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A REVIEW ON AMYOTROPHIC LATERAL SCLEROSIS

***Duddela Yamini (M. Pharm)**

Sri Padmavati Mahila Visvavidyalayam.

***Corresponding Author: Duddela Yamini**
Sri Padmavati Mahila Visvavidyalayam.

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscular paralysis reflecting degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord. Gradually, spasticity may develop in the weakened atrophic limbs, affecting manual dexterity and gait. Patients with bulbar onset ALS usually present with dysarthria and dysphagia for solid or liquids, and limbs symptoms can develop almost simultaneously with bulbar symptoms, and in the vast majority of cases will occur within 1–2 years. Paralysis is progressive and leads to death due to respiratory failure within 2–3 years for bulbar onset cases and 3–5 years for limb onset ALS cases. Two percent of apparently sporadic patients have *SOD1* mutations, and *TARDBP* mutations also occur in sporadic cases. The diagnosis is based on clinical history, examination, electromyography, and exclusion of 'ALS-mimics' (*e.g.* cervical spondylotic myelopathies, multifocal motor neuropathy, Kennedy's disease) by appropriate investigations. Signs of upper motor neurone and lower motor neurone damage not explained by any other disease process are suggestive of ALS. The management of ALS is supportive, palliative, and multidisciplinary. Analysis of large patient samples drawn from clinic based populations or population registries consistently show that the overall median survival from onset of symptoms for ALS ranges between 2–3 years for bulbar onset cases and 3–5 years for limb onset ALS cases. Large clinic cohort studies have shown 3 year and 5 year survival tares to be around 48% and 24% respectively, with approximately 4% surviving longer than 10 years, whereas 5 year survival reported in population based studies is much lower and ranges from 4–30%

KEYWORDS: Amyotrophic lateral sclerosis (ALS), Motor neurone disease (MND), Charcot's disease, Lou Gehrig's disease, (EMG): electromyography; (PMA): progressive muscular atrophy; (PLS): primary lateral sclerosis, (MND): motor neurone disease; (PBP): progressive bulbar palsy; (PMA): progressive muscular atrophy; (CSF): cerebrospinal fluid; (WFN): World Federation of Neurology; (FALS).

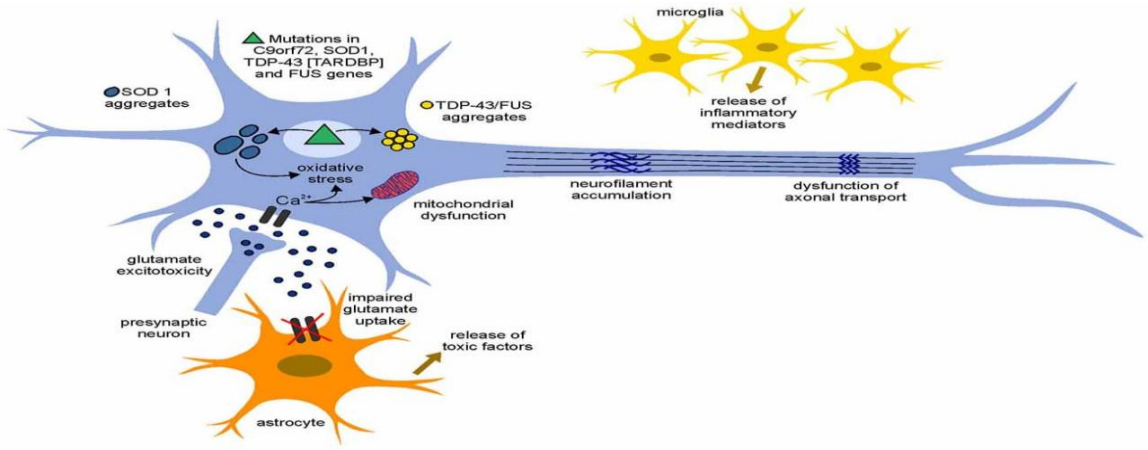
INTRODUCTION

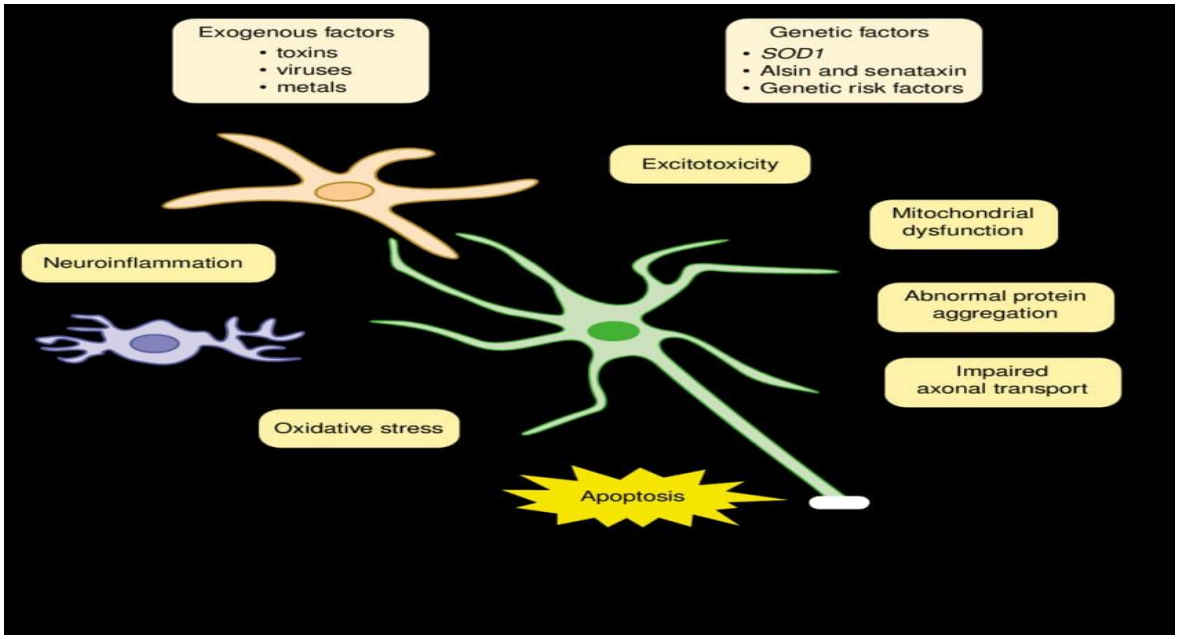
Amyotrophic lateral sclerosis (ALS) is a progressive nervous system disease that affects nerve cells in brain and spinal cord, causing loss of muscle control. ALS is often called Lou Gehrig's disease after the baseball player who was diagnosed with it. Doctors usually don't know why ALS occurs. Some cases are inherited. ALS often begins with muscle twitching and weakness in limb, slurred speech. Eventually ALS affects control of the muscles needed to move, speak, eat and breathe. There is no cure for this fatal disease.

ALS is categorized in two forms. The most common form is sporadic (90-95%) which has no obvious genetically inherited component. The remaining 5-10% of the cases is familial type ALS (FALS) due to their associated genetic dominant inheritance factor. The first onset of symptoms is usually between the ages of 50 and 65. Signs & symptoms of ALS vary greatly from person to person, depending on which neurons are affected. The most common signs & symptoms include difficulty walking or doing normal daily activities, Tripping and falling, Weakness in leg, feet or ankles, Hand weakness or clumsiness, Slurred speech or trouble swallowing, muscle cramps and twitching in arms, shoulders & tongue, inappropriate crying, laughing or yawning, cognitive & behavioral changes.ALS often starts in hands, feet or limbs and then spreads to other parts of body. As disease advances and nerve cells are destroyed the muscles get weaker. This eventually affects chewing, swallowing, speaking and breathing.

ALS should not be considered as a single disease entity but rather a clinical diagnosis. The defining feature of ALS is the death of both upper motor neurons (located in the motor cortex of the brain) and lower motor neurons (located in the brainstem and spinal cord). In ALS with frontotemporal dementia, neurons throughout the frontal and temporal lobes of the brain die as well. The pathological hallmark of ALS is the presence of

inclusion bodies (abnormal aggregations of protein) known as Bunina bodies in the cytoplasm of motor neurons. In about 97% of people with ALS, the main component of the inclusion bodies is TDP-43 protein however, in those with SOD1 or FUS mutations; the main component of the inclusion bodies is SOD1 protein or FUS protein. The genes known to be involved in ALS can be grouped into three general categories based on their normal function: protein degradation, the cytoskeleton, and RNA processing.





ALS affects the nerve cells that control voluntary muscle movements such as walking and talking (motor neurons). ALS causes the motor neurons to gradually deteriorate and the die. Motor neurons extend from brain to spinal cord to muscles throughout the body. When neurons are damaged they stop sending messages to muscles, so that muscles can't function. The risk factor of ALS include Heredity, it is most commonly seen in 40 and mid 60's, smoking, environmental toxin exposure, military service. Complications due to ALS are speaking problems, eating problems, and dementia.

Amyotrophic lateral sclerosis is difficult to diagnose early because it can mimic other neurological diseases. It can be diagnosed by using Electromyogram, nerve condition study, MRI, Blood & urine test, spinal tap (Lumbar puncture), Muscle biopsy. Treatment cant reverse the damage of amyotrophic lateral sclerosis, but they can slow the progression of symptoms prevent complications and make more comfortable & independent.FDA has approved two main drugs for treating ALS are Riluzole (Rilutek), Edaravone (Radicava). Physical therapy, regular exercise, Occupational therapy, speech therapy, Nutritional support, Psychological & social support is necessary to recover from ALS.

Pathogenesis of motor neurone degeneration in ALS

The exact molecular pathway causing motor neurone degeneration in ALS is unknown, but as with other neurodegenerative diseases, is likely to be a complex interplay between multiple pathogenic cellular mechanisms which may not be mutually exclusive.[77,78] These include.

1. Genetic factors 20% of cases with autosomal dominant FALS and 2% of patients with SALS show mutations in the Copper-Zinc superoxide dismutase (SOD1) gene.[82] Mutations in the gene are though to cause disease through a toxic gain of function rather than causing impairment of the antioxidant function of the SOD1 enzyme.[77] Other genes causing familial MND include alsin (ALS2)[83,84], senataxin (ALS4)[85], Vesicle associated membrane protein (VAPB, ALS8)[86], Angiogenin[87,88] and a mutation in the p150 subunit of dynactin (DCTN1).[89,90] Recently, mutations in TARDBP gene (encoding the TAR-DNA binding protein TDP-43) located on chromosome 1p36.22 have been linked to familial and sporadic ALS.[91-93] Several other gene mutations have been identified in sporadic cases which may increase susceptibility to ALS, such as mutations in the KSP repeat region in the NEFH gene (encoding neurofilament heavy subunit)[94,95], apolipoprotein E ∑4 genotype (APOE)[96], decreased expression of EAAT2 protein[97,98] and alterations in the Vascular endothelial growth factor (VEGF) gene[99] to name a few (See Table 2).

2. Excitotoxicity This is the term for neuronal injury induced by excessive glutamate induced stimulation of the postsynaptic glutamate receptors such as cell surface NMDA receptors and AMPA receptors.[77,100] This over stimulation of glutamate receptors is thought to result in massive calcium influx into the neurons, leading to increased nitric oxide formation and thereby neuronal death. Glutamate levels in CSF are elevated in some patients with ALS.[101,102] This elevation has been attributed to the loss of the glial cell excitatory amino acid transporter EAAT2.[103]

3. Oxidative stress Oxidative stress has longed been linked to neurodegeneration and it is known that accumulation of reactive oxygen species (ROS) cause cell death. As mutations in the anti-oxidant enzyme superoxide dismutase 1 (SOD1) gene can cause familial ALS, there is significant interest in this mechanism underlying neurodegenerative process in ALS. This hypothesis is supported by the finding of biochemical changes reflecting free radical damage and abnormal free radical metabolism in CSF and post mortem tissue samples of ALS patients.[104-107] In addition, fibroblasts cultured from ALS patients shows increased sensitivity to oxidative damage controls.[108]

4. Mitochondrial dysfunction Abnormalities in mitochondrial morphology and biochemistry have been reported in sporadic ALS patients, SOD1 transgenic mice and cellular models.[109-115] Mitochondria from ALS patients show elevated calcium levels and decreased activity of respiratory chain complexes I and IV, implicating defective energy metabolism.[112,116] Mitochondrial DNA mutations have been described in ALS patients.[117-119]

5. Impaired axonal transport Motor neuron axons may reach up to one metre in length in humans, and rely on efficient intracellular transport systems. These systems consist of anterograde (slow and fast) and retrograde transport systems, and rely on molecular 'motors', the kinesin complex of proteins (for anterograde) and the dynein-dynactin complex (for retrograde).[120] SOD1 transgenic mouse models of ALS show evidence of slowed anterograde transport and retrograde transport. Although no such findings have been observed in humans with ALS, mutations in the kinesin genes are known to cause neurodegenerative motor nerve diseases in humans such as hereditary spastic paraplegia and Type 2A Charcot-Marie-Tooth disease. Mutations in the dynactin complex cause a lower motor neuron disorder with vocal cord paralysis in humans.[89]

6. Neurofilament aggregation Abnormal assembly with accumulation of neurofilaments are commonly seen in several neurodegenerative conditions including SALS and FALS.[111] In addition, mutations in KSP repeat region of the neurofilament heavy (NFH) gene are found in about 1% of sporadic cases.[94,95] Neurofilament proteins together with Peripherin (an intermediate filament protein) are found in the majority of axonal inclusions motor neurones of ALS patients. A toxic isoform of peripherin (peripherin 61), has been found to be toxic to motor neurones even when expressed at modest levels and is detectable in spinal cords of ALS patients but not controls.[121]

7. Protein aggregation Intra-cytoplasmic inclusions are a hallmark of both sporadic and familial ALS (See histopathology section). However, it is still unclear as to whether aggregate formation directly causes cellular toxicity and have a key role in pathogenesis, if aggregates may be innocent by-products of the neurodegeneration process, or if formation of the aggregates may actually be a being a beneficial process by being part of a defence mechanism to reduce intracellular concentrations of toxic proteins.[77,78]

8. Inflammatory dysfunction and contribution of nonneuronal cells Although ALS is not primarily a disorder of autoimmunity or immune dysregulation, there is considerable evidence that inflammatory processes and non-neuronal cells may play a part in pathogenesis of ALS. Microglial and dendritic cell activation is a prominent pathology in human ALS and transgenic SOD1 mice.[112-116] These activated non-neuronal cells produce inflammatory cytokines such as interleukins, COX-2, TNFα and MCP-1, and evidence of upregulation is found in CSF or spinal cord specimens of ALS patients or in vitro models.[117-120] Despite this evidence, immunomodulatory therapies are yet to show promise as neuroprotective agents in clinical trials of ALS.

9. Deficits in neurotrophic factors and dysfunction of signalling pathways Decreased levels of neurotrophic factors (e.g. CTNF, BDNF, GDNF and IGF-1) have been

observed in ALS patients post-mortem and in in vitro models. In addition, deletion of the hypoxia-response element in the vascular endothelial growth factor (VEGF) gene was found to cause a motor neurone disease in mice.[94] In humans, three mutations in the VEGF gene were found to be associated with increased risk of developing sporadic ALS[99], although a recent meta-analysis by the same authors failed to show an association between VEGF haplotypes and increase the risk of ALS in humans.[95] The final process of cell death in ALS motor neurones is thought to closely resemble a programmed cell death pathway (apoptosis). Biochemical markers of apoptosis are detected in the terminal stages of human and models of ALS.[46-50] Key elements of the normal apoptotic pathway are found to be involved in cell death in ALS, including the caspase family of proteolytic enzymes, the Bcl2 family of oncoproteins (anti-apoptotic and proapoptotic oncogenes) and the apoptosis inhibitor family of proteins (IAPs).[77]

Differential diagnosis ALS must be differentiated from the "ALS mimic syndromes" which are unrelated disorders that may have a similar presentation and clinical features to ALS or it's variants.[5,74] The most important conditions are shown in Table 3.

Diagnostic methods

Electrophysiological studies

Patients in whom a diagnosis of ALS is suspected on clinical grounds should have electrophysiological studies primarily to document lower motor dysfunction in clinically involved and uninvolved regions, and secondarily to exclude other disease processes. The first published criteria for electrodiagnosis of ALS were by Lambert in 1957 and 1969.[86,87] The revised El-Escorial criteria[9] have proposed electrophysiological criteria for the diagnosis of ALS, which have been future refined in December 2006 at an consensus conference on Awaji Island, Japan.[10] It is important to bear in mind that clinical neurophysiological examination is used in the diagnosis of ALS when the diagnosis is clinically suspected, and suggestive neurophysiological abnormalities alone cannot clinch the diagnosis without clinical support.

1. Nerve conduction studies (motor and sensory) Nerve conduction studies are required for the diagnosis principally to define and exclude other disorders of peripheral nerve, neuromuscular junction and muscle that may mimic or confound the diagnosis of ALS, and these studies should generally be normal or near normal, unless the compound muscle potential is small.[9] In ALS, the distal motor latency (DML) and motor conduction velocity (MCV) remain almost normal, never falling below 70% of the upper or lower limit of normal.[188- 190] Motor studies are also important in excluding multifocal motor neuropathy, by the detection of partial conduction block. A marked reduction of proximal amplitude or negative-peak area as compared with the distal ones (over 50%), in short segments, (excluding entrapment sites) implies partial conduction block.[91] F-wave studies are particularly useful in assessing proximal conduction and abnormalities have been reported in ALS. These include increased F-wave latency with normal frequency and increased amplitude, and slowing of F-wave velocity with decreased F-wave frequency. Prominent UMN features may be associated with an increased F-wave frequency.[88] The sensory nerve conduction studies can be abnormal in the presence of entrapment syndromes and coexisting peripheral nerve disease.[9] There is also recent evidence sub-clinical involvement of the sensory system in 10–20% of patients with ALS, suggesting an additional polyneuropathy or sensory ganglionopathy.[192,193]

2. Conventional electromyography Concentric needle electromyography (EMG) provides evidence of LMN dysfunction which is required to support a diagnosis of ALS, and should be found in at least two of the four CNS regions: brainstem (bulbar/cranial motor neurons), cervical, thoracic, or lumbosacral spinal cord (anterior horn motor neurons). For the brainstem region it is sufficient to demonstrate EMG changes in one muscle (e.g. tongue, facial muscles, jaw muscles). For the thoracic spinal cord region it is sufficient to demonstrate EMG changes either in the paraspinal muscles at or below the T6 level or in the abdominal muscles. For the cervical and lumbosacral spinal cord regions at least two muscles innervated by different roots and peripheral nerves must show EMG changes.[9]

Table 1: Diagnostic errors and most common 'ALS mimic syndromes.

Final diagnosis	Characteristic features	Distinguishing diagnostic features and investigations
Cerebral lesions	Focal motor cortex lesions very rarely mimic ALS, but frontal lesions with co-existent cervical or lumbo-sacral root damage may cause confusion.	MRI/CT; no EMG evidence of widespread chronic partial denervation (CPD) in limbs
Skull base lesions	Lower cranial nerve signs (bulbar symptoms and signs; wasting of tongue, often asymmetrical); seldom significant long tract signs unless foramen magnum involved in addition	MRI; CT with bone windows; no EMG evidence of CPD in limbs unless wasting of C8/T1 muscles (rare, but present in some lesions at foramen magnum or high cervical level)
Cervical spondylotic	Progressive limb weakness. Asymmetrical onset;	Pain in root distribution, but pain may not

myelopathy	combined UMN and LMN signs in arm(s); spastic paraparesis; occasionally fasciculations in arms.	be severe and may resolve quickly; often progression followed by clinical stabilisation; no bulbar involvement; MRI evidence of spinal cord and root compression; no evidence of CPD on EMG (NB: patients may have coexistent lumbo-sacral motor radiculopathy with lower limb denervation)
Other cervical myelopathies • Foramen magnum lesions • Intrinsic and extrinsic tumours • Syringomyelia	Progressive weakness; foramen magnum lesions and high cervical cord lesions may be associated with focal (C8/T1) wasting; syringomyelia	usually associated with LMN signs and dissociated sensory loss Usually involvement of cerebellar and/or sensory pathways; MRI of head and cervical spine reveal pathology
Conus lesions and lumbo-sacral radiculopathy	Progressive mixed UMN and LMN syndrome	Usually significant sensory symptoms if not signs; bladder involvement; MRI thoracic and lumbo-sacral region; EMG evidence of radiculopathy
Inclusion body myositis (IBM)	Progressive weakness; bulbar symptoms; sometimes respiratory muscle weakness	Characteristic wasting and weakness of deep finger flexors and quadriceps femoris; EMG evidence of myopathy; muscle biopsy as definitive test (rimmed vacuoles)
Cramp/fasciculation/myokymia syndromes	Cramps, undulating muscle contractions, +/- weakness, stiffness (Isaac's syndrome; peripheral nerve hyperexcitability syndrome)	EMG evidence of myokymia; ~30% VGKC antibodies; ~20% associated with thymoma or lung cancer; association with other autoimmune diseases
Multifocal motor neuropathy (MFMN)	Focal asymmetrical onset, often upper limb; pure LMN syndrome; may stabilise for months or years; M:F 4:1;	Conduction block on nerve conduction studies (NCS); weakness often out of proportion to wasting; improvement with intravenous immunoglobulin (IVIG) in ~70%
Kennedy's disease (X-linked bulbar and spinal muscular atrophy) Males symptomatic; slowly progressive bulbar and limb weakness	Males symptomatic; slowly progressive bulbar and limb weakness	Family history; fasciculations of facial muscles; gynaecomastia; proximal symmetrical weakness in addition to foot drop; mild sensory neuropathy on NCS; positive DNA test for CAG repeat mutation in exon 1 of androgen receptor gene

The revised El-Escorial criteria require that both evidence of active or ongoing denervation and chronic partial denervation is required for the diagnosis of ALS, although relative proportions vary from muscle to muscle.[9] Signs of active denervation consist of.

1. fibrillation potentials
2. positive sharp waves

Signs of chronic denervation consist of.

1. large motor unit potentials of increased duration with an increased proportion of polyphasic potentials, often of increased amplitude
2. reduced interference pattern with firing rates higher than 10 Hz (unless there is a significant UMN component, in which case the firing rate may be lower than 10 Hz)
3. unstable motor unit potentials. Fasciculation potentials are an important characteristic finding in ALS, although they can be seen in normal muscles (benign fasciculations) and are not present in all muscles in ALS patients. In benign fasciculations the morphology of the fasciculation potentials are normal, whereas in fasciculation potentials associated with neurogenic change there are abnormal and complex morphology.[10,94] The Awaji group suggest that the presence of abnormal complex fasciculation potentials in a muscle showing neurogenic change, can be considered equivalent in importance to fibrillation potentials or positive sharp waves.[10]

3. Transcranial magnetic stimulation and Central motor conduction studies

Transcranial magnetic stimulation (TMS) allows a noninvasive evaluation of corticospinal motor pathways, and allows detection of UMN lesions in patients who lack UMN signs. Motor amplitude, cortical threshold, central motor conduction time and silent periods can be easily evaluated using this method.[95] Central motor

conduction time (CMCT) is often marginally prolonged to muscles of at least one extremity in ALS patients. Electrophysiological features compatible with UMN involvement include.[9]

1. Up to a 30% increase in central motor conduction time determined by cortical magnetic stimulation and.
2. Low firing rates of motor unit potentials on maximal effort.

Marked prolongation in the CMCT is seen in FALS patients with *D90A SOD1* mutations and patients with the flail arm and flail leg variants.[96-98]

4. Quantitative electromyography

Motor unit number estimation (MUNE) is a special electrophysiological technique that can provide a quantitative estimate of the number of axons innervating a muscle or group of muscles. MUNE consists of a number of different methods (incremental, multiple point stimulation, spiketriggered averaging, F-wave, and statistical methods), with each having specific advantages and limitations. Despite the lack of a perfect single method for performing MUNE, it may have value in the assessment of progressive motor axon loss in ALS, and may have use as an end-point measure in clinical trials.[99]

Neuroimaging studies

The most important use of neuroimaging is in the diagnosis of ALS to exclude treatable structural lesion that mimics ALS by producing varying degrees of UMN and LMN signs, especially in those with clinically probable or possible ALS. The WFN revised criteria state that imaging studies are not required in cases that have clinically definite disease with bulbar or pseudobulbar onset as it is unlikely that structural lesions can mimic clinically definite disease.[9] Magnetic resonance imaging (MRI) can be used in revealing lesions in the corticospinal tracts in ALS. The most characteristic finding in ALS is hyperintensity of the corticospinal tracts on T2-weighted, proton density weighted and FLAIR-weighted MRI, and is best visualized in the brain and brainstem and to a lesser extent in the spinal cord.[200-203] T2 weighted MRI may also show hypointensity of the primary motor cortex, usually along the posterior bank of the precentral gyrus, although this is an inconsistent and non-specific finding.[204] More advanced neuroimaging modalities such as magnetic resonance spectroscopy, diffusion weighted imaging (DWI)/diffusion tensor imaging (DTI), magnetic resonance voxel-based morphometry and functional imaging techniques (fMRI, PET and SPECT) have a limited role in routine clinical practice but have shown promise in understanding pathophysiology of the disease *in vivo*, identification of potential biomarkers of disease progression and identifying disease changes earlier in the course of the disease facilitating earlier diagnosis.[5-10]

Muscle biopsy and neuropathalogical studies

Biopsy of skeletal muscle or other tissues is not required for diagnosis, unless to rule out a mimic syndrome (e.g. Inclusion body myositis). In addition, muscle biopsy may be used to demonstrate LMN dysfunction in a body region when clinical or electrophysiological findings do not support this. Histological findings that are compatible with the diagnosis of ALS include.[9]

- Scattered hypertrophied muscle fibres.
- No more than a moderate number of target or targetoid fibres.
- Fibre type grouping of no more than mild-to-moderate extent.
- The presence of a small number of necrotic muscle fibres.

Other laboratory studies

There are few other investigations that may be considered mandatory in the work-up of an ALS patient. Clinical laboratory tests that may be abnormal in otherwise typical case of ALS include.[9]

- Muscle enzymes (serum creatine kinase [unusual above ten times upper limit of normal], ALT, AST, LDH)
- Serum creatinine (related to loss of skeletal muscle mass)
- Hypochloremia, increased bicarbonate (related to advanced respiratory compromise)
- Elevated CSF protein (uncommonly more than 100 mg/dl)

Management

The management of ALS/MND has considerably changed over the past two decades, with a emphasis on coordinated multidisciplinary care between specialist, community based therapists and palliative care teams. Although the condition is considered incurable, many of the symptoms arising during the course of the disease are treatable, and all efforts should be made to improve quality of life and help maintain the patient's autonomy for as long as possible. Advanced directives on end of life care, respiratory and nutritional management during late stages of life are important issues, and should be discussed with patients and relatives at the earliest opportunity that they are willing to do this. Patients with ALS and their relatives are likely to suffer from depression, feelings of hopelessness and anxiety regarding end-of-life issues following the diagnosis or as the disease progresses.[11,12] Therefore, psychological support in the form of counselling and palliative care should be offered to the patients and relatives early.[74,13]

Symptomatic treatments

Symptomatic treatments aim to improve quality of life of patients and care givers. The main symptoms encountered in ALS and their management.

Ventilatory management

Respiratory insufficiency occurs commonly in patients with ALS and is a major cause of mortality. The presenting symptoms of respiratory muscle weakness include dyspnoea on exertion or talking, orthopneoa,

disturbed sleep, excessive daytime somnolence, morning headaches, fatigue, anorexia, depression, poor concentration, vivid nightmares and nocturia. Clinical signs evident on examination include tachypnoea, use of accessory breathing muscles, paradoxical movement of the abdomen, weak cough and rarely papilloedema.[74,14] Measurements of the forced vital capacity (FVC) or relaxed (slow) vital capacity (SVC) are the most widely available measures for detecting respiratory decline. Measurement of the Sniff nasal inspiratory pressure (SNIP) is a good measure of diaphragmatic strength and is probably more accurate than vital capacity, although both measurements underestimate respiratory function in patients with bulbar impairment. The American Academy of Neurology (AAN) ALS Practice Parameter (1999) recommends starting non-invasive ventilation when forced vital capacity declines to 50% of the predicted value.[15] However, patients can develop respiratory failure with a forced vital capacity above 70% of the predicted value, therefore a forced vital capacity of 75% or less is probably more appropriate as a threshold for closer monitoring of respiratory symptoms.[16-18] A SNIP of 32% (~25 cms H2O) or less is highly predictive of respiratory failure.[19] Overnight oximetry can reveal episodes of desaturation consistent with nocturnal hypoventilation. Abnormalities of arterial or venous (ear lobe) blood gases, such as respiratory acidosis are a late but important finding that signifies the need for respiratory support. Respiratory support is usually provided by non-invasive ventilation (NIV) or invasive ventilation via tracheotomy. Bi-level positive pressure devices (BiPAP) are the commonly used form of NIV, whereas continuous positive pressure (CPAP) ventilation is not usually helpful.[220] The timing of initiating NIV treatment varies between counties and centres, but most published international guidelines such as those by the EALSC's work shop group[21] and EFNS task force[22], suggest the criteria proposed by the European ALS/MND Consortium and European Neuromuscular Centre workshop on non-invasive ventilation in MND in May 2002, and are shown in Table 5.[74] NIV is usually initially used for intermittent nocturnal support to alleviate symptoms of nocturnal hypoventilation, although as respiratory function worsens, patients tend to require increasing daytime support and eventually continuous support. Observational studies and a recent randomised controlled trial involving 92 ALS patients show that NIV improves survival and quality of life.[23,24] In patients with severe bulbar impairment, NIV improves sleep-related symptoms, but is unlikely to confer a large survival advantage.

Nutritional management

Dysphagia is a common symptom of ALS and leads to increased risk of aspiration, malnutrition, weight loss and dehydration. Malnutrition and dehydration can also occur inpatients whom have severe upper limb weakness, especially if they live alone, as this leads to difficulties in meal preparation or prolonged meal times. ALS is associated with a hyper metabolic state, therefore patients require increased calorie intake.[25,26] Early management of dysphagia includes dietary advice, modification of food consistency (blending solid, adding thickening agents to liquids) and educating patients on special swallowing techniques (such as supraglottic swallowing and postural changes ('Chin tuck manoeuvre').[74,22] Most guidelines state that supplementary enteral feeding should be considered when body weight falls by > 10% of the pre-diagnostic or baseline weight.[74,22] The three options available for enteric feeding include percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG) or radiologically inserted gastrostomy (RIG), and nasogastric tube (NGT) feeding. PEG is the standard procedure for enteral feeding, although the procedure requires mild sedation and therefore has implications in patients with respiratory weakness. To minimize risks, evidence suggests that PEG should be performed before VC falls below 50% of predicted.[74,27] Although it may be possible to insert PEG with NIV assistance, PRG/RIG insertion is a better alternative in these patients.[28-30] NGT is a relatively non-invasive option, but is limited by discomfort and problems associated with long term use such as frequent replacement, and should only be considered in patients who cannot undergo PEG or RIG insertion.

Disease modifying treatments

Despite many clinical trials and various advances in the understanding of ALS, there has been little success in the search for disease modifying or neuroprotective agents. Riluzole is the only approved drug that has been shown to have a modest effect on prolonging life in ALS patients.[31-37] The mechanism of action of riluzole is not entirely certain but is thought to include interference with N-methyl-D-aspartate (NMDA) receptor mediated responses, stabilisation of the inactivated state of voltagedependent sodium channels, inhibition of glutamate release from pre-synaptic terminals, and increasing of extracellular glutamate uptake.[38] The conclusion of a recent Cochrane Collaboration meta-analysis stated that riluzole at 100 mg probably prolongs median survival by 2–3 months when taken for a 18 month duration (in patients clinically probable or definite El Escorial ALS, with symptoms less than 5 years, FVC > 60% and age < 75 years).[39] The absolute risk reduction with the 100 mg dose at 12 months was 9%, with the numbers needed-to treat to delay one death (NNT) after 12 months is 11.[39] The drug is generally well tolerated with the most common side effects being asthenia, nausea, gastrointestinal upset and abnormal liver function tests, and therefore liver function should be regularly monitored during therapy.[40] Over 100 other neuroprotective agents have been studied in animal models and humans. Some agents that have been evaluated in phase II or III human clinical trials and have shown inconclusive evidence or failed to demonstrate effectiveness for routine clinical practice include: • Subcutaneous recombinant human insulin-like growth

factor (IGF-1, ormyotrophin), neurotrophins including brain derived neurotrophic factor, ciliary neurotrophic factor, glial cell line derived neurotrophic factor and oral xaliproden.[241-245] • Ceftriaxone • Talampanel (8-methyl-7H-1,3-dioxolo(2,3)benzodiazepine) • Tamoxifen • Minocycline • TCH346 • Coenzyme Q10 • Vitamin E • Celecoxib • Creatine • Copaxone • ONO 2506 – A randomised placebo-controlled investigate efficacy and safety of ONO-2506PO in the presence of riluzole was negative overall in 2004 but showed a trend towards improved survival in those who started the drug within 14 months of onset. The use of gene therapy approach to deliver neurotrophic factors directly to neurons by means of genetically engineered adeno-associated viruses (AAV) expressing neurotrophic factor genes has been evaluated in *SOD1* mouse models with some promising results[57], but human studies are not yet underway. Another approach is the use of autologous stem cell transplantation, but to date there have been no convincing results from human studies.[58,59] The recent discovery of the ability to re-programme human skin fibroblast generate pluripotent stem cells (Induced pluripotent stem cells; iPS)[60] would allow patient and disease specific stem cells to produced, leading to better disease models and eventually better autologous cell replacement therapies.

Symptomatic treatments for ALS

Symptoms	**Drugs**	**Other treatments**
Cramps	Carbamazepine • Phenytoin Quinine	• Physiotherapy • Physical exercise Massage • Hydrotherapy
Spasticity	• Baclofen • Tizanidine • Dantrolene • Botulinum toxin type A	• Physiotherapy • Hydrotherapy • Cryotherapy
Excessive watery saliva	• Atropine • Hyoscine hydrobromide • Hyoscine butylbromide • Hyoscine scopoderm • Glycopyrronium • Amitriptyline	Home suction device • Dark grape juice • Sugar-free citrus lozenges • Nebulisation • Steam inhalation • Injections of botulinum toxin into parotid glands • Irradiation of the salivary glands
Persistent saliva and bronchial secretions	• Carbocisteine • Propranolol • Metoprolol	• Home suction device • Assisted cough insufflator-exsufflator • Rehydration (jelly or ice) • Pineapple or papaya juice • Reduced intake of diary products, alcohol, and caffeine
Excessive or violent yawning	Baclofen	
Laryngospasm	Lorazepam	Reassurance
Pain	• Simple analgesics • Non-steroidal anti-inflammatory drugs • Opioids	Comfort (seating, sleeping, day and night care)
Emotional lability	Tricyclic antidepressant • Selective serotonin-reuptake inhibitors • Levodopa • Dextrometorphan and quinidine	
Communication difficulties		• Speaking techniques • Low-tech augmentative and alternative communication tools • Voice amplifiers • Light writers • Scanning systems operated
Constipation Hydration • Increased fibre intake	• Lactulose • Senna	Hydration • Increased fibre intake
Depression	• Amitriptyline • Citalopram	Psychological support, counselling

Insomnia	• Amitriptyline • Zolpidem	Comfort, analgesia
Anxiety	Lorazepam	Psychological support, counselling
Fatigue	Modafinil	

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REFERENCES

1. Pasinelli P, Brown RH: Molecular biology of amyotrophic lateral sclerosis: insights from genetics. *Nat Rev Neurosci*, 2006; 7: 710-723.
2. Rothstein JD, Tsai G, Kuncl RW, Clawson L, Cornblath DR, Drachman DB, Pestronk A, Stauch BL, Coyle JT: Abnormal excitatory amino acid metabolism in amyotrophic lateral sclerosis. *Ann Neurol*, 1990; 28: 18-25.
3. Shaw PJ, Forrest V, Ince PG, Richardson JP, Wastell HJ: CSF and plasma amino acid levels in motor neuron disease: elevation of CSF glutamate in a subset of patients. *Neurodegeneration*, 1995; 4: 209-216.
4. Rothstein JD, Van Kammen M, Levey AI, Martin LJ, Kuncl RW: Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. *Ann Neurol*, 1995; 38: 73-84.
5. Pamela J, Shaw PGI, Falkous Gavin, Mantle David: Oxidative damage to protein in sporadic motor neuron disease spinal cord. *Annals of Neurology*, 1995; 38: 691-695.
6. Ferrante RJ, Browne SE, Shinobu LA, Bowling AC, Baik MJ, Mac- Garvey U, Kowall NW, Brown RH Jr, Beal MF: Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis. *J Neurochem*, 1997; 69: 2064 2074.
7. R Glenn Smith YKH, Mark P Mattson, Stanley H Appel: Presence of 4-hydroxynonenal in cerebrospinal fluid of patients with sporadic amyotrophic lateral sclerosis. *Annals of Neurology*, 1998; 44: 696-699.
8. Hideo Tohgi TA, Kinya Yamazaki, Takahiko Murata, Eri Ishizaki, Chiaki Isobe: Remarkable increase in cerebrospinal fluid 3-nitrotyrosine in patients with sporadic amyotrophic lateral sclerosis. *Annals of Neurology*, 1999; 46: 129-131.
9. Aguirre LvDB T, Goetschalckx K, Tilkin P, Mathijis G, Cassiman JJ, Robberecht W: Increased sensitivity of fibroblasts from amyotrophic lateral sclerosis patients to oxidative stress. *Annals of Neurology*, 1998; 43: 452-457.
10. Atsumi T: The ultrastructure of intramuscular nerves in amyotrophic lateral sclerosis. *Acta Neuropathol*, 1981; 55: 193-198.
11. Afifi AK, Aleu FP, Goodgold J, MacKay B: Ultrastructure of atrophic muscle in amyotrophic lateral sclerosis. *Neurology*, 1966; 16: 475-481.
12. Hirano A, Donnenfeld H, Sasaki S, Nakano I: Fine structural observations of neurofilamentous changes in amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol*, 1984; 43: 461-470.
13. Siklos L, Engelhardt J, Harati Y, Smith RG, Joo F, Appel SH: Ultrastructural evidence for altered calcium in motor nerve terminals in amyotropic lateral sclerosis. *Ann Neurol*, 1996; 39: 203-216.
14. Kong J, Xu Z: Massive mitochondrial degeneration in motor neurons triggers the onset of amyotrophic lateral sclerosis in mice expressing a mutant SOD1. *J Neurosci*, 1998; 18: 3241-3250.
15. Krasnianski A, Deschauer M, Neudecker S, Gellerich FN, Muller T, Schoser BG, Krasnianski M, Zierz S: Mitochondrial changes in skeletal muscle in amyotrophic lateral sclerosis and other neurogenic atrophies. *Brain*, 2005; 128: 1870-1876.
16. Hirano M, Angelini C, Montagna P, Hays AP, Tanji K, Mitsumoto H, Gordon PH, Naini AB, DiMauro S, Rowland LP: Amyotrophic lateral sclerosis with ragged-red fibers. *Arch Neurol*, 2008; 65: 403-406.
17. Wiedemann FR, Winkler K, Kuznetsov AV, Bartels C, Vielhaber S, Feistner H, Kunz WS: Impairment of mitochondrial function in skeletal muscle of patients with amyotrophic lateral sclerosis. *J Neurol Sci*, 1998; 156: 65-72.
18. Dhaliwal GK, Grewal RP: Mitochondrial DNA deletion mutation levels are elevated in ALS brains. *Neuroreport*, 2000; 11: 2507-2509.
19. Falk R Wiedemann GM, Christian Mawrin, M Flint Beal, Eric A Schon: Mitochondrial DNA and respiratory chain function in spinal cords of ALS patients. *Journal of Neurochemistry*, 2002; 80: 616-625.
20. Ro LS, Lai SL, Chen CM, Chen ST: Deleted 4977-bp mitochondrial DNA mutation is associated with sporadic amyotrophic lateral sclerosis: a hospital-based case-control study. *Muscle Nerve*, 2003; 28: 737-743.
21. Grierson AJ, Miller C: Axonal transport and amyotrophic lateral sclerosis. In *Amyotrophic Lateral Sclerosis* 2nd edition. Edited by: Brown Jr RH, Swash M, Pasinelli P. Informa healthcare, 2006; 309-318.
22. Williamson TL, Cleveland DW: Slowing of axonal transport is a very early event in the toxicity of ALS-linked SOD1 mutants to motor neurons. *Nat Neurosci*, 1999; 2: 50-56.
23. Borchelt DR, Wong PC, Becher MW, Pardo CA, Lee MK, Xu ZS, Thinakaran G, Jenkins NA, Copeland NG, Sisodia SS, *et al.*: Axonal transport of mutant superoxide dismutase 1 and focal axonal abnormalities in the proximal axons of transgenic mice. *Neurobiol Dis*, 1998; 5: 27-35.
24. Murakami T, Nagano I, Hayashi T, Manabe Y, Shoji M, Setoguchi Y, Abe K: Impaired retrograde axonal transport of adenovirusmediated E. coli LacZ gene

in the mice carrying mutant SOD1 gene. *Neurosci Lett*, 2001; 308: 149-152.
25. De Vos KJ, Grierson AJ, Ackerley S, Miller CCJ: Role of Axonal Transport in Neurodegenerative Diseases. *Annual Review of Neuroscience*, 2008; 31: 151-173.
26. Reid E, Kloos M, Ashley-Koch A, Hughes L, Bevan S, Svenson IK, Graham FL, Gaskell PC, Dearlove A, Pericak-Vance MA, *et al.*: A kinesin heavy chain (KIF5A) mutation in hereditary spastic paraplegia (SPG10). *Am J Hum Genet*, 2002; 71: 1189-1194.
27. Zhao C, Takita J, Tanaka Y, Setou M, Nakagawa T, Takeda S, Yang HW, Terada S, Nakata T, Takei Y, *et al.*: Charcot-Marie-Tooth disease type 2A caused by mutation in a microtubule motor KIF1Bbeta. *Cell*, 2001; 105: 587-597.
28. Carpenter S: Proximal axonal enlargement in motor neuron disease. *Neurology*, 1968; 18: 841-851.
29. Hirano A, Nakano I, Kurland LT, Mulder DW, Holley PW, Saccomanno G: Fine structural study of neurofibrillary changes in a family with amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol*, 1984; 43: 471-480.
30. Al-Chalabi A, Andersen PM, Nilsson P, Chioza B, Andersson JL, Russ C, Shaw CE, Powell JF, Leigh PN: Deletions of the heavy neurofilament subunit tail in amyotrophic lateral sclerosis. *Hum Mol Genet*, 1999; 8: 157-164.
31. Corbo M, Hays AP: Peripherin and neurofilament protein coexist in spinal spheroids of motor neuron disease. *J Neuropathol Exp Neurol*,1992; 51: 531-537.
32. Robertson J, Doroudchi MM, Nguyen MD, Durham HD, Strong MJ, Shaw G, Julien J-P, Mushynski WE: A neurotoxic peripherin splice variant in a mouse model of ALS. *J Cell Biol*, 2003; 160: 939-949.
33. Troost D, Oord JJ van den, de Jong JM, Swaab DF: Lymphocytic infiltration in the spinal cord of patients with amyotrophic lateral sclerosis. *Clin Neuropathol*, 1989; 8: 289-294.
34. Troost D, Oord JJ Van den, Vianney de Jong JM: Immunohistochemical characterization of the inflammatory infiltrate in amyotrophic lateral sclerosis. *Neuropathol Appl Neurobiol*, 1990; 16: 401-410.
35. Kawamata T, Akiyama H, Yamada T, McGeer PL: Immunologic reactions in amyotrophic lateral sclerosis brain and spinal cord tissue. *Am J Pathol*, 1992; 140: 691-707.
36. Henkel JS, Engelhardt JI, Siklos L, Simpson EP, Kim SH, Pan T, Goodman JC, Siddique T, Beers DR, Appel SH: Presence of dendritic cells, MCP-1, and activated microglia/macrophages in amyotrophic lateral sclerosis spinal cord tissue. *Ann Neurol*, 2004; 55: 221-235.
37. Hall ED, Oostveen JA, Gurney ME: Relationship of microglial and astrocytic activation to disease onset and progression in a transgenic model of familial ALS. *Glia*, 1998; 23: 249-256.
38. Almer G, Guegan C, Teismann P, Naini A, Rosoklija G, Hays AP, Chen C, Przedborski S: Increased expression of the pro-inflammatory enzyme cyclooxygenase-2 in amyotrophic lateral sclerosis. *Ann Neurol*, 2001; 49: 176-185.
39. Robertson J, Beaulieu JM, Doroudchi MM, Durham HD, Julien JP, Mushynski WE: Apoptotic death of neurons exhibiting peripherin aggregates is mediated by the proinflammatory cytokine tumor necrosis factor-alpha. *J Cell Biol*, 2001; 155: 217-226.
40. Sekizawa T, Openshaw H, Ohbo K, Sugamura K, Itoyama Y, Niland JC: Cerebrospinal fluid interleukin 6 in amyotrophic lateral sclerosis: immunological parameter and comparison with inflammatory and non-inflammatory central nervous system diseases. *J Neurol Sci*, 1998; 154: 194-199.
41. Wilms H, Sievers J, Dengler R, Bufler J, Deuschl G, Lucius R: Intrathecal synthesis of monocyte chemoattractant protein-1 (MCP-1) in amyotrophic lateral sclerosis: further evidence for microglial activation in neurodegeneration. *J Neuroimmunol*, 2003; 144: 139-142.
42. Anand P, Parrett A, Martin J, Zeman S, Foley P, Swash M, Leigh PN, Cedarbaum JM, Lindsay RM, Williams-Chestnut RE, *et al.*: Regional changes of ciliary neurotrophic factor and nerve growth factor levels in post mortem spinal cord and cerebral cortex from patients with motor disease. *Nat Med*, 1995; 1: 168-172.
43. Elliott JL, Snider WD: Motor neuron growth factors. *Neurology*, 1996; 47: S47-53.
44. Oppenheim RW: Neurotrophic survival molecules for motoneurons: an embarrassment of riches. *Neuron*, 1996; 17: 195-197.
45. Oosthuyse B, Moons L, Storkebaum E, Beck H, Nuyens D, Brusselmans K, Van Dorpe J, Hellings P, Gorselink M, Heymans S, *et al.*: Deletion of the hypoxia-response element in the vascular endothelial growth factor promoter causes motor neurondegeneration. *Nat Genet*, 2001; 28: 131-138.
46. Lambrechts D, Poesen K, Fernandez-Santiago R, Al-Chalabi A, Del Bo R, Van Vaught PW, Khan S, Marklund S, Brockington A, Van Marion I, *et al.*: Meta-analysis of VEGF variations in ALS: increased susceptibility in male carriers of the -2578AA genotype. *J Med Genet*, 2008.
47. Guegan C, Przedborski S: Programmed cell death in amyotrophic lateral sclerosis. *J Clin Invest*, 2003; 111: 153-161.
48. Pasinelli P, Borchelt DR, Houseweart MK, Cleveland DW, Brown RH Jr: Caspase-1 is activated in neural cells and tissue with amyotrophic lateral sclerosis-associated mutations in copper-zinc superoxide dismutase. *Proc Natl Acad Sci USA*, 1998; 95: 15763-15768.
49. Pasinelli P, Houseweart MK, Brown RH Jr, Cleveland DW: Caspase- 1 and -3 are sequentially activated in motor neuron death in Cu, Zn superoxide dismutase-mediated familial

amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA*, 2000; 97: 13901-13906.
50. Li M, Ona VO, Guegan C, Chen M, Jackson-Lewis V, Andrews LJ, Olszewski AJ, Stieg PE, Lee JP, Przedborski S, Friedlander RM: Functional role of caspase-1 and caspase-3 in an ALS transgenic mouse model. *Science*, 2000; 288: 335-339.
51. Vukosavic S, Dubois-Dauphin M, Romero N, Przedborski S: Bax and Bcl-2 interaction in a transgenic mouse model of familial amyotrophic lateral sclerosis. *J Neurochem*, 1999; 73: 2460-2468.
52. Sathasivam S, Ince PG, Shaw PJ: Apoptosis in amyotrophic lateral sclerosis: a review of the evidence. *Neuropathol Appl Neurobiol*, 2001; 27: 257-274.
53. Pasinelli P, Brown RH: Molecular biology of amyotrophic lateral sclerosis: insights from genetics. *Nat Rev Neurosci*, 2006; 7: 710-723.
54. Wharton S, Ince PG: Pathology of Motor Neurone Disorders. In *Motor Neuron Disorders Volume 28*. Edited by: Shaw PJ, Strong MJ. Philadelphia: Butterworth Heinemann, 2003; 17-41.
55. Iwata M, Hirano A: Sparing of the Onufrowicz nucleus in sacral anterior horn lesions. *Ann Neurol*, 1978; 4: 245-249.
56. Ince PG: Neuropathology. In *Amyotrophic lateral sclerosis* Edited by: Brown RJ, Meininger V, Swash M. London: Martin Dunitz; 2000; 83-112.
57. Koichi Okamoto YM, Yukio Fujita: Bunina bodies in amyotrophic lateral sclerosis. *Neuropathology*, 2008; 28: 109-115.
58. Mizuno Y, Amari M, Takatama M, Aizawa H, Mihara B, Okamoto K: Transferrin localizes in Bunina bodies in amyotrophic lateral sclerosis. *Acta Neuropathologica*, 2006; 112: 597-603.
59. Bunina TL: [On intracellular inclusions in familial amyotrophic lateral sclerosis.]. *Zh Nevropatol Psikhiatr Im S S Korsakova*, 1962; 62: 1293-1299.
60. Piao YS, Wakabayashi K, Kakita A, Yamada M, Hayashi S, Morita T, Ikuta F, Oyanagi K, Takahashi H: Neuropathology with clinical correlations of sporadic amyotrophic lateral sclerosis: 102 autopsy cases examined between 1962 and 2000. *Brain Pathol*, 2003; 13: 10-22.
61. Ince PG, Evans J, Knopp M, Forster G, Hamdalla HHM, Wharton SB, Shaw PJ: Corticospinal tract degeneration in the progressive muscular atrophy variant of ALS. *Neurology*, 2003; 60: 1252-1258.
62. Leigh PN, Whitwell H, Garofalo O, Buller J, Swash M, Martin JE, Gallo JM, Weller RO, Anderton BH: Ubiquitin-immunoreactive intraneuronal inclusions in amyotrophic lateral sclerosis. Morphology, distribution, and specificity. *Brain*, 1991; 114(Pt 2): 775-788.
63. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, *et al.*: Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*, 2006; 314: 130-133.
64. Tan C-F, Eguchi H, Tagawa A, Onodera O, Iwasaki T, Tsujino A, Nishizawa M, Kakita A, Takahashi H: TDP-43 immunoreactivity in neuronal inclusions in familial amyotrophic lateral sclerosis with or without SOD1 gene mutation. *Acta Neuropathologica*, 2007; 113: 535-542.
65. Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, Mann D, Tsuchiya K, Yoshida M, Hashizume Y, Oda T: TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochemical and Biophysical Research Communications*, 2006; 351: 602-611.
66. RM Liscic LTG, J Zidar, MA Gitcho, NJ Cairns: ALS and FTLD: two faces of TDP-43 proteinopathy. *European Journal of Neurology*, 2008; 15: 772-780.
67. Warton S, Ince PG: Pathology of Motor Neuron Disorders. In *Motor neuron disorders* Edited by: Shaw PJ, Strong MJ. Philadelphia: Butterworth Heinemann; 2003:17-41. *Blue books of practical neurology*.
68. Leigh PN, Dodson A, Swash M, Brion JP, Anderton BH: Cytoskeletal abnormalities in motor neuron disease. An immunocytochemical study. *Brain*, 1989; 112(Pt 2): 521 535.
69. Brownell B, Oppenheimer DR, Hughes JT: The central nervous system in motor neurone disease. *J Neurol Neurosurg Psychiatry*, 1970; 33: 338-357.
70. Al-Sarraj S, Maekawa S, Kibble M, Everall I, Leigh N: Ubiquitin-only intraneuronal inclusion in the substantia nigra is a characteristic feature of motor neurone disease with dementia. *Neuropathol Appl Neurobiol*, 2002; 28: 120-128.
71. Swash M, Leader M, Brown A, Swettenham KW: Focal loss of anterior horn cells in the cervical cord in motor neuron disease. *Brain*, 1986; 109(Pt 5): 939-952.
72. Lawyer T Jr, Netsky MG: Amyotrophic lateral sclerosis. *AMAnArch Neurol Psychiatry*, 1953; 69: 171-192.
73. Dyck PJ, Stevens JC, Mulder DW, Espinosa RE: Frequency of nerve fiber degeneration of peripheral motor and sensory neurons in amyotrophic lateral sclerosis. Morphometry of deep and superficial peroneal nerves. *Neurology*, 1975; 25: 781-785.
74. Bradley WG, Good P, Rasool CG, Adelman LS: Morphometric and biochemical studies of peripheral nerves in amyotrophic lateral sclerosis. *Ann Neurol*, 1983; 14: 267-277.
75. Konagaya M, Sakai M, Matsuoka Y, Konagaya Y, Hashizume Y: Upper motor neuron predominant degeneration with frontal and temporal lobe atrophy. *Acta Neuropathol*, 1998; 96: 532-536.
76. Tan CF, Kakita A, Piao YS, Kikugawa K, Endo K, Tanaka M, Okamoto K, Takahashi H: Primary lateral sclerosis: a rare upper-motorpredominant form of amyotrophic lateral sclerosis often accompanied by frontotemporal lobar degeneration with ubiquitinated neuronal inclusions? Report of an

autopsy case and a review of the literature. *Acta Neuropathol*, 2003; 105: 615-620.
77. Sasaki S, Iwata M: Atypical form of amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*, 1999; 66: 581-585.
78. Sasaki S, Iwata M: Motor neuron disease with predominantly upper extremity involvement: a clinicopathological study. *Acta Neuropathol*, 1999; 98: 645-650.
79. Ota S, Tsuchiya K, Akiyama H: "Forme fruste" of amyotrophic lateral sclerosis with dementia: a report of five autopsy cases without dementia and with ubiquitinated intraneuronal inclusions. *Neuropathology*, 2005; 25: 326-335.
80. Okamoto K, Hirai S, Yamazaki T, Sun XY, Nakazato Y: New ubiquitin-positive intraneuronal inclusions in the extra-motor cortices in patients with amyotrophic lateral sclerosis. *Neurosci Lett*, 1991; 129: 233-236.
81. Wightman G, Anderson VER, Martin J, Swash M, Anderton BH, Neary D, Mann D, Luthert P, Leigh PN: Hippocampal and neocortical ubiquitin-immunoreactive inclusions in amyotrophic lateral sclerosis with dementia. *Neuroscience Letters*, 1992; 139: 269-274.
82. Matsumoto S, Hirano A, Goto S: Ubiquitin-immunoreactive filamentous inclusions in anterior horn cells of Guamanian and non-Guamanian amyotrophic lateral sclerosis. *Acta Neuropathol*, 1990; 80: 233-238.
83. Dickson DW, Josephs KA, Amador-Ortiz C: TDP-43 in differential diagnosis of motor neuron disorders. *Acta Neuropathol*, 2007; 114: 71-79.
84. Robertson J, Sanelli T, Xiao S, Yang W, Horne P, Hammond R, Pioro EP, Strong MJ: Lack of TDP-43 abnormalities in mutant SOD1 transgenic mice shows disparity with ALS. *Neurosci Lett*, 2007; 420: 128-132.
85. Mackenzie IR, Bigio EH, Ince PG, Geser F, Neumann M, Cairns NJ, Kwong LK, Forman MS, Ravits J, Stewart H, *et al.*: Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations. *Ann Neurol*, 2007; 61: 427-434.
86. Lambert EH, Mulder DW: Electromyographic studies in amyotrophic lateral sclerosis. *Proc Staff Meet Mayo Clin*, 1957; 32: 441-446.
87. Lambert E: Electromyography in amyotrophic lateral sclerosis. In *Motor neuron disease* Edited by: Norris F, Kurland L. New York: Grune and Stratton, 1969; 135-153.
88. de Carvalho M, Swash M: Nerve conduction studies in amyotrophic lateral sclerosis. *Muscle Nerve*, 2000; 23: 344-352.
89. Mills KR, Nithi KA: Peripheral and central motor conduction in amyotrophic lateral sclerosis. *J Neurol Sci*, 1998; 159: 82-87.
90. Cornblath DR, Kuncl RW, Mellits ED, Quaskey SA, Clawson L, Pestronk A, Drachman DB: Nerve conduction studies in amyotrophic lateral sclerosis. *Muscle Nerve*, 1992; 15: 1111-1115.
91. de Carvalho M, Johnsen B, Fuglsang-Frederiksen A: Medical technology assessment. Electrodiagnosis in motor neuron diseases and amyotrophic lateral sclerosis. *Neurophysiol Clin*, 2001; 31: 341-348.
92. Isaacs JD, Dean AF, Shaw CE, Al-Chalabi A, Mills KR, Leigh PN: Amyotrophic lateral sclerosis with sensory neuropathy: part of a multisystem disorder? *J Neurol Neurosurg Psychiatry*, 2007; 78: 750-753.
93. Pugdahl K, Fuglsang-Frederiksen A, de Carvalho M, Johnsen B, Fawcett PR, Labarre-Vila A, Liguori R, Nix WA, Schofield IS: Generalised sensory system abnormalities in amyotrophic lateral sclerosis: a European multicentre study. *J Neurol Neurosurg Psychiatry*, 2007; 78: 746-749.
94. Janko M, Trontelj JV, Gersak K: Fasciculations in motor neuron disease: discharge rate reflects extent and recency of collateral sprouting. *J Neurol Neurosurg Psychiatry*, 1989; 52: 1375-1381.
95. Eisen AA, Shtybel W: AAEM minimonograph #35: Clinical experience with transcranial magnetic stimulation. *Muscle Nerve*, 1990; 13: 995-1011.
96. Osei-Lah AD, Turner MR, Andersen PM, Leigh PN, Mills KR: A novel central motor conduction abnormality in D90Ahomozygous patients with amyotrophic lateral sclerosis. *Muscle Nerve*, 2004; 29: 790-794.
97. Vucic S, Kiernan MC: Abnormalities in cortical and peripheral excitability in flail arm variant amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*, 2007; 78: 849-852.
98. Cappellari A, Ciammola A, Silani V: The pseudopolyneuritic form of amyotrophic lateral sclerosis (Patrikios' disease). *Electromyogr Clin Neurophysiol*, 2008; 48: 75-81.
99. Bromberg MB, Brownell AA: Motor Unit Number Estimation inthe Assessment of Performance and Function in Motor Neuron Disease. *Physical Medicine and Rehabilitation Clinics of North America*, 2008; 19: 509-532.
100. Goodin DS, Rowley HA, Olney RK: Magnetic resonance imaging in amyotrophic lateral sclerosis. *Ann Neurol*, 1988; 23: 418-420.
101. Thorpe JW, Moseley IF, Hawkes CH, MacManus DG, McDonald WI, Miller DH: Brain and spinal cord MRI in motor neuron disease. *J Neurol Neurosurg Psychiatry*, 1996; 61: 314-317.
102. Abe K, Fujimura H, Kobayashi Y, Fujita N, Yanagihara T: Degeneration of the pyramidal tracts in patients with amyotrophic lateral sclerosis. A premortem and postmortem magnetic resonance imaging study. *J Neuroimaging*, 1997; 7: 208-212.
103. Waragai M: MRI and clinical features in amyotrophic lateral sclerosis. *Neuroradiology*, 1997; 39: 847-851.
104. Oba H, Araki T, Ohtomo K, Monzawa S, Uchiyama G, Koizumi K, Nogata Y, Kachi K, Shiozawa Z, Kobayashi M: Amyotrophic lateral sclerosis: T2

shortening in motor cortex at MR imaging. *Radiology*, 1993; 189: 843-846.
105. Ellis CM, Simmons A, Andrews C, Dawson JM, Williams SC, Leigh PN: A proton magnetic resonance spectroscopic study in ALS: correlation with clinical findings. *Neurology*, 1998; 51: 1104-1109.
106. Ellis CM, Simmons A, Jones DK, Bland J, Dawson JM, Horsfield MA, Williams SC, Leigh PN: Diffusion tensor MRI assesses corticospinal tract damage in ALS. *Neurology*, 1999; 53: 1051-1058.
107. Kalra S, Arnold D: Neuroimaging in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis*, 2003; 4:243-248.
108. Turner MR, Kiernan MC, Leigh PN, Talbot K: Biomarkers in amyotrophic lateral sclerosis. *The Lancet Neurology*, 2009; 8: 94-109.
109. Turner MR, Cagnin A, Turkheimer FE, Miller CC, Shaw CE, Brooks DJ, Leigh PN, Banati RB: Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C](R)-PK11195 positron emission tomography study. *Neurobiol Dis*, 2004; 15: 601-609.
110. Turner MR, Leigh PN: Positron emission tomography (PET) – its potential to provide surrogate markers in ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord*, 2000; 1(Suppl 2): S17-22.
111. Averill AJ, Kasarskis EJ, Segerstrom SC: Psychological health in patients with amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis*, 2007; 8: 243-254.
112. Wicks P, Abrahams S, Masi D, Hejda-Forde S, Leigh PN, Goldstein LH: Prevalence of depression in a 12-month consecutive sample of patients with ALS. *European Journal of Neurology*, 2007; 14: 993-1001.
113. Mitsumoto H, Rabkin JG: Palliative care for patients with amyotrophic lateral sclerosis: "prepare for the worst and hope for the best". *Jama*, 2007; 298: 207-216.
114. Heffernan C, Jenkinson C, Holmes T, Macleod H, Kinnear W, Oliver D, Leigh N, Ampong MA: Management of respiration in MND/ ALS patients: an evidence based review. *Amyotroph Lateral Scler*, 2006; 7: 5-15.
115. Miller RG, Rosenberg JA, Gelinas DF, Mitsumoto H, Newman D, Sufit R, Borasio GD, Bradley WG, Bromberg MB, Brooks BR, *et al.*: Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 1999; 52: 1311.
116. Lechtzin N, Wiener CM, Shade DM, Clawson L, Diette GB: Spirometry in the supine position improves the detection of diaphragmatic weakness in patients with amyotrophic lateral sclerosis. *Chest*, 2002; 121: 436-442.
117. Gruis KL, Brown DL, Schoennemann A, Zebarah VA, Feldman EL: Predictors of noninvasive ventilation tolerance in patients with amyotrophic lateral sclerosis. *Muscle Nerve*, 2005; 32: 808-811.
118. Schmidt EP, Drachman DB, Wiener CM, Clawson L, Kimball R, Lechtzin N: Pulmonary predictors of survival in amyotrophic lateral sclerosis: use in clinical trial design. *Muscle Nerve*, 2006; 33: 127-132.
119. Lyall RA, Donaldson N, Polkey MI, Leigh PN, Moxham J: Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. *Brain*, 2001; 124: 2000-2013.
120. Radunovic A, Mitsumoto H, Leigh PN: Clinical care of patients with amyotrophic lateral sclerosis. *Lancet Neurol*, 2007; 6: 913-925.
121. Andersen PM, Borasio GD, Dengler R, Hardiman O, Kollewe K, Leigh PN, Pradat PF, Silani V, Tomik B: Good practice in the management of amyotrophic lateral sclerosis: clinical guidelines. An evidence-based review with good practice points. EALSC Working Group. *Amyotroph Lateral Scler*, 2007; 8: 195-213.
122. Andersen PM, Borasio GD, Dengler R, Hardiman O, Kollewe K, Leigh PN, Pradat PF, Silani V, Tomik B: EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. *Eur J Neurol*, 2005; 12: 921-938.
123. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ: Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. *Lancet Neurol*, 2006; 5: 140-147.
124. Bourke SC, Bullock RE, Williams TL, Shaw PJ, Gibson GJ: Noninvasive ventilation in ALS: Indications and effect on quality of life. *Neurology*, 2003; 61: 171-177.