal motor neuropathy (NCS, electromyography, ganglioside GM1 antibodies)
- Chronic inflammatory demyelinating neuropathy (NCS, lumbar puncture)
- Cramp-fasciculation syndrome (NCS, electromyography)
- Neuromyotonia (antibodies to voltage-gated potassium channels)
- Hereditary spastic paraparesis plus (gene mutation testing)
- Hereditary motor neuropathy with pyramidal features
- Radiculoplexopathy (NCS, electromyography, MRI)
- Paraneoplastic syndrome (serum markers, imaging, bone marrow biopsy sample)
- Heavy metal poisoning (urine or blood screens)
- Mononeuritis multiplex (NCS, electromyography, vasculitic screen, serology)

Disorders of neuromuscular junction

- Myasthenia gravis (acetylcholine receptor antibodies, MuSK antibodies, repetitive stimulation, single-fibre electromyography)
- Lambert-Eaton myasthenic syndrome (repetitive stimulation)

Structural CNS and spinal lesions

- Syringomyelia or syringobulbia (MRI)
- Tabes dorsalis (syphilis serology)
- Multiple sclerosis (MRI, oligoclonal bands, evoked responses)
- Monomelic spinal muscular atrophy (Hirayama's disease; electromyography, MRI)
- Lyme disease (Lyme serology)
- Human T-lymphotropic virus-1 (HIV)

Myopathy

- Inclusion body myositis (electromyography, CK, muscle biopsy sample)
- Polymyositis (electromyography, CK, muscle biopsy sample, autoimmune screens)
- Dermatomyositis (electromyography, CK, skin, and muscle biopsy sample)
- Polyglucosan body disease (NCS, electromyography, muscle or nerve biopsy sample)

Endocrine

- Thyrotoxicosis (thyroid function tests, electromyography, muscle biopsy sample)
- Hyperparathyroidism (calcium ion and parathyroid testing)
- Subacute combined degeneration (vitamin B₁₂ concentrations)
- Coeliac disease (serum testing, bowel biopsy sample)

ALS=amyotrophic lateral sclerosis. CK=creatine kinase. NCS=nerve conduction studies. MuSK=muscle-specific tyrosine kinase.

insensitively delivered diagnosis for the entire disease course, and initial indecision about the diagnosis in atypical cases can delay the process of accepting the terminal prognosis of the disease. Scheduling a follow-up appointment soon after diagnosis is beneficial to answer questions not dealt with during the initial consultation and can help provide further information about support networks, which are well established in most developed nations.⁸¹

Although rare, the existence of several disorders that mimic ALS necessitates a thorough diagnostic

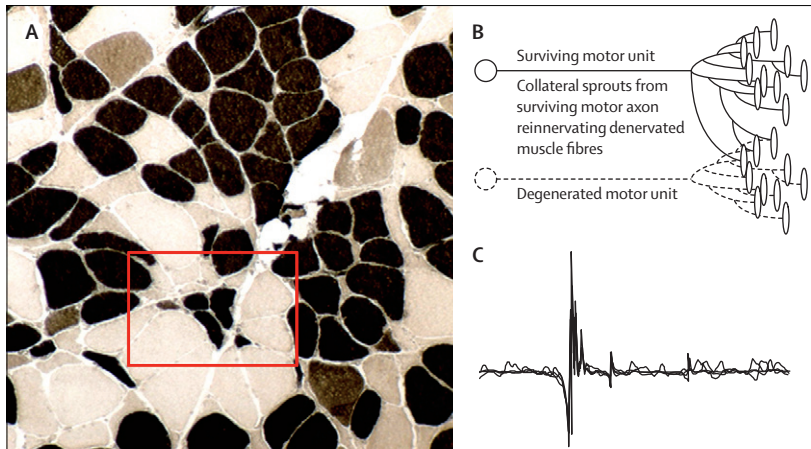


Figure 4: Investigation findings in ALS

(A) Biopsy sample of the left vastus lateralis muscle from a patient with ALS, stained with ATPase pH 9.4. The biopsy sample highlights grouped atrophic fibres with both type I and type II fibres (mixed-type fibres, encompassed by red box). (B) Pathophysiology of motor unit degeneration and reinnervation; with superimposition (C) of ten traces demonstrating the typically large, polyphasic, unstable (complex) motor units observed in established ALS (sweep duration 50 ms), with late components, indicating some re-innervation. ALS=amyotrophic lateral sclerosis.

assessment, which usually includes structural imaging and neurophysiological and laboratory investigations, to reduce the likelihood of an incorrect diagnosis (panel 2).²⁰ In cases of pure LMN syndromes, genetic testing for Kennedy's disease, an X-linked bulbospinal atrophy, and spinal muscular atrophy is important.⁸² Muscle biopsy samples can be of further diagnostic value for excluding unusual myopathies such as polyglucosan body disease⁸³ or for confirming the presence of ALS by indicating atrophy of mixed-fibre types (figure 4A).⁸⁴

Routine neurophysiological investigations of patients with ALS include nerve conduction studies, electromyography, and, less commonly, transcranial magnetic stimulation.^{20,85} Nerve conduction studies are essential to exclude disorders that mimic ALS, particularly demyelinating motor neuropathies.⁸⁶ Motor nerve conduction is normal in the early stages of ALS, but in advanced disease the compound muscle action potential amplitude becomes reduced, indicating denervation.⁸⁷ Sensory nerve conduction is typically normal in patients with ALS, differentiating ALS from demyelinating neuropathies.⁸⁸ Prominent abnormalities of sensory nerve conduction studies should raise suspicion of an alternative diagnosis. In patients presenting with predominantly LMN findings, treatable disorders such as multifocal motor neuropathy should be taken into account, with indication of conduction block in at least two motor nerves outside the common entrapment sites.⁸⁹

In addition to nerve conduction studies, electromyography is useful for the identification of LMN loss (figure 4B). The electromyographical findings indicating LMN loss include fibrillation potentials, positive sharp waves, and chronic neurogenic changes (figure 4C).^{86,90} These electromyographical abnormalities have been

recently incorporated into the revised El Escorial criteria to help with the diagnosis of ALS, complementing the clinical features of LMN involvement.⁹⁰ Fibrillation potentials and positive sharp waves can be evident in muscles that seem clinically normal.⁸⁶ Electromyography can therefore help with an early diagnosis by establishing the presence of subclinical LMN involvement.

Motor units that survive can fire spontaneously as fasciculation potentials, clinically visible as involuntary muscle twitching—a typical feature of ALS.⁹¹ When detected in the tongue, fasciculations are highly specific for ALS.⁹² The presence of fasciculations in the absence of other electromyographical findings should be interpreted with caution and can be a sign of less serious disorders, especially “benign” cramp-fasciculation syndrome.⁹³ Conversely, recently revised consensus guidelines (known as the Awaji Island criteria) have recommended that fasciculations should be thought to be equivalent to fibrillation potentials in individuals with clinically suspected ALS.⁹⁰ Furthermore, fasciculations in ALS are complex (“malignant”), indicating re-innervation, and have diagnostic importance when combined with chronic neurogenic changes (figure 4C).

There is discussion about how successful clinicians are at diagnosing ALS when using the combined approaches of clinical assessment and laboratory investigation. This matter was taken into account by the Scottish ALS registry, which identified a false positive rate of 8%.¹⁵ Other data from population-based studies have reported similar false-positive rates, with a false-negative rate approaching 44%.^{94,95} In false-positive cases, the main reasons for diagnostic revision included failure to progress, development of atypical features, and results of follow-up neurophysiological and neuroradiological investigations.^{15,94} Multifocal motor neuropathy was the most frequent disorder misdiagnosed as ALS, followed by Kennedy's disease.⁹⁴

Advances in neuroimaging

The greatest contribution of neuroimaging to the diagnostic pathway in ALS so far has been the ability of MRI to exclude alternative pathological causes. However, the imaging discipline is evolving, and multimodal neuroimaging has made major progress in the confirmation that ALS is a multisystem cerebral neurodegenerative disorder.⁹⁶ The key neuroimaging findings, some with potential as biomarkers, are discussed in panel 3.

Management and prevention

Riluzole, an inhibitor of glutamate release, is a disease-modifying (neuroprotective) therapy for patients with ALS (panel 4). In two large randomised controlled trials, riluzole extended survival of patients by 3–6 months.^{126–128} This benefit seemed greater for management of patients in specialised multidisciplinary ALS clinics than in other settings,¹²⁹ with most beneficial effects seen in patients with moderate functional impairment.¹³⁰

Panel 3: Key neuroimaging findings in ALS

MRI corticospinal tract hyperintensity

Hyperintensity of the corticospinal tracts as seen on MRI can be prominent in ALS,^{85,97} but this feature is not specific to the disease (figure 5A).

Cerebral atrophy detection with MRI

Voxel-based morphometry has quantified grey and white matter to detect cerebral atrophy in patients with ALS⁹⁸ linked to cognitive impairment,⁹⁹ with notable differences in regional emphasis between patients with sporadic disease and those with familial disease who have a longer life expectancy.¹⁰⁰ 3-Dimensional rendering of the brain by use of MRI might also serve to highlight focal abnormality (figure 6).

Magnetic resonance spectroscopy

The measurement of proton-containing metabolites such as *N*-acetylaspartate (expressed as a ratio with creatine/ phosphocreatine or choline) has served as a marker of neuronal loss. Patients with ALS have a reduced primary motor cortex *N*-acetylaspartate to creatine ratio compared with controls,¹⁰¹ and use of magnetic resonance spectroscopy seems particularly sensitive in the detection of upper motor neuron dysfunction, distinguishing patients with progressive muscular atrophy from those with ALS.¹⁰²

Diffusion tensor imaging

Diffusion tensor imaging can be used to exploit the sensitivity of MRI to identify the direction of water diffusion, which is expected to be restricted (ie, anisotropic) within intact neuronal pathways and more diffuse (isotropic) in regions of reduced integrity. Quantifiable measures such as fractional anisotropy and mean diffusivity are powerful surrogate markers of neuronal pathological changes,¹⁰³ and inter-connectivity between neuronal pathways can be mapped using the allied technique of tractography (figure 5B).¹⁰⁴ Use of diffusion tensor imaging can detect reduced fractional anisotropy within the corticospinal tract of patients with ALS.¹⁰⁵

Functional studies

Results of PET activation studies with 2-¹⁸F-fluoro-2-deoxy-D-glucose and H₂¹⁵O have indicated widespread extramotor changes in patients with ALS,¹⁰⁶ with frontal deficits linked to neuropsychological impairment,¹⁰⁷ providing clear application to

the emerging clinicopathological overlap between ALS and FTD.¹⁰⁸ Non-invasive study of brain activation by functional MRI exploits differences in the resonant properties of oxyhaemoglobin versus deoxyhaemoglobin (blood oxygenation level dependent [BOLD]-functional MRI). By analysing whole-brain BOLD-functional MRI activity in the resting state, functionally interconnected brain regions can be identified.¹⁰⁹ Results from studies in patients with ALS have shown both “default mode” and sensorimotor network activation changes.¹¹⁰ This technique has the potential to further delineate the extramotor cerebral pathological changes in patients with ALS.

Molecular imaging

Receptor ligand PET has been used to study molecular mechanisms in ALS. Data from ¹¹C-flumazenil PET have indicated reduced inhibitory GABAergic cortical effects in ALS,¹¹¹ in keeping with the hypothesis of cortical hyperexcitability as a fundamental aspect of ALS pathogenesis.¹¹² Use of the benzodiazepine receptor PET ligand ¹¹C-PK11195 revealed widespread microglial activation in ALS,¹¹³ supported by the finding of inflammatory biomarkers in the cerebrospinal fluid.¹¹⁴ The pronounced frontotemporal reductions in the binding of the 5-HT_{1A} receptor ligand ¹¹C-WAY100635 in patients with ALS,¹¹⁵ and data from neuropathological receptor studies that revealed similar changes in FTD,¹¹⁶ suggest that serotonergic mechanisms warrant further study in relation to pathogenesis. Finally, paramagnetic properties of small particles of iron oxide, which can be used as intravenous contrast agents, might indicate the start of the era of molecular MRI,¹¹⁷ with potential to understand inflammatory mechanisms¹¹⁸ and therapeutic stem-cell tracking.¹¹⁹

Detection of presymptomatic markers of disease

The poor definition of the population at risk for sporadic ALS impedes attempts to identify an early, presymptomatic diagnostic biomarker. Results from a diffusion tensor imaging study of presymptomatic patients with a highly penetrant dominant *SOD1* gene mutation revealed changes in the posterior limb of the internal capsule not seen in healthy controls, which might be among the earliest detectable changes.¹²⁰

ALS=amyotrophic lateral sclerosis. FTD=frontotemporal dementia.

Symptomatic treatments remain the cornerstone of management for patients with ALS (panel 5).²⁸ For some patients, these treatments not only alleviate symptoms but also improve survival and quality of life.¹³¹ Optimum care for patients with ALS is provided within a multidisciplinary environment where physiotherapists, occupational therapists, speech therapists, respiratory physicians, gastroenterologists, and social workers collaborate to guide symptomatic management through the course of disease.¹³² Multidisciplinary models of care have developed as a predictor of survival, reducing the risk of death by 45%

at 5 years. Compared with patients managed in a general neurology clinic, patients managed in a specialised clinic had a better quality of life, possibly attributable to more effective use of resources, with benefits derived after a single visit.¹³²

Respiratory function and nutrition are crucial symptomatic concerns for patients with ALS, with respiratory failure being the main cause of death.⁸¹ Expert consensus guideline recommendations have been developed for key care concerns in ALS, including respiratory management, nutrition, and palliative care.^{81,131} A positive outlook should be emphasised.¹³³

Panel 4: Controversy in ALS—clinical trials

Although clinical trials of ALS have been done since the 1980s, riluzole is the only drug of proven efficacy for treatment of this disorder. The failure of ALS clinical trials to lead to substantial benefits has been attributed to several potential design problems at preclinical and clinical levels:

Preclinical

- Inappropriate mouse model. Until recently, the SOD1 mouse model has been the benchmark for testing potential neuroprotectants in ALS.¹²¹ However, as SOD1 mutations account for about 2% of all ALS cases, the mouse model might have little relevance to human sporadic disease. Furthermore, this model undergoes a series of stereotypical changes that begin with hind limb weakness. The recent development of mouse models with mutations in the gene encoding TDP-43 is a potential advance in therapeutic development for ALS, providing basic scientists with a new, perhaps more relevant, platform for studying novel therapies.¹²²
- Inappropriate timing of introducing drugs and dosing problems. Some investigators have studied the effects of presymptomatic delivery of drugs on disease onset.¹²³ Although this timing might contribute towards understanding the subclinical processes that underlie motor neuron degeneration, it seems to be of little relevance for treatment of sporadic ALS. Many preclinical studies have also examined ultra-high doses of drugs that would probably translate into plasma concentrations far beyond that tolerable by human patients. Some investigators have advocated that the highest tolerable dose should not be assumed to produce the best outcome.¹²⁴

Clinical

- Trial design. There is increasing need for more effective screening of pharmacological drugs during phase 2 trials because after this period of clinical development a decision is made to proceed with confirmatory testing (ie, a phase 3 trial) or to reject the drug as ineffective. The distinction between phase 2 and phase 3 trials in ALS becomes blurred, because providing preliminary evidence of drug efficacy in this disease at the phase 2 level is difficult. The absence of an effective biomarker is a major contributing reason. Therefore, the dilemma remains whether to use efficient statistical strategies for minimising trial duration and sample size, to increase the chance of proceeding with a phase 3 trial (ie, higher false-positive rate), or to do phase 3 clinical trials tailored as phase 2 clinical trials (ie, higher false-negative rate). The latter approach is perhaps one that is now rarely done, given recent advances in statistical design.¹²⁵ Investigators are also proceeding with phase 3 clinical trials, even in the absence of preliminary evidence of efficacy in human patients.
- Choice of primary endpoint. Changes in the primary endpoint establish whether a trial will be successful. The choice of the correct primary endpoint in ALS clinical trials has been debated. Trials that use functional scales and measures of strength as primary endpoints have dominated the field, whereas trials mainly concerned with improved survival of patients have been few and far between recently. The design and clinical benefits of the former include: smaller sample size, shorter trial duration, and clinically meaningful treatment effects. Nevertheless, measurement of survival might be the only means of determining whether a treatment effect truly exists, given the large extent of motor neuron loss from the time of symptom onset. For example, riluzole has small but significant effects on the function of patients, detectable with sample sizes far beyond that required to realise its survival benefit.

ALS=amyotrophic lateral sclerosis.

Respiratory failure indicates combined degeneration of central respiratory centres and motor neurons contributing to the phrenic nerve. Respiratory compromise is commonly present at diagnosis in patients with ALS.²⁸ Nocturnal hypoxia, and associated symptoms of lethargy, loss of

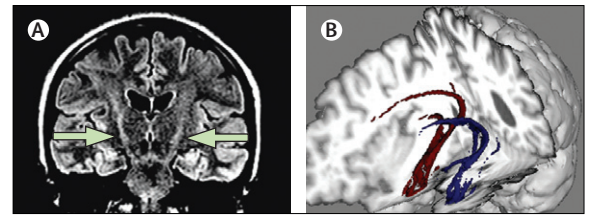


Figure 5: Standard and experimental MRI sequences in patients with ALS
(A) T2-weighted FLAIR sequence shows hyperintense corticospinal tracts in a patient with ALS on this coronal view (arrows), but this feature is neither sensitive nor specific in the absence of other more obvious clinical symptoms. (B) Diffusion tensor tractography is a research-based MRI technique that has potential to study extramotor and motor neuronal pathway involvement in ALS (superior oblique cut-out brain section viewed from left). In this patient with an unusual ALS phenotype that included prominent aphasia, reconstruction of the temporal lobe white matter projection fibres indicated that there were fewer fibres on the left (blue) compared with the right (red) side. ALS=amyotrophic lateral sclerosis. FLAIR=Fluid-attenuated inversion-recovery.

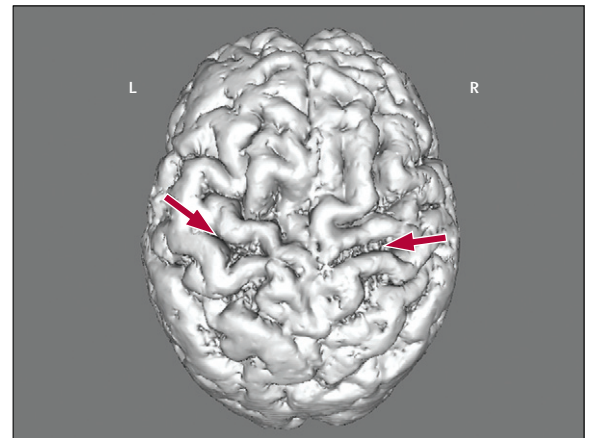


Figure 6: 3-Dimensional MRI of a brain of a patient with primary lateral sclerosis, as shown from above
Arrows show visibly widened precentral sulci with relative atrophy of the adjacent gyri, notably the motor strips. Macroscopic atrophy as seen here is rare in patients with typical ALS, but is more frequently noted in those with primary lateral sclerosis, who have a predominantly upper motor neuron burden of disease. This figure highlights the late stage of a corticomotoneuronal process postulated to be inherent in ALS more generally. ALS=amyotrophic lateral sclerosis.

concentration, morning headaches, and unrefreshed sleep are consequences of central dysfunction. Diaphragmatic weakness can be diagnosed with spirometry, with vital capacity undergoing a progressive decline over the course of disease. Measures of inspiratory muscle strength, such as maximum inspiratory pressure and sniff nasal inspiratory pressure, are more accurate predictors of respiratory dysfunction than is vital capacity, and might be more feasible in patients with substantial facial muscle weakness (ie, who are unable to form a tight lip seal).^{28,81}

Although undertaking polysomnography might be the optimum approach to identify nocturnal hypoxic episodes, nocturnal pulse oximetry is usually adequate in patients with ALS.⁸¹ Non-invasive ventilation improves quality of life in patients with ALS and improves survival.¹³⁴ Guidelines for instituting non-invasive ventilation rely on a combination of symptoms that

Panel 5: Symptomatic care in ALS**Weakness and disability**

- Orthotics (eg, ankle foot orthosis, neck collars)
- Physiotherapy
- Adaptive aids (eg, walking frame, wheelchair)

Dysphagia

- Assessment by speech therapist and dietitian
- Safe swallowing techniques and modified diet
- Insertion of gastrostomy tube

Dyspnoea and poor cough

- Ventilatory support
- Morphine or benzodiazepines
- Chest physiotherapy
- Suction machine
- Manually assisted coughing techniques

Pain (ie, musculoskeletal pain and cramps, fasciculations and spasticity, skin pressure pain caused by immobility)

- Physiotherapy, NSAIDs
- Muscle relaxants (baclofen, botulinum toxin)
- Anticonvulsants (eg, gabapentin)
- Re-positioning and pressure area care
- Opioid drugs
- Pressure-relieving cushions and mattress

Dysarthria

- Assessment by speech pathologist
- Communication aids
- Educate family and caregivers

Cognitive changes (frontal lobe dysfunction or dementia)

- Explain symptomatology to caregivers and family
- Antidepressant therapies

Sialorrhoea

- Anticholinergic antidepressants (eg, amitriptyline)
- Anticholinergic drugs (eg, glycopyrronium bromide)
- Botulinum toxin injections
- Radiation of salivary glands
- Mouth-care products
- Suction

Thickened saliva

- Natural remedies (eg, papaya)
- Ensure adequate hydration
- Saline nebulisers; nebulised N-acetylcysteine
- Suctioning of the mouth
- Mouth care

Emotional lability

- Educate patients with ALS and caregivers
- Amitriptyline
- Benzodiazepines
- Dextromethorphan hydrobromide/quinidine sulfate

Depression and anxiety

- Counselling
- Benzodiazepines
- Antidepressants

Sleep disturbance

- Treat underlying problem
- Respiratory review, non-invasive ventilation
- Benzodiazepines, tricyclic antidepressants

Constipation

- Dietary changes (eg, increase fluid and fibre intake)
- Use formulations high in bran, bulk, or fibre
- Regular oral aperients (Movicol [Norgine, the Netherlands] or suppositories).

ALS=amyotrophic lateral sclerosis. Data from Andersen and colleagues⁸¹ and Miller and colleagues.¹³¹

signify respiratory muscle weakness (dyspnoea and orthopnoea), along with signs of respiratory muscles weakness, including substantial desaturation on overnight oximetry, increased partial pressure of carbon dioxide (PCO₂) of less than 65 mm Hg and reduced forced vital capacity of less than 80% or sniff nasal inspiratory pressure of less than 40 cmH₂O.^{28,81} Patients with substantial bulbar impairment and sialorrhoea might not tolerate non-invasive ventilation, and appropriate management of secretions is crucial.²⁸ In patients with ALS who are intolerant of non-invasive ventilation, when this form of ventilation is no longer sufficient because of progressive respiratory muscle weakness, invasive ventilation via tracheostomy is an

option.⁸¹ Although invasive ventilation prolongs survival, this approach is rarely used in most countries because of the practical challenges involved, the expense, and the profound loss of quality of life.¹³⁵ In terms of symptomatic therapy, subcutaneous morphine provides great relief in patients who have dyspnoea at rest.^{81,136}

Malnutrition is a key determinant of prognosis.¹³⁷ The development of malnutrition in ALS is multifactorial, and includes reduced food intake secondary to dysphagia, as well as hypermetabolism.^{81,138} About 50–60% of patients with ALS have a hypermetabolic state,^{139,140} which seems to be stable over the course of the disease and is dependent on age, sex, and fat-free mass.¹³⁹ The increase in metabolic rate, as measured by resting energy

Panel 6: Controversy in ALS—alternative and off-label treatments

Given the terminal nature of ALS, the fact that patients are often willing to experiment with unproven therapies is not surprising. Popular alternative and off-label treatments have included insulin-like growth factor-1, lithium carbonate,⁷⁰ minocycline,¹⁴⁴ and stem-cell therapy. Patients should take caution when starting alternative and off-label treatments. As identified by some ALS clinical trials, some treatments can accelerate the progression of muscle weakness and negatively affect survival.

To keep the ALS community informed of available alternative and off-label treatments, an internet-based initiative, ALSUntangled, has been established recently.¹⁴⁵ ALSUntangled enables the exchange of information about new alternative and off-label treatments between patients with ALS and clinicians. Patients with ALS are encouraged to share newly hypothesised alternative and off-label treatments, as the goal of this initiative is to consolidate and convey information about cost, scientific and ethical basis, and potential benefits and risks of every so-called treatment.

ALS=amyotrophic lateral sclerosis.

expenditure, is associated with reduced survival.¹³⁹ Although the mechanisms that underlie a hypermetabolic state are unclear, dysfunction of muscle mitochondria is implicated in the pathogenesis of ALS.¹⁴¹

Insertion of a percutaneous gastrostomy tube ensures sufficient caloric and fluid intake, and should be offered to patients who have substantial weight loss, even in the absence of dysphagia.⁸¹ Implementing a gastrostomy should be discussed early in the disease course because morbidity increases when vital capacity is less than 50%.¹⁴²

Attention to the many symptoms that might develop during the course of the disease is essential to improve the quality of life for patients with ALS (panel 5).¹⁴³ The terminal phase of ALS can be associated with restlessness, anxiety, pain, and dyspnoea, and well coordinated multi-disciplinary palliative care is needed. Finally, patients might also seek alternative treatments (panel 6), often with little evidence of benefit for ALS, and at great personal financial cost.¹⁴⁶

Conclusions

“Let us keep looking, in spite of everything. Let us keep searching. It is indeed the best method of finding, and perhaps thanks to our efforts, the verdict we will give such a patient tomorrow will not be the same we must give this man today.”

Charcot (1889)

By contrast with the previous century of little progress, the recent developments in understanding, particularly with regards to the genetics, clinical phenotypes, and

more general pathophysiology of ALS, encourage realistic hope that new treatment approaches will emerge.

Contributors

BCC and MCZ did the literature search and contributed to sections on management and prevention of ALS. OH and MRT contributed to the review of the literature and the writing of the paper. MCK did the literature review, coordinated authors' writing, revision, and editing, wrote the first draft, prepared figures, and finalised the manuscript. JRB wrote the section on clinical phenotypes and on FTD-ALS, and was involved in revising the manuscript. SV searched the literature, was involved in writing and proofreading the paper, and helped prepare the figures. AE contributed to the sections on management and prevention of ALS and to the writing of the paper.

Conflicts of interest

OH has consulted for ONO Pharmaceuticals and KNOPP Pharmaceuticals, and has received research support from Sanofi-Aventis and Serono Pharmaceuticals. OH has received advisory board fees from Novartis, Biogen, and Merck Sorono, and has received travel and accommodation sponsorship from Merck Sorono. She is the inventor of a patent held by the Royal College of Surgeons in Ireland for the use of angiogenin as a therapeutic in ALS. Funding sources include the National Health and Medical Research Council of Australia (project grants 510233 and 568743; MCK); the Motor Neurone Disease Research Institute of Australia (MCK); the Irish Health Research Board (OH); American ALS Association (OH); the Irish Motor Neurone Disease Research Foundation (OH); and the Medical Research Council (Lady Edith Wolfson Clinician Scientist Fellowship; MRT). SV has received the Clive and Vera Ramacciotti grant and the Charles Viertel grant, and has received fees for advisory board from Merck Serono Australia, Novartis Australia, and Biogen (not related to the topic covered in this paper). BCC, AE, JRB, and MCZ declare that they have no conflicts of interest.

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